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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

9*H*-Xanthen-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 Polygalaceae families), and in a few families of fungi, lichens and bacteria [1–3]. Parent xanthone itself **1** (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 geosynthesis from aromatic precursors [4]. The chemical profile of xanthone nucleus can be highly variable (from

Abbreviations: Abs, absorbance; Ac, acetyl; Bn, benzyl; Bu, butyl; CoMFA, Comparative Molecular Field Analysis; CoMSIA, Comparative Molecular Similarity Indices Analysis; Et, ethyl; geranyl, -$CH_2CH{=}C(Me)$-$(CH_2)_2$-$CH{=}C(Me)_2$; glc, glucose; IC_{50}, inhibitory effect at 50%; isoprenyl, -CH_2-$CH{=}C(Me)_2$; Me, methyl; MLR, multiple linear regression; NA, no activity was found; NT, not tested; PNP, *p*-nitrophenol; PNPG, *p*-nitrophenol glucoside; QSAR, quantitative structure-activity relationship; rha, rhamnose; ref, reference; TBS, *tert*-butyltrimethylsilyl; xyl, xylose.

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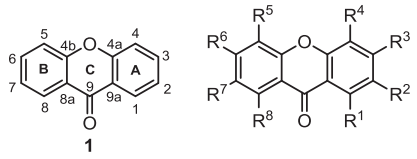


Fig. 1. Chemical structure and numbering system of the xanthone skeleton.

R^1 to R^8, Fig. 1), containing hydroxyl, methoxyl, prenyl or glycosyl as simple substituents or appearing as complex units, such as dimers, polycyclic or xanthonolignoid structures [1,3,5]. 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], antimalarial [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 (vii) 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 botanic 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 unites 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 gluconeogenesis and involves six enzymes, including two α-amylases (salivary and pancreatic) and four mucosal α-glucosidases [*N*-terminal subunits of maltase-glucoamylase (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, 10^{17} times faster than the uncatalyzed reaction, making GHs some of the most proficient enzymes. Salivary and pancreatic α-amylases belong to the GH13 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

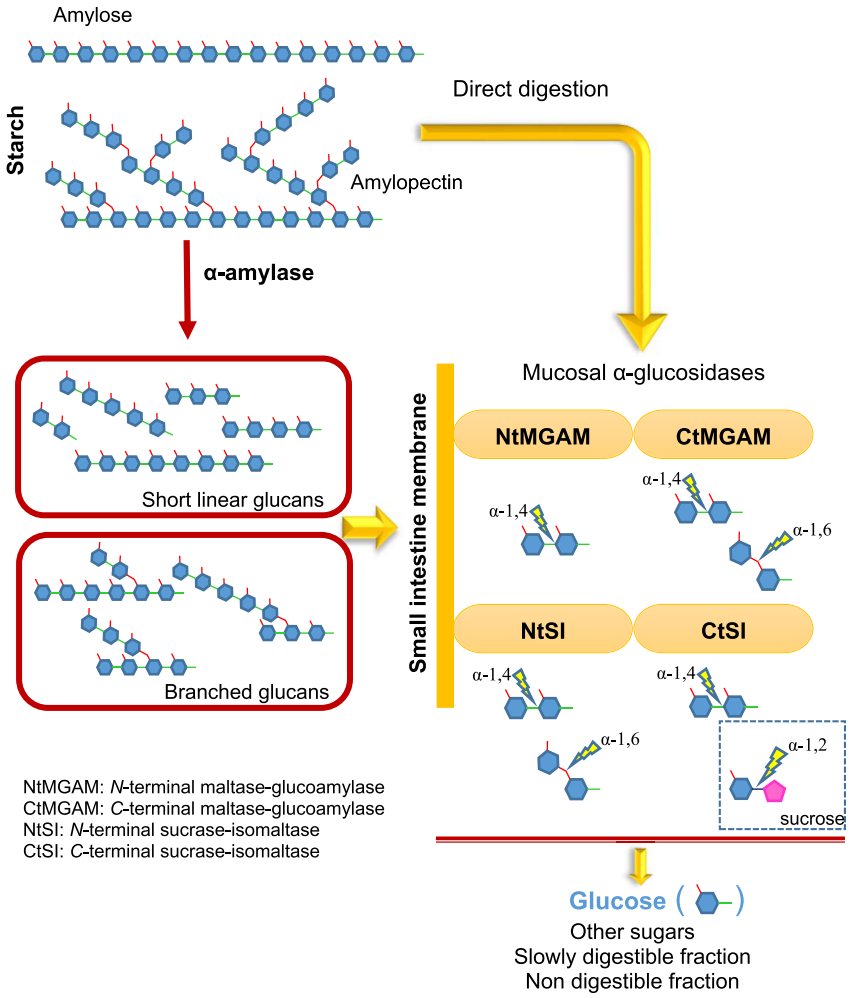


Fig. 2. Schematic diagram of the human digestion process by the digestive enzymes.

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 sucrose 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

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, 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 monitorized 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)):

$$\%\ Inhibition = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100, \quad (1)$$

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

In some cases, the IC_{50} 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 (λ_{ex} 360 nm; λ_{em} 460 nm) on release of 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]:

$$\%\ Enzyme\ activity = \frac{Net\ \ FL_{sample}}{\text{Net } FL_{control}} \times 100, \quad (2)$$

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 (λ_{ex} 363 nm; λ_{em} 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.

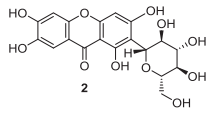
Mangiferin **2**, a *C*-glucosyl xanthone (2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one), is the most abundant natural glycosylated xanthone and widely reported in the literature for their biological activities [75–77]. Several groups dedicate their research to study the inhibitory 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	Amount (μL)	Range	Temp. (°C)	Time (min)	Amount (μL)	Conc. (mM)	Temp. (°C)	Time (min)		λ (nm)	Read	
yeast	–	250 U/mL	–	–	–	–	–	–	500	37	–	–	400	Kinetics	[40]
yeast	20	0.1 U/mL	DMSO	10	–	–	–	40	1	37	15	–	405	Kinetics	[41]
yeast	25	0.2 U/mL	DMSO	625	1–250 (μM)	–	–	25	3	37	30	Na_2CO_3 0.1 M	401	End point	[42]
yeast	–	–	–	–	–	–	–	–	–	37	30	–	405	End point	[43]
yeast	50	0.01 U/mL	DMSO	10	–	–	–	50	1	–	30	NaOH 2 M	405	End point	[44]
yeast	30	2 U/mL	–	20	–	37	5	–	3	37	30	Na_2CO_3 1 M	405	End point	[45]
yeast	50	20 U/mL	phosphate buffer	100	10–100 (μM)	37	10	100	20	37	30	Na_2CO_3 0.2 M	405	End point	[46]
yeast	100	0.35 U/mL	DMSO	50	–	37	10	100	2.5	37	20	Na_2CO_3 1 M	405	End point	[47]
yeast	20	0.6 U/mL	H_2O/0.5% DMSO	120	–	37	15	20	5	37	–	Na_2CO_3 0.2 M	405	End point	[48]
yeast	30	–	phosphate buffer	80	–	37	15	30	3	37	5	–	405	End point	[49]
yeast	20	0.2 U/mL	phosphate buffer	10	–	37	15	20	2.5	37	15	Na_2CO_3	405	End point	[50]
yeast	20	0.2 U/mL	phosphate buffer/5% DMSO	8	–	37	15	20	2.5	37	15	Na_2CO_3 0.2 M	405	End point	[51]
yeast	20	0.4 U/mL	H_2O/0.5% DMSO	120	–	37	15	20	5	37	30	Na_2CO_3 0.2 M	405	End point	[52]
yeast	30	0.2 U/mL	phosphate buffer/5% DMSO	120	–	37	15	20	5	37	30	Na_2CO_3 1 M	405	End point	[53]
yeast	20	0.2 U/mL	–	–	–	37	15	20	0.7	37	30	–	400	End point	[54]
yeast	20	0.4 U/mL	DMSO	20	–	37	30	10	3	37	60	Na_2CO_3 0.1 M	405	End point	[55]
yeast	–	–	–	–	–	37	30	–	–	37	60	–	400	End point	[56–61]
yeast	–	0.05 U/mL	phosphate buffer/5% DMSO	–	–	28	10	–	1	28	30	–	405	End point	[62]
yeast	80	0.05 U/mL	DMSO	10	–	28	10	20	1	28	35	–	405	End point	[63]
rat intestine	100	1 U/mL	H_2O/DMSO	50	–	25	10	50	5	25	5	–	405	Before and after incubation	[64]
rice	–	1.4 μg/mL	MES buffer		0.003–3 mg/mL	25	15	–	2	70	90	Na_2CO_3 1 M	405	End point	[65]
_	–	0.2 U/mL	phosphate buffer	–	–	–	–	–	0.7	37	–	–	400	Kinetic	[70]
_	10	20 U/mL	DMSO	2200	–	–	–	10	3	37	30	Na_2CO_3 0.1 M	405	End point	[74]
_	20	0.8 U/mL	phosphate buffer	120	–	37	15	20	5	37	15	Na_2CO_3 0.2 M	405	End point	[69]
_	20	0.2 U/mL	phosphate buffer	10	3.1–62.5 (μM)	37	15	20	4.5	37	–	–	400	Kinetic	[71,72]
_	20	0.2 U/mL	DMSO	20	–	37	15	20	2	–	–	Na_2CO_3 0.2 M	405	End point	[73]

*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) isomaltase (from rat) maltase (from rat)	$IC_{50} = 87$ μg/mL $IC_{50} = 216$ μg/mL $42\%^{300\ \mu g/mL}$[a]	(data not shown) (data not shown) (data not shown)	[78]
Roots of *Salacia oblonga*	α-glucosidase (yeast-derived)	$IC_{50} = 22.7$ μg/mL	acarbose ($IC_{50} = 53.9$ μg/mL)	[39,66]
Rhizoma of *Anemarrhena asphodeloides*[b]	α-glucosidase (from rice)	$IC_{50} = 96.1$ μg/mL	acarbose ($IC_{50} = 2.39$ μg/mL)	[64]
Leaves of *Aquilaria sinensis*	α-glucosidase (no source indication)	$IC_{50} = 126.5 \pm 17.8$ μg/mL (299.7 μM)	acarbose ($IC_{50} = 372.0 \pm 37.8$ μg/mL) (576.2 μM)	[69]
Whole plant *of Iris loczyi* and rhizomes of *Iris unguicularis*	α-glucosidase (no source indication)	$IC_{50} = 0.478 \pm 0.001$ mM	acarbose ($IC_{50} = 1.52 \pm 0.004$ mM)	[70,79]
Whole plant of *Swertia kouitchensis*	α-glucosidase (from Saccharomyces)	$IC_{50} = 296 \pm 52$ μM	acarbose ($IC_{50} = 627 \pm 28$ μM)	[48]
Whole plant of *Swertia mussotii*	α-glucosidase (maltase)	$IC_{50} = 13 \pm 0.2$ μM	acarbose ($IC_{50} = 39.6 \pm 0.1$ μM)	[71]
	α-glucosidase (maltase)	$IC_{50} = 13.3 \pm 0.1$ μM	acarbose ($IC_{50} = 39.8 \pm 0.1$ μM)	[72]
Leaves and stems of *Cyclopia genistoides*[c]	α-glucosidase (mammalian source)	$53\%^{100\ \mu M}$	acarbose ($50\%^{65\mu M}$)	[67]
From synthesis	α-glucosidase (from Saccharomyces)	NA	1-deoxynojirimycin ($79.6\%^{100\ \mu M}$)	[80]
	β-glucosidase (from almonds)	NA	1-deoxynojirimycin ($81.2\%^{100\ \mu M}$)	
From synthesis	α-glucosidase (from rat intestine)	$IC_{50} = 52171.37$ μM	acarbose ($IC_{50} = 1824.23$ μM)	[64]
From synthesis[d]	α-glucosidase (no source indication)	$IC_{50} = 85.35 \pm 6.39$ μg/mL	acarbose ($IC_{50} = 900$ μg/mL)	[73]

[a] Percentage of inhibition at the highest tested concentration (in superscript).
[b] In this work, mangiferin 7-O-β-D-glucopyranoside **3** was also isolated and presented an $IC_{50} = 158$ μg/mL.
[c] In this work, isomangiferin (4-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one) **4** was also isolated and presented 50% inhibition for 100 μM concentration.
[d] In this work, isomangiferin **4** was also isolated and presented and $IC_{50} = 76.98 \pm 5.18$ μg/mL.

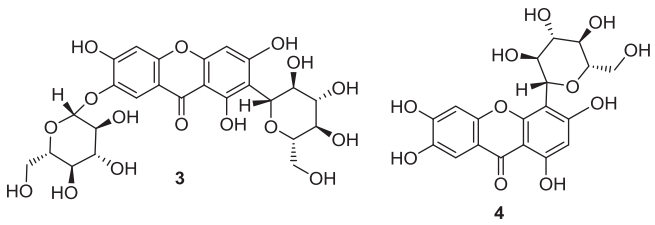


Fig. 3. Chemical structure of mangiferin 7-O-β-D-glucopyranoside **3** and isomangiferin **4**.

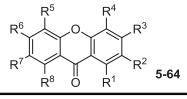
sources, being the results listed in Table 2.

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 IC_{50} values of 96.1 μg/mL and 158 μg/mL, respectively, higher than the IC_{50} of acarbose ($IC_{50} = 2.39$ 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 IC_{50} 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 ($IC_{50} = 900$ 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 specie 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 IC_{50} values of 383 ± 18, 360 ± 39, 371 ± 22, 184 ± 23, 126 ± 23 and 451 ± 41 μM, respectively (acarbose, $IC_{50} = 627 \pm 28$ 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 diglycoside 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 (IC_{50} ranging from 23.2 ± 1.5 to 44.5 ± 1.1 μM) when compared with the positive control, acarbose ($IC_{50} = 15.2 \pm 0.6$ 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.



5-64

Swertia kouitchensis[*]

Comp.	R^1	R^3	R^4	R^5	R^7	R^8	IC_{50} (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	H	OMe	H	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)-glc	OMe	H	OMe	H	H	956 ± 35	[48]
12	*O*-glc (6-1)-glc	OMe	H	OMe	H	OH	693 ± 47	[48]
13[A]	OH	OMe	H	H	*O*-glc (2-1)-rha	OH	> 1717	[48]
14	OH	OMe	H	H	*O*-rha	*O*-glc	714 ± 55	[48]
15[B]	OH	OMe	H	OH	H	*O*-glc	126 ± 23	[48]
16	*O*-glc (6-1)-xyl	OMe	H	H	OMe	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	H	OMe	OMe	> 1676	[48]
19	*O*-glc (6-1)-glc	OMe	H	H	OMe	OH	801 ± 65	[48]
20	OH	OMe	OMe	H	*O*-glc (6-1)-xyl	OH	1642 ± 97	[48]
21[C]	OH	OH	H	OH	H	*O*-glc	634 ± 33	[48]
22[D***]	OH	OMe	H	H	*O*-xyl (2-1)-rha	OH	> 1810	[48]
23	OH	OMe	H	H	*O*-glc (6-1)-xyl	OH	1126 ± 72	[48]
24[E]	R^1, R^3, R^7 = OH; R^2 = glc						1508 ± 116	[48]
Positive control: acarbose							627 ± 28	[48]

Swertia corymbosa[**]

Comp.	R^1	R^3	R^6	R^7	R^8	IC_{50} (μM)	Ref.
25	OH	OH	H	H	H	35.2 ± 0.9	[74]
26	OH	OH	OH	H	OH	39.0 ± 1.4	[74]
27[F]	OH	OH	H	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]
Positive control: acarbose						15.2 ± 0.6	[74]

Swertia mussotii Franch[**]

Comp.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	IC_{50} (μM)	Ref.
13[A]	OH	H	OMe	H	H	H	*O*-glc (2-1)-rha	OH	75.8 ± 1.3	[71]
21[C]	OH	H	OH	H	OH	H	H	*O*-glc	> 500	[71]
22[D]	OH	H	OMe	H	H	H	*O*-xyl (2-1)-rha	OH	31.1 ± 0.2	[71]
									31.6 ± 0.4	[72]
24[E]	OH	glc	OH	H	H	H	OH	H	140.4 ± 0.8	[71]
27[F]	OH	H	OH	H	H	H	OH	OH	7.09 ± 0.08	[71]
									7.3 ± 0.2	[72]
30	*O*-glc	H	OMe	H	OMe	OH	H	H	87.6 ± 1.5	[72]
31	*O*-glc	H	OMe	H	OMe	OMe	H	H	5.4%[40μM]	[81]
32	*O*-glc (6-1)-xyl	H	OMe	H	OMe	OMe	H	H	NA	[81]
33	OH	H	OMe	H	H	H	*O*-xyl (1−2)-rha (1−3)-rha	OH	84.5 ± 1.2	[71]
34	*O*-glc	H	OH	H	H	H	OH	OH	> 500	[71]
35	OH	H	OMe	OMe	H	H	*O*-glc	OH	133.7 ± 3.0	[71]
									134.5 ± 3.0	[72]
36	OH	H	OMe	H	H	H	*O*-glc	OH	394.9 ± 2.0	[71]
									395.0 ± 1.8	[72]
37	OH	H	OMe	OMe	H	H	*O*-glc	H	115.0 ± 2.4	[71]
									114.8 ± 2.3	[72]
38	*O*-glc	H	OMe	H	H	H	OMe	OMe	83.8 ± 1.2	[71]
39	OH	H	OMe	OMe	H	OH	H	OMe	> 500	[71]
									20.2 ± 0.3	[72]
40	OH	H	OMe	H	H	H	OH	OMe	> 500	[71]
41	OH	H	OMe	OMe	H	H	OH	OH	5.42 ± 0.07	[71]
42	OH	H	OMe	H	H	H	OMe	OH	107.8 ± 0.1	[71]
									108.2 ± 0.1	[72]
43	OH	H	OMe	H	H	H	OMe	OMe	142.1 ± 0.2	[71]
									142.2 ± 0.3	[72]
44	OH	H	OMe	H	H	H	OH	OH	30.6 ± 0.1	[71]
45	OH	H	OH	H	OH	H	H	OH	5.3 ± 0.1	[71]
									5.2 ± 0.3	[72]
46	OH	H	OMe	OMe	H	H	OH	OMe	77.4 ± 0.1	[71]
47	OH	H	OMe	OMe	H	H	OMe	OMe	65.8 ± 0.1	[71]
48	OH	H	OH	H	H	H	OMe	OH	71.2 ± 0.2	[71]

Table 3 (*continued*)

Swertia mussotii Franch**										
Comp.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	IC_{50} (μM)	Ref.
									71.6 ± 0.4	[72]
49	OH	H	OMe	H	H	H	OH	H	17.6 ± 0.1	[71]
									18.1 ± 0.2	[72]
50	OH	H	OH	H	H	H	OH	H	31.8 ± 0.1	[71]
51	OH	H	OH	H	H	H	OMe	OMe	18.0 ± 0.1	[71]
									18.3 ± 0.2	[72]
52	OH	H	OMe	OMe	OH	H	H	OH	82.2 ± 0.2	[71]
53	OH	H	OMe	OMe	OMe	H	H	OMe	40.1 ± 0.1	[71]
54	OH	H	OMe	H	OMe	H	H	OMe	75.8 ± 0.1	[71]
Positive control: acarbose									39.6 ± 0.1	[71]
									39.8 ± 0.1	[72]
									$98.8\%^{40\mu M}$	[81]

*Swertia bimaculata**									
Comp.	R^1	R^2	R^3	R^4	R^5	R^7	R^8	IC_{50} (μM)	Ref.
15[B]	OH	H	OMe	H	OH	H	*O*-glc	389 ± 23	[52]
21[C]	OH	H	OH	H	OH	H	*O*-glc	679 ± 58	[52]
22[D]	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	OH	OMe	OMe	H	OH	258 ± 19	[52]
62	OH	H	*O*-glc	OMe	OMe	H	H	> 1000	[52]
63	*O*-glc	H	OH	OMe	OMe	H	OH	578 ± 39	[52]
64	OH	H	*O*-glc	H	OMe	H	OH	> 1000	[52]
Positive control: acarbose								426 ± 45	[52]

*Assays performed on α-glucosidase from *Saccharomyces cerevisiae*.
**Assays performed on an unknown source of α-glucosidase.
[A–F] These compounds were isolated from the signed sources, presenting different IC_{50} values.
[D]***In another work, xanthone **22** was also tested and presented an $IC_{50} = 36$ μM, with acarbose used as positive control ($IC_{50} = 24$ μM) [46].

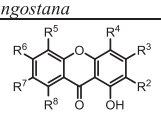
[74]. Xanthone **27** along with xanthones **13**, **21**, **22**, **24**, and **30**–**54** were also obtained from whole parts of *S. mussotii* [71]. The inhibitory effect of compound **27**, vary with its origin, *S. corymbosa* [74] and *S. mussotii* [71,72], showing different IC_{50}s, $IC_{50} = 23.2 \pm 1.5$ 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 ($IC_{50} = 15.2 \pm 0.6$ μM), while in the second one, was more active than the positive control ($IC_{50} = 39.6 \pm 0.1$ μM). Nevertheless, xanthones **41** and **45** were the most active compounds from whole parts of *S. mussotii,* with $IC_{50} = 5.42 \pm 0.07$ and 5.3 ± 0.1 or 5.2 ± 0.3 μM, respectively, that were considerably lower than the IC_{50} obtained for acarbose ($IC_{50} = 39.6 \pm 0.1$ μM). The authors also disclosed that, generally, glycosylated xanthones (**13**, **21**, **24** and **30**–**38**) were poor inhibitors of α-glucosidase activity, except for compound **22** which presented an $IC_{50} = 31.1 \pm 0.2$ 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 [81]. From the 13 xanthones isolated from *S. bimaculata* **15**, **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 ($IC_{50} = 142 \pm 17$, 136 ± 14 and 258 ± 19 μM, respectively), considering the effect of the positive control acarbose ($IC_{50} = 426 \pm 45$ 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*-glc-(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.

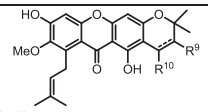
Among the 16 xanthones isolated from the fruit case of *G. mangostana* **65**–**80** (IC_{50} ranging from 1.5 ± 0.1 to 63.5 ± 1.7 μM), only compounds **70** ($IC_{50} = 58.5 \pm 0.4$ μM), **71** ($IC_{50} = 50.5 \pm 2.8$ μM), **75** ($IC_{50} = 63.5 \pm 1.7$ μM) and **80** ($IC_{50} = 45.0 \pm 0.2$ μM) exhibited IC_{50} values higher than the obtained for the positive control (1-deoxynojirimycin, $IC_{50} = 39.5 \pm 0.5$ μM) while α-mangostin **65**, mangostingone **67**, γ-mangostin **69** and smeathxanthone A **74** reached IC_{50} 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**, $IC_{50} = 5.0 \pm 0.1$ μM; mangostingone **67**, $IC_{50} = 9.8 \pm 0.3$ μM *vs* garcinone D **68**, $IC_{50} = 29.9 \pm 1.8$ μM). The same conclusion was driven by the authors when they used maltose as substrate, instead PNGP in the α-glucosidase inhibitory activity assay, although with less potency (Table 5). Similarly, α-mangostin **65**, γ-mangostin **69**, gartanin **73** and smeathxanthone A **74** were the more active tested compounds, with IC_{50} values of 53.3, 17.5, 37.7 and 35.3 μM, respectively, when compared with the positive control 1-deoxynorijirimycin ($IC_{50} = 68.8$ 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* [45] and from the resin of *Garcinia hanburyi* [49] on *Saccharomyces cerevisiae* α-glucosidase activity.

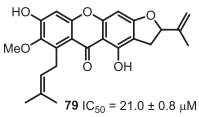
Garcinia mangostana



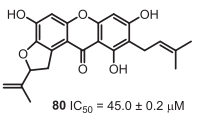
	R^2	R^3	R^4	R^5	R^6	R^7	R^8	
65	isoprenyl	OH	H	H	OH	OMe	isoprenyl	IC_{50} = 5.0 ± 0.1 μM
66	isoprenyl	OMe	H	H	OH	OMe	isoprenyl	IC_{50} = 14.4 ± 0.1 μM
67	isoprenyl	OH	H	H	OH	OMe		IC_{50} = 9.8 ± 0.3 μM
68	isoprenyl	OH	H	H	OH	OMe		IC_{50} = 29.9 ± 1.8 μM
69	isoprenyl	OH	H	H	OH	OH	isoprenyl	IC_{50} = 1.5 ± 0.1 μM
70	isoprenyl	OMe	H	OH	H	H	H	IC_{50} = 58.5 ± 0.4 μM
71	isoprenyl	OMe	H	OH	H	H	OH	IC_{50} = 50.5 ± 2.8 μM
72	isoprenyl	OH	isoprenyl	OH	H	H	H	IC_{50} = 21.5 ± 0.8 μM
73[A]	isoprenyl	OH	isoprenyl	OH	H	H	OH	IC_{50} = 10.8 ± 0.6 μM
74[B]	geranyl	OH	H	OH	H	H	OH	IC_{50} = 6.9 ± 1.1 μM
75	isoprenyl	OH	H	H	OH	OMe	CH_2CHO	IC_{50} = 63.5 ± 1.7 μM



76[C] R^9-R^{10} = CH=CH IC_{50} = 34.2 ± 2.2 μM
77 R^9-R^{10} = $CH(OH)-CH_2$ IC_{50} = 30.5 ± 1.8 μM
78 R^9-R^{10} = C(OH)=CH IC_{50} = 31.7 ± 2.3 μM



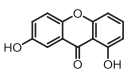
79 IC_{50} = 21.0 ± 0.8 μM



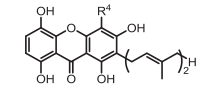
80 IC_{50} = 45.0 ± 0.2 μM

Positive control: 1-deoxynojirimycin (IC_{50} = 39.5 ± 0.5 μM)

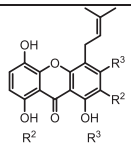
Garcinia nobilis



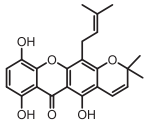
81[D] IC_{50} = 145 ± 1.3 μM



74[B] R^4 = H IC_{50} = 394 ± 2.4 μM
82 R^4 = isoprenyl IC_{50} = 227 ± 0.5 μM



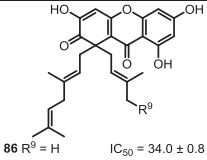
	R^2	R^3	
73[A]	isoprenyl	OH	IC_{50} = 84 ± 0.2 μM
83	H	H	NA
84	isoprenyl	OMe	IC_{50} = 76 ± 4.1 μM



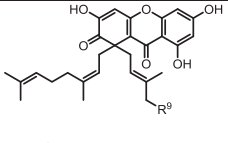
85 NA

Positive control: 1-deoxynojirimycin (IC_{50} = 441 ± 0.01 μM)

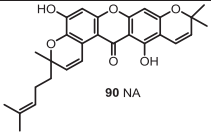
Garcia cowa[3*]



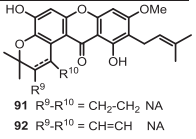
86 R^9 = H IC_{50} = 34.0 ± 0.8 μM
87 R^9 = isoprenyl IC_{50} = 36.4 ± 0.5 μM



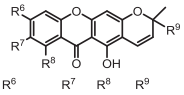
88 R^9 = H IC_{50} = 11.7 ± 0.1 μM
89 R^9 = isoprenyl IC_{50} = 55.3 ± 0.2 μM



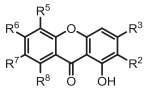
90 NA



91 R^9-R^{10} = CH_2-CH_2 NA
92 R^9-R^{10} = CH=CH NA



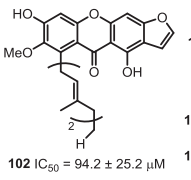
	R^6	R^7	R^8	R^9	
76[C]	Me	OH	OMe	isoprenyl	IC_{50} = 34.6 ± 0.2 μM
93	isoprenyl	OH	OMe	H	NA
94	Me	OMe	OH	isoprenyl	NA
95	Me	OMe	OMe	isoprenyl	IC_{50} = 26.2 ± 0.9 μM
96	Me	OH	OMe	geranyl	IC_{50} = 18.6 ± 0.3 μM



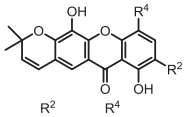
	R^2	R^3	R^5	R^6	R^7	R^8	
65	isoprenyl	OH	H	OH	OMe	isoprenyl	IC_{50} = 7.8 ± 0.5 μM
66	isoprenyl	OMe	H	OH	OMe	isoprenyl	IC_{50} = 8.7 ± 0.3 μM
97	geranyl	OH	H	OH	OMe	H	NA
98	isoprenyl	OMe	H	OMe	OMe	H	NA
99	isoprenyl	OH	isoprenyl	OH	OMe	isoprenyl	NA
100	isoprenyl	OMe	H	OH	OH	isoprenyl	NA
101[E]	H	OH	H	OH	OMe	geranyl	IC_{50} = 23.4 ± 0.9 μM

Positive control: acarbose (IC_{50} = 8.0 ± 1.7 μM)

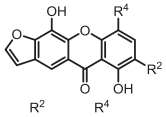
Garcinia xanthochymus



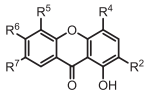
102 IC_{50} = 94.2 ± 25.2 μM



103 OH IC_{50} = 36.7 ± 20.0 μM
104 OH NA



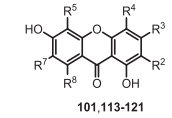
105 OH IC_{50} = 142.3 ± 10.8 μM
106 OH IC_{50} = 133.8 ± 19.3 μM



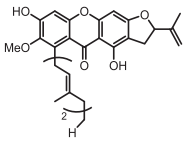
	R^2	R^4	R^5	R^6	R^7	
81[D]	H	H	H	H	OH	NA
107		OH	OH	H	H	IC_{50} = 85.5 ± 12.8 μM
108	OH		OH	H	H	IC_{50} = 29.8 ± 5.2 μM
109	H	OH	OH	H	H	IC_{50} = 358.0 ± 50.8 μM
110	OH	H	H	H	OH	IC_{50} = 31.4 ± 4.2 μM
111	OH		OH	OH	H	IC_{50} = 27.5 ± 8.6 μM
112		OH	OH	OH	H	IC_{50} = 4.1 ± 0.3 μM

Positive control: acarbose (IC_{50} = 900 0 ± 3 0 μM)

Garcinia oblongifolia



101,**113-121**

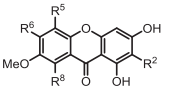


122 IC_{50} = 21.2 ± 9.7 μM

	R^2	R^3	R^4	R^5	R^7	R^8	
101[E]	H	OH	H	H	OMe	geranyl	IC_{50} = 12.4 ± 2.7 μM
113	isoprenyl	OH	H	geranyl	OH	isoprenyl	NA
114	H	OMe	isoprenyl	OH	H	H	IC_{50} = 9.4 ± 1.8 μM
115	isoprenyl	OH	H	isoprenyl	OMe	H	IC_{50} = 53.5 ± 16.6 μM
116	H	OH	isoprenyl	H	OMe	geranyl	IC_{50} = 14.1 ± 1.7 μM
117	H	OMe	geranyl	OH	H	isoprenyl	IC_{50} = 7.8 ± 2.4 μM
118	isoprenyl	OH	H	H	OMe	geranyl	IC_{50} = 10.7 ± 1.7 μM
119		OH	H	H	OMe	geranyl	IC_{50} = 28.0 ± 11.8 μM
120		OH	H	H	OMe	geranyl	IC_{50} = 70.3 ± 4.6 μM
121	isoprenyl	OH	H	H	OH	geranyl	IC_{50} = 1.7 ± 0.5 μM

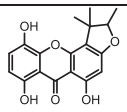
Positive control: acarbose (IC_{50} = 900 ± 3 μM)

Garcinia fusca

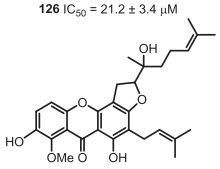


65, **97**, **118-120**, **123-125**

	R^2	R^5	R^6	R^8	
65	isoprenyl	H	OH	isoprenyl	IC_{50} = 11.4 ± 2.3 μM
97	geranyl	H	OH	H	IC_{50} = 44.0 ± 2.0 μM
118	isoprenyl	H	OH	geranyl	IC_{50} = 20.7 ± 1.5 μM
119		H	OH	geranyl	IC_{50} = 168.7 ± 1.5 μM
120		H	OH	geranyl	IC_{50} = 18.2 ± 1.5 μM
123		isoprenyl	OH	isoprenyl	IC_{50} = 8.3 ± 1.8 μM
124		H	OMe	isoprenyl	IC_{50} = 94.4 ± 0.9 μM
125	isoprenyl	H	OMe	isoprenyl	IC_{50} = 18.2 ± 1.5 μM



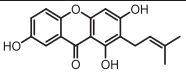
126 IC_{50} = 21.2 ± 3.4 μM



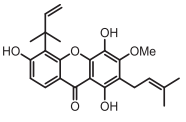
127 IC_{50} = 69.0 ± 2.7 μM

Positive control: acarbose (IC_{50} = 214.5 ± 2.3 μM)

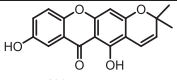
Garcinia paucinervis



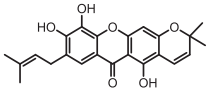
128 IC_{50} > 100 μM



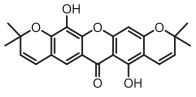
129 IC_{50} = 8.90 ± 3.35 μM



130 IC_{50} > 100 μM



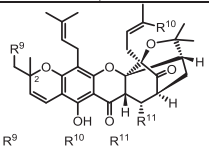
131 IC_{50} = 29.36 ± 0.81 μM



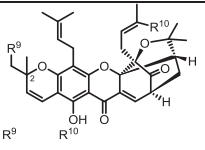
132 IC_{50} > 100 μM

Positive control: acarbose (IC_{50} = 2.88 ± 0.85 μM)

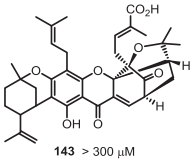
Garcinia hanburyi[6*]



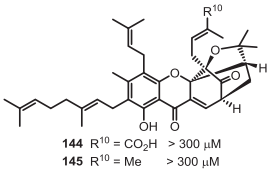
	R^9	R^{10}	R^{11}		
133	isoprenyl	CO_2H	OMe (2*R*)	IC_{50} = 108.75 ± 6.86 μM	
134	isoprenyl	CO_2H	OMe (2*S*)	IC_{50} = 282.70 ± 11.60 μM	
135	isoprenyl	CO_2H	OEt (2*R*)	IC_{50} = 111.80 ± 17.3 μM	
136	isoprenyl	CO_2H	OEt (2*S*)	> 300 μM	
137	isoprenyl	CO_2H	OH	IC_{50} = 194.70 ± 5.37 μM	
138	H	CO_2H	OMe	IC_{50} = 136.35 ± 5.73 μM	



	R^9	R^{10}	
139	H	Me	IC_{50} = 140.95 ± 5.16 μM
140	isoprenyl	Me (2*R*)	IC_{50} = 209.2 ± 29.00 μM
141	isoprenyl	Me (2*S*)	> 300 μM
142	H	CO_2H	> 300 μM



143 > 300 μM



144 R^{10} = CO_2H > 300 μM
145 R^{10} = Me > 300 μM

Positive control: acarbose (IC_{50} = 386.1 ± 7.3 μM)

NA: no activity was found.
[A-E] These compounds were isolated from the signed sources, presenting different IC_{50} values.

Table 5
Kinetic profile of isolated xanthones **65**–**80** from the fruit case *Garcinia mangostana* against α-glucosidase from *Saccharomyces cerevisiae*, using PNGP as substrate and inhibitory activity using maltose as substrate [44].

Comp.	PNGP		Maltose
	K_i (μM)	Type of inhibition	IC_{50} (μM)
65	7.3 ± 2.1	mixed	53.3
66	14.8 ± 3.4	mixed	192.0
67	8.1 ± 1.7	mixed	85.7
68	NT	NT	140.2
69	1.4 ± 0.1	mixed	17.5
70	NT	NT	> 200
71	NT	NT	> 200
72	12.3 ± 0.4	mixed	137.2
73	8.5 ± 0.3	mixed	37.7
74	2.8 ± 0.3	mixed	35.3
75	NT	NT	> 200
76	NT	NT	92.2
77	23.0 ± 1.5	mixed	102.5
78	NT	NT	155.6
79	18.1 ± 3.2	mixed	191.2
80	NT	NT	> 200
Positive control: 1-deoxynorijirimycin	NT	NT	68.8

NT: not tested.

assays showed that all of the tested compounds are mixed-type inhibitors (Table 5) [44]. Xanthone derivative mangostenone 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 $IC_{50} = 21.0 \pm 0.8$ μM (positive control 1-deoxynorjirimycin, $IC_{50} = 39.5 \pm 0.5$ μM) [44,68] and against β-glucosidase activity (from almond) presented an $IC_{50} = 212 \pm 18$ μM, being not active to inhibit the action of enzymes such as α-mannosidase (from jack been), 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 ($IC_{50} = 441 \pm 0.01$ μM). The xanthones gartanin **73** (IC_{50} 84 ± 0.2 μM) and 8-hydroxycudraxanthone G **84** (IC_{50} 76 ± 4.1 μM) were the most active compounds [54]. 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 $IC_{50} = 39.5 \pm 0.5$ and 441 ± 0.01 μM); however, the reported IC_{50} 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 IC_{50} value of ten derivatives. α-Mangostin **65** (IC_{50} 7.8 ± 0.5 μM) and β-mangostin **66** (IC_{50} 8.7 ± 0.3 μM) exhibited the highest α-glucosidase inhibitory activity, similar to the positive control acarbose ($IC_{50} = 8.0 \pm 1.7$ μM). The other tested compounds were less effective, with IC_{50} 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 ($IC_{50} = 4.1 \pm 0.3$ μM) whilst IC_{50} 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 ($IC_{50} = 900.0 \pm 3.0$ 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-dimethylallyl moiety at C-2. In the absence of the catechol ring system, the activity decreased, as observed in compounds **103** ($IC_{50} = 36.7 \pm 20.0$ μM), **107** ($IC_{50} = 85.5 \pm 12.8$ μM) and **105** ($IC_{50} = 142.3 \pm 10.8$ μM). Moreover, the 1,1-dimethylallyl side chain located at C-2 in 1,4,5-trihydroxyylated xanthone core (**107**, $IC_{50} = 85.5 \pm 12.8$ μM) seemed to enhance the inhibitory activity when compared with the 1,4,5-trihydroxyxanthone **109** ($IC_{50} = 358.0 \pm 50.8$) [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 IC_{50} values ranging from 1.7 ± 0.5 to 70.3 ± 4.6 μM, significantly lower than the IC_{50} obtained for acarbose, $IC_{50} = 900 \pm 3$ μM [63]. Another detail is observed for rubraxanthone **101**, that showed an IC_{50} value of 12.4 ± 2.7 μM [63], lower than that previously reported for this compound isolated from *G. cowa* ($IC_{50} = 23.4 \pm 0.9$ μM) (Table 4) [55].

Nguyen et al. isolated from the roots of *G. fusca* 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 (IC_{50} values varying from 8.3 ± 1.8 to 168.7 ± 1.5 μM) than the positive control acarbose ($IC_{50} = 214.5 \pm 2.3$ μM). Fuscaxanthons J **123** was the most active one with an IC_{50} value of 8.3 ± 1.8 μM followed by α-mangostin **65** ($IC_{50} = 11.4 \pm 2.3$ 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**, $IC_{50} = 11.4 \pm 2.3$ μM < **118**, $IC_{50} = 20.7 \pm 1.5$ μM), whilst the presence of a methoxy group at C-6 decreased the activity (**65**, $IC_{50} = 11.4 \pm 2.3$ μM < **125**, $IC_{50} = 18.2 \pm 1.5$ 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 ($IC_{50} = 2.88 \pm 0.85$ μM). Compounds **129** and **131** displayed moderate inhibitory activity with IC_{50} values of 8.90 ± 3.35 and 29.36 ± 0.81 μM, respectively. The remaining derivatives were ineffective, with $IC_{50} > 100$ μM (Table 4) [45].

Apart from the highly diverse number of xanthones already described, 13 caged polyprenylated derivatives **133**–**145** have been isolated from the resin of *G. hanburyi* with a unique 4-oxatricyclo [4.3.1.0]dec-2-one scaffold and tested for their α-glucosidase inhibitory activity (Table 4). Compounds **133**–**135** and **137**–**140** showed inhibitory effects with IC_{50} values varying from 108.75 ± 6.86 to 282.70 ± 11.60 μM whilst compounds **136** and **141**–**145** presented $IC_{50} > 300$ μM (acarbose, $IC_{50} = 386.1 \pm 7.3$ 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 *Cudrania tricuspidata* and among them seven derivatives have IC_{50} values ranging from 16.2 ± 0.4 to 52.9 ± 2.1 μM (Table 6) [43]. Xanthone **153** was the most active compound (IC_{50} 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 ($IC_{50} = 23.4$ μM) and 1-deoxynojirimycin ($IC_{50} = 3.5$ 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 IC_{50} values ranging from 3.2 to 77.3 μg/mL (acarbose, $IC_{50} = 735$ 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 are beneficial to the activity (when compared the higher IC_{50} 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 xx 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 cochinchinense* a series of twelve prenyl-type polyoxygenated xanthones **65**, **69**, **127** and **171**–**179** and tested their α-glucosidase inhibitory activity and kinetic profile [24]. Apart from the derivative **179** ($IC_{50} = 72.2$ μM), all xanthones were better inhibitors, with IC_{50} ranging from 1.7 to 30.7 μM, than the positive control deoxynojirimycin ($IC_{50} = 39.5$ μM). The most active xanthones were α-mangostin **65** ($IC_{50} = 5.7$ μM), γ-mangostin **69** ($IC_{50} = 1.7$ μM) and caratoxanthone A **171** ($IC_{50} = 4.8$ μM), presenting the derivatives **65** and **69** similar inhibitory effects to those reported when the compounds were isolated from *G. mangostana* (respectively, $IC_{50} = 5.0 \pm 0.1$ 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 (IC_{50} γ-mangostin **69** < IC_{50} 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].

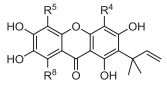
A group of seven xanthone-type compounds **180**–**186** isolated from the cultures of *Aspergillus versicolor*, a fungal endophyte of *Huperzia serrate* was screened against their ability to inhibit α-glucosidase activity. Thus, derivative **183** showed a higher efficacy ($IC_{50} = 0.26$ mM) than the positive control acarbose ($IC_{50} = 0.38$ mM), whilst xanthone **184** ($IC_{50} = 2.98$ mM) showed a weak inhibition. However, these results should be carefully analyzed due to the absence of errors associated with the IC_{50} 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 chrysogenum* SCSIO 41001, showed a potent inhibitory effect against α-glucosidase activity, presenting an $IC_{50} = 0.04$ mM, significantly lower than the positive control acarbose ($IC_{50} = 0.28$ 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 $IC_{50} = 14.7$ and 17.1 μM, respectively, were the most active compounds. The parent xanthone **1** was also tested, but showed no inhibitory effect with an $IC_{50} > 200$ 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 alkoxyl, heterocyclic or hydroxylalkoxyl 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-deoxynojirimycin ($IC_{50} = 26.4$ μM) (Table 8) [56].

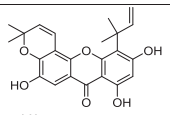
One year later, the same group prepared six 1,3-dihydroxybenzoxanthones **215**–**220** and the results showed an enhanced inhibitory activity (IC_{50} values ranging from 5.8 to 39.9 μM), when compared with 1,3-dihydroxyxanthone **25** ($IC_{50} = 160.8$ μM, Table 8) and even better than the positive control, 1-deoxynojirimycin ($IC_{50} = 26.4$ μM), except for xanthones **218** ($IC_{50} = 31.3$ μM) and **220** ($IC_{50} = 39.9$ μM) (Table 9). The authors postulate that, the extended π-conjugated systems of benzoxanthones **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** toward yeast's α-glucosidase activity were elucidated by experimental and docking studies, which indicate a noncompetitive 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 were 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.

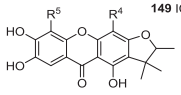
Cudrania tricuspidata



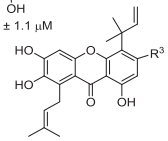
	R^4	R^5	R^8	
146	H	H	isoprenyl	IC_{50} = 35.8 ± 1.7 μM
147	isoprenyl	H	H	IC_{50} = 38.2 ± 0.8 μM
148	H	isoprenyl	H	IC_{50} = 52.9 ± 2.1 μM



149 IC_{50} = 24.9 ± 1.1 μM



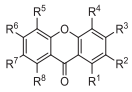
	R^4	R^5	
150	H	isoprenyl	> 100 μM
151	isoprenyl	H	IC_{50} = 32.0 ± 2.7 μM



152 R^3 = OH IC_{50} = 37.7 ± 1.8 μM
153 R^3 = OMe IC_{50} = 16.2 ± 0.4 μM

Positive controls: voglibose (IC_{50} = 23.4 μM), 1-deoxynojirimycin (IC_{50} = 3.5 μM)

Securidaca inappendiculata

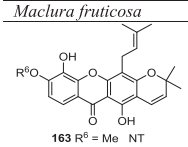


50, **81**, **154-162**

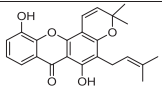
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	
50	OH	H	OH	H	H	H	OH	H	IC_{50} = 3.2 μg/mL
81[A]	OH	H	H	H	H	H	OH	H	IC_{50} = 35.8 μg/mL
154	OH	OMe	OH	H	H	H	OH	H	IC_{50} = 7.6 μg/mL
155	OH	OMe	H	H	OH	OMe	H	OMe	IC_{50} = 59.0 μg/mL
156	OH	H	OH	OMe	H	H	OH	H	IC_{50} = 12.8 μg/mL
157	OH	H	OMe	OMe	H	H	OH	H	IC_{50} = 13.2 μg/mL
158	OH	H	H	OMe	H	H	OH	H	IC_{50} = 27.6 μg/mL
159	OH	OMe	OH	H	H	H	OH	OMe	IC_{50} = 63.4 μg/mL
160	H	OH	H	H	H	H	OMe	H	IC_{50} = 77.3 μg/mL
161	OH	OMe	OH	H	H	OH	OMe	H	NA
162	OMe	OMe	H	H	H	H	OH	H	IC_{50} = 48.5 μg/mL

Positive control: acarbose (IC_{50} = 735 μg/mL)

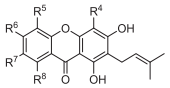
Maclura fruticosa



163 R^6 = Me NT
164 R^6 = H NA



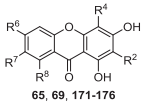
165 NT



	R^4	R^5	R^6	R^7	R^8	
166	prenyl	OH	H	H	H	NA
167	prenyl	OH	OH	prenyl	H	NT
168	H	H	H	OH	prenyl	NA
169	prenyl	OH	OH	H	H	NT
170	H	OH	H	H	H	NT

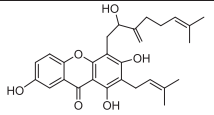
Positive control: acarbose (IC_{50} = 1.55 ± 0.39 mM)

Cratoxylum cochinchinense

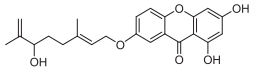


65, **69**, **171-176**

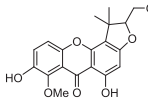
	R^2	R^3	R^4	R^6	R^7	R^8	
65	isoprenyl	OH	H	OH	OMe	isoprenyl	IC_{50} = 5.7 μM
69	isoprenyl	OH	H	OH	OH	isoprenyl	IC_{50} = 1.7 μM
171		OH	geranyl	H	OH	H	IC_{50} = 4.8 μM
172	isoprenyl	OH	geranyl	H	OH	H	IC_{50} = 17.4 μM
173	isoprenyl	OH	isoprenyl	H	OH	H	IC_{50} = 25.5 μM
174		OH	H	OH	OMe	isoprenyl	IC_{50} = 30.7 μM
175	H	OH	H	H	Ogeranyl	H	IC_{50} = 20.6 μM
176	isoprenyl	Ogeranyl	H	H	OH	H	IC_{50} = 28.4 μM



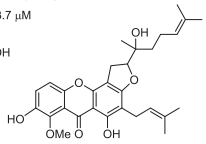
177 IC_{50} = 10.1 μM



178 IC_{50} = 13.7 μM



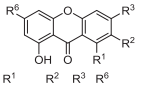
179 IC_{50} = 72.7 μM



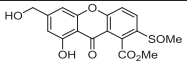
127 IC_{50} = 16.1 μM

Positive control: deoxynojirimycin (IC_{50} = 39.5 μM)

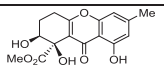
Aspergillus versicolor (fungal endophyte of *Huperzia serrata*)



	R^1	R^2	R^3	R^6	
180	CO_2Me	OH	H	CO_2Me	NA
181	H	OH	H	CH_2OH	NA
182	CO_2Me	OH	H	CH_2OH	NA
183	CO_2Me	OH	H	CO_2H	IC_{50} = 0.26 mM
184	CO_2Me	H	OH	Me	IC_{50} = 2.98 mM



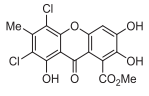
185 NA



186 NA

Positive control: acarbose (IC_{50} = 0.38 mM)

Penicillium chrysogenum SCSIO 41001



187 IC_{50} = 0.04 mM

Positive control: acarbose (IC_{50} = 0.28 mM)

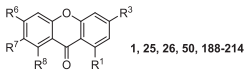
NA: no activity was found. NT: not tested.
[A] 1,7-Dihydroxyxanthone **79** was also isolated from the stem bark of *Harungana madagascariensis* presenting no inhibitory effect, at 800 μM, on Saccharomyces sp. α-glucosidase activity [positive controls used in this assay were deoxynojirimycin (IC_{50} = 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 cochinchinense* [41] against *Saccharomyces cerevisiae* α-glucosidase.

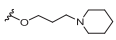
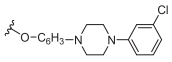
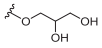
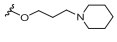
Comp.	*Cudrania tricuspidata*		Comp.	*Cratoxylum cochinchinense*	
	PNGP K_i (μM)	Type of inhibition		PNGP K_i (μM)	Type of inhibition
146	31.7	mixed	**65**	7.3	mixed
147	8.9	mixed	**69**	1.4	mixed
148	7.4	mixed	**127**	9.9	mixed
149	5.8	mixed	**171**	4.2	mixed
150	NT	NT	**172**	13.4	mixed
151	15.7	mixed	**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-deoxynorijirimycin	NT				

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].

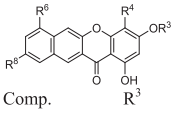


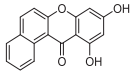
1, 25, 26, 50, 188-214

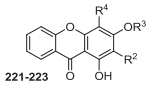
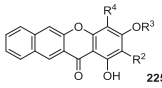
Comp.	R^1	R^3	R^6	R^7	R^8	IC_{50} (μM)
1	H	H	H	H	H	> 200
25	OH	OH	H	H	H	160.8
26	OH	OH	OH	H	OH	17.1
50	OH	OH	H	OH	H	14.7[a]
188	OH	H	H	H	H	177.4
189	OH	H	H	H	OH	91.5
190	OH	H	OH	H	H	131.4
191	OH	OH	H	H	OH	81.8
192	OH	OH	OH	H	H	41.5
193	OAc	OAc	H	H	H	31.9
194	OAc	H	H	H	H	> 200
195	OAc	H	OAc	H	H	138.9
196	OAc	OAc	H	OAc	H	46.5
197	OAc	OAc	OAc	H	OAc	49.7
198	OH	OMe	H	H	H	172.9
199	OH	OEt	H	H	H	110.8
200	OH	OBu	H	H	H	130.1
201	OH	Opentyl	H	H	H	120.9
202	OH	Oheptyl	H	H	H	113.8
203	OH	Ooctyl	H	H	H	123.7
204	OH	Odecayl	H	H	H	115.6
205	OH	OBn	H	H	H	98.2
206	OH		H	H	H	66.6
207	OH		H	H	H	53.0
208	OH		H	H	H	115.4
209	OH		H	H	H	61.8
210	OH		H	H	H	> 200
211	OH		H	H	H	> 200
212	OH	H		H	H	63.5
213	OH	H		H	H	132.7
214	OH	H		H	H	> 200
Positive control: 1-deoxynojirimycin						26.4

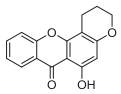
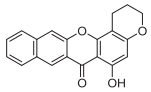
[a] In another work, 1,3,7-trihydroxyxanthone **50** presented an $IC_{50} = 14.7 \pm 1.1$ μM, with 1-deoxynojirimycin used as positive control ($IC_{50} = 26.4$ μM) [58].

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



Comp.	R^3	R^4	R^6	R^8	IC_{50} (μM)
215	H	H	H	H	9.3 [a]
216	H	H	H	OH	5.8
217	H	H	OH	H	8.0
218	Me	H	H	H	31.3
219	H	NO_2	H	H	20.1
220					39.9


221-223

225-228

Comp.	R^2	R^3	R^4	IC_{50} (μM)
221	H	H	NO_2	235.2
222	H	H	NH_2	102.3
223	H	C_3H_8Br	H	146.6
224				198.1
225	NO_2	H	H	5.9
226	NH_2	H	H	6.3
227	H	H	NH_2	8.3
228	H	C_3H_8Br	H	29.7
229				67.3
Positive control: 1-deoxynojirimycin				26.4

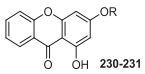
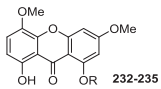
[a] In another work, compound **215** presented an IC_{50} value of 9.3 ± .4 μM, with 1-deoxynojirimycin (IC_{50} = 26.4 μM)as positive control [57].

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 **221**–**229** were prepared from the corresponding 1,3-dihydroxy (benzo) xanthones and tested towards α-glucosidase activity (positive control 1-deoxynojirimycin (IC_{50} = 26.4 μM, Table 9) [59]. As previously reported, a higher inhibitory effect was observed for the benzoxanthone derivatives **225**–**229** (IC_{50} = 5.9–67.3 μM) when compared with the xanthone derivatives **221**–**224** (IC_{50} 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 hydroxylnaphthalene 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 IC_{50} values obtained with those of the previously reported parent

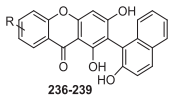
Table 10
Inhibitory effect of synthetic xanthones **230**–**235** on α-glucosidase activity[a] [b] [84].

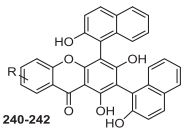

230-231

232-235

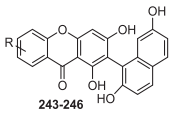
Comp.	R	% Inhibition	Comp.	R	% Inhibition
230		31.0	**232**		42.1
231		43.1	**233**		30.9
			234		66.2
			235		34.5

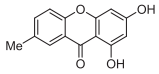
[a] Positive control: data not shown.
[b] Percentage of inhibition at the highest tested concentration (100 μM).

Table 11
Inhibitory effect of synthetic xanthones **236**–**247** on baker's yeast α-glucosidase activity [60].





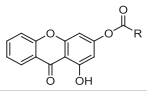


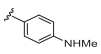
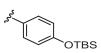
Comp.	R	IC_{50} (μM)	Comp.	R	IC_{50} (μM)	Comp.	R	IC_{50} (μM)
236	H	47.7	**240**	H	10.1	**243**	H	75.4
237	6-OH	10.5	**241**	6-OH	6.2	**244**	6-OH	47.6
238	6-OH 8-OH	8.1	**242**	7-Me	6.4	**245**	6-OH 8-OH	17.4
239	7-Me	26.5				**246**	7-Me	112.1
						247		> 200
Positive control: 1-deoxynojirimycin								40

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 β-naphthol group presented a higher inhibitory effect than the corresponding parent compounds (Table 8) [respectively **25** (IC_{50} = 160.8 μM), **192** (IC_{50} = 41.5 μM), **26** (IC_{50} = 17.1 μM) and **247** (IC_{50} > 200 μM)], whereas compounds **240**–**242** with two β-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 μM) were more active than the positive control 1-deoxynojirimycin (IC_{50} = 40 μM), while the remaining derivatives showed IC_{50} > 40 μM. In addition, the authors have made inhibitory kinetics studies using Lineweaver–Burk plots, to evaluate the type of yeast's α-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 μM for compound **26**, 29.2 μM for compound **238** and 50.9 μM for compound **245**, respectively, showing that the compound **238** is the xanthone that better inhibits α-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 α-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 μM) than the precursor xanthone **25** (IC_{50} = 145.0 ± 15.0 μM) to inhibit α-glucosidase activity. Moreover, compounds **248**–**250**, **254**, **256**–**258**, **260**–**263** were more effective

Table 12
Inhibitory effect of synthetic xanthones **248**–**263** on baker's yeast α-glucosidase activity[a] [b] [61].



Comp.	R	IC_{50} (μM)	Comp.	R	IC_{50} (μM)
248		36.1 ± 5.3	**256**		13.3 ± 1.4
249		30.6 ± 7.9	**257**		23.2 ± 3.9
250		21.6 ± 2.5	**258**		19.8 ± 2.6
251		46.7 ± 3.2	**259**		58.2 ± 4.9
252		42.0 ± 0.1	**260**		10.6 ± 1.7
253		42.6 ± 4.4	**261**		31.6 ± 0.8
254		23.7 ± 2.0	**262**		21.8 ± 0.6
255		105.5 ± 1.5	**263**		11.6 ± 2.2

[a] Positive control: 1-deoxynojirimycin (IC_{50} 40 μM).
[b] In this work, 1,3-dihydroxyxanhtone **25** was also tested and presented an IC_{50} = 145.0 ± 15.0 μM.

than the positive control, 1-deoxynojirimycin ($IC_{50} = 40\ \mu M$). 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 α-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 α-glucosidase, is favored by π-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 α-glucosidase. The inhibitory constants K_i were 17.8 μM for compound **256**, 13.3 μM for compound **260** and 18.0 μM for compound **263**, showing that compound **260** better binds to the enzyme, inhibiting it more efficiently [61].

In order to predict the α-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), Nπ (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 α-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 electronegativity 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 α-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 α-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 Suite) 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 [87] 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 α-glucosidase inhibitory activity [88].

QSAR 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 α-glucosidase inhibitory effect. Cross-validation analysis using LOO method confirmed the validity of the models [89].

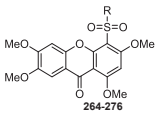
Saqib et al. tested the known 41 xanthones **25**, **26**, **50**, **188**–**193**, **195**–**209**, **212**, **213** and **215**–**229** in three-dimensional quantitative structure-activity relationship (3D-QSAR) studies, in order to provide information about the 3D structural features for α-glucosidase 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 α-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 α-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 α-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 α-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 α-glucosidase [91]. Molecular docking studies were also applied to evaluate plausible binding modes of mangiferin **2** to α-glucosidase. The results showed that mangiferin bonds to both allosteric and orthosteric sites by π-π 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].

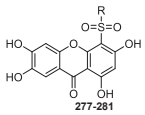
A docking-based virtual screening of 189 xanthone derivatives was performed by Lakehal et *al.* to provide insights into their binding mechanism toward NtMGAM. From binding mode analysis, 20 top-scoring xanthones [see structures **176** (Table 6) and **264**–**282** (Table 13)] revealed that sulfonamide 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].

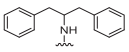
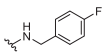
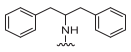
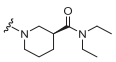
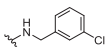
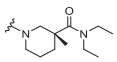
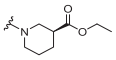
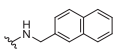
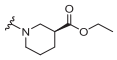
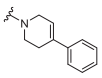
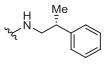
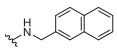
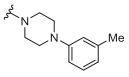
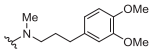
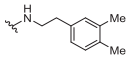
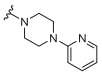
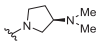
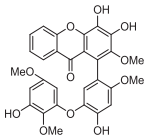
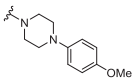
4. Conclusions

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 α-glucosidase. The comparison of results is difficult due to the variability of the experimental

Table 13
Chemical structure of xanthones **264**–**282** used in the molecular docking studies toward α-glucosidase [93].





Comp.	R	Comp.	R	Comp.	R
264		**271**		**277**	
265		**272**		**278**	
266		**273**		**279**	
267		**274**		**280**	
268		**275**		**281**	
269		**276**		**282**[a]	
270					

[a] This compound is not a sulfonamide xanthone.

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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