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Fruitful decade of fungal metabolites as anti-diabetic agents from 2010 to 2019: emphasis on α-glucosidase inhibitors

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Abstract In recent years the prevalence of diabetes has increased globally and by 2040 the number of diabetic people has been estimated to increase to 642 million. Various classes of drugs are available to treat Type ll diabetes. However, these drugs are associated with certain side effects. α-Glucosidase is an intriquing target enzyme to treat Type II diabetes, and α-glucosidase inhibitors are considered as first-line drugs for Type ll patients. Fungi, in general, produce natural products with some amazing chemical diversity and many fungal metabolites have illustrated a wide range of biological and pharmacological effects. In this review the focus is on describing the α-glucosidase effects and their potential as anti-diabetic agents of various metabolites isolated from fungi.

Keywords Fungi · Secondary metabolites · α-Glucosidase · Anti-diabetic

Introduction

Diabetes mellitus (DM) is a metabolic disorder associated with insulin resistance and the inability of the pancreatic β-cells to produce insulin, which leads to hyperglycemia. Moreover, hyperglycemia is associated with polyuria, weight loss, ketoacidosis, polydipsia, and other life-threatening health conditions (Usman et al. 2019). AGIs are an intriguing class of pharmaceutical drugs most often considered as first-line antidiabetic drugs for Type ll patients (Hossain and Pervin 2018; Usman et al. 2019). However, in

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some studies, it has been reported that AGIs can be employed as second-line antidiabetic drugs if these inhibitors are used as combination therapy with metformin (Chan et al. 2018).

The α-glucosidase enzyme (EC 3.2.1.20) has been considered as an important therapeutic target to treat carbohydrate mediated illnesses. It is well known that the secretion of α-glucosidase occurs in the small intestine and this enzyme catalyzes the cleavage of disaccharides and oligosaccharides into monosaccharides in the final step of carbohydrate digestion. Moreover, the conversion of complex carbohydrates into monosaccharides enhances the glucose body level (Abbas et al. 2019). Numerous studies have demonstrated that α-glucosidase inhibitors slow down the absorption and digestion of carbohydrates and therefore reduce the postprandial blood glucose concentrations which thus require less demand for insulin. α-Glucosidase inhibitors are considered mild compared to other oral antihyperglycemic agents because of their confined operation in the intestine rather than regulating various complex biochemical operations within the body (Abbas et al. 2019).

Fungi are considered one of the richest sources of natural products among living organisms because fungi have a unique metabolic system and can synthesise various types of natural products with quite intriquing chemical diversity (Srivastava 2019). After the discovery of penicillin (penicillin F) in 1929 by Alexander Fleming, substantial research on fungi lead to the isolation of thousands of new fungal metabolites with a diverse range of biological and pharmacological effects (Srivastava 2019). Besides, penicillins (antibacterial), echinocandin B (antifungal), cyclosporin A (immunosuppressive, and lovastatin (cholesterol-lowering) are all fungal originated and marketed pharmaceutical drugs. Furthermore, these factors evidently illustrate the significance of fungal metabolites to be a sustainable resource for new pharmaceutical agents.

Currently, acarbose and miglitol are two commercially available drugs with activity described as α-glucosidase inhibitors (AGIs). These pharmaceutical drugs furthermore inhibit the absorption of carbohydrates from the gut and thus these anti-diabetic drugs are either administered alone or in combination with insulin (Bhatia et al. 2019; Hung et al. 2012). However, serious gastrointestinal damage and liver injuries have been associated with the use of these AGIs, and this has restricted their clinical usage (Yin et al. 2014; Kao et al. 2016; Usman et al. 2019). Therefore, there is a crucial need to discover and develop new and safer anti-diabetic drugs with low toxicity. Natural products for this purpose would be ideal if they could combat such diseases without creating other secondary health issues. Plant secondary metabolites have especially been widely studied for their potential anti-diabetic properties. It is thus conceivable that diverse compounds derived from fungal sources could be developed or transformed into new therapeutics against diabetes. This review article describes some small molecules isolated in the last decade (2010 to 2019) from various fungi and developed as inhibitors of α-glucosidase, and thus represent potential anti-diabetic drug leads.

Alkaloids

Alkaloids are nitrogen containing natural products and have been recognized substances in the treatment of human diseases for many years (Pervaiz et al. 2016; Rehman and Khan 2016). Literature indicated that a significant number of alkaloids from plant sources have been identified as α-glucosidase inhibitors (Yin et al. 2014). On the other hand, a number of alkaloids have been reported from various fungi possessing a diverse range of biological effects (Mahmood et al. 2010). Some alkaloids have also been reported from various fungi, which illustrated α-glucosidase inhibition. Valle et al. reported that benzomalvin A (**1**), quinolactacins A1 (**2**), A2 (**3**) in a mixture between B (**4**) and asperphenamate (**5**) (Fig. 1) were produced from the fungus *Penicillium spathulatum* (Valle et al. 2016).

Moreover, the crude extract of *P. spathulatum* displays α-glucosidase effects with IC_{50}: 56.5 μg/mL. Indeed, compounds **1** (IC_{50}: 383.2 μg/mL), the mixture of **2** and **3** (IC_{50}: 273.3 μg/mL), **4** (IC_{50}: 57.3 μg/mL), and **5** (IC_{50}: 8.3 μg/mL) display a reasonable degree of α-glucosidase inhibition (Table 1). With an in vivo oral sucrose tolerance evaluation; compound **1** was also tested in normal and hyperglycemic mice ($p < 0.05$). Further docking studies revealed a higher binding affinity of **1** to yeast and mammalian α-glucosidase and this activity has been reported as even higher than that of acarbose. The formalin assay studies substantiated antihyperalgesic activity

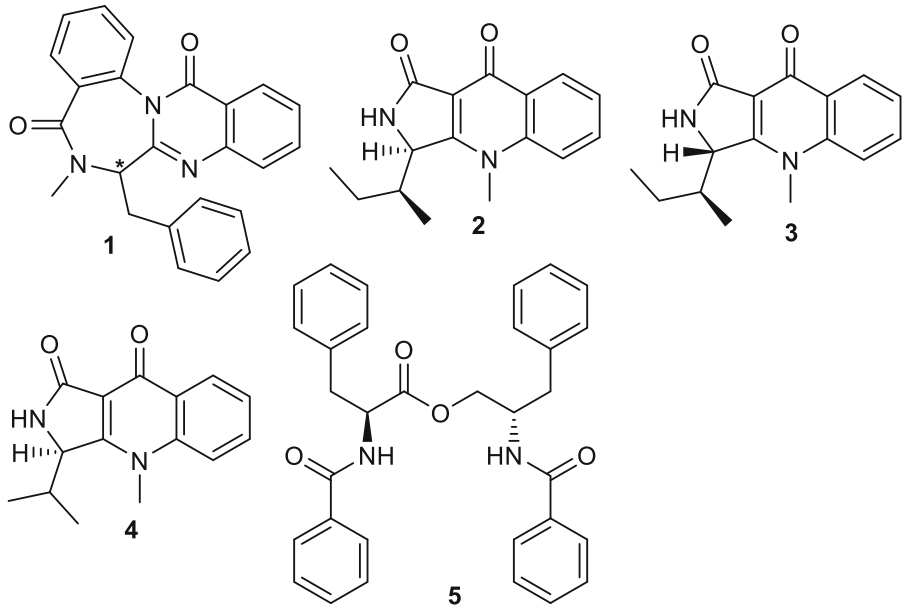


Fig. 1 Structures of alkaloids **1–5**

($p < 0.05$) of compound **1** in hyperglycemic mice (Valle et al. 2016). Benzomalvin A (**1**) was also previously reported from the fungus *Penicillium* sp (Sun et al. 1994), quinolactacins A1 (**2**), A2 (**3**) from the fungus *Xylariaceae* sp (Nong et al. 2014), and quinolactacin B (**4**) from the fungus *Penicillium* sp. (Takahashi et al. 2000; Kakinuma et al. 2000). On the other hand, asperphenamate (**5**) was reported as a fungal metabolite from *Penicillium* sp. (Frisvad et al. 2013; Arai et al. 2017) and the fungus *Aspergillus versicolor* (Hou et al. 2017) as well as a plant metabolite reported from *Antidesma ghaesembilla* (Schaefer et al. 2017) and *Erythrina droogmansiana* (Yaya et al. 2014).

Isoindolinone type alkaloids, viz., the sterenins A-C (**6–8**) (Ito-Kobayashi et al. 2008; Wang et al. 2014) and K-M (**9–11**) Wang et al. 2014) (Fig. 2) were reported from the fungus *Stereum* sp. and tested for their potential as α-glucosidase inhibitors. The chemical diversity generated among these alkaloids is mainly due to the different substituent groups on nitrogen (Wang et al. 2014). These compounds possess α-glucosidase effects with IC_{50}: 3.31 to 36.6 µM (Table 1). Notably, alkaloid **8** illustrated potent inhibition with IC_{50}: 3.31 µM. SAR studies demonstrated that the different substituents on nitrogen play a most important role and when there is no substituent (R = H) the activity was enhanced (alkaloid **8**). On the other hand, various alky substituents attached to the nitrogen dramatically decreased activities (Wang et al. 2014). Penicidone C (**12**) was reported from *Penicillium* sp. (He et al. 2019; Ge et al. 2008) and demonstrated α-glucosidase inhibition with a low IC_{50}: 51.9 µM (He et al. 2019).

Azaphilones

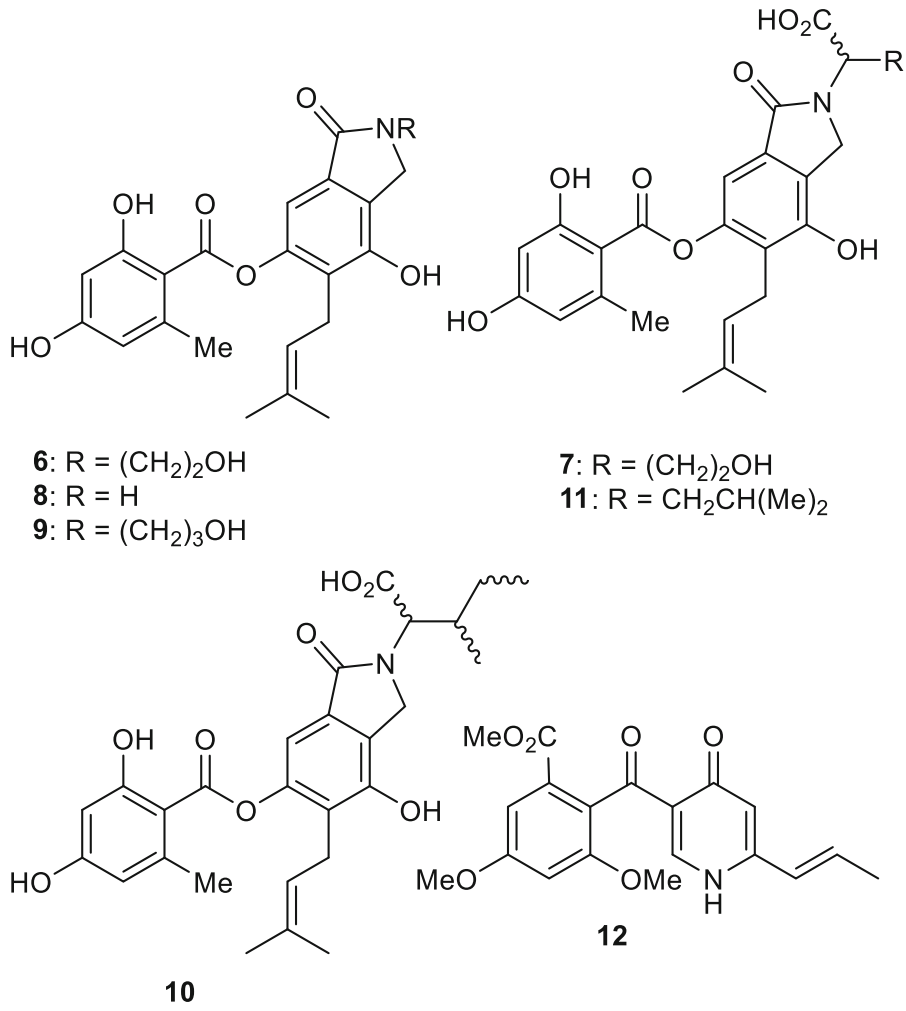
Most of the azaphilones have been reported from two fungi families viz., Xylariaceae and Trichocomaceae and most of these compounds were reported from the fungal genera viz., *Chaetomium*, *Penicillium*, *Monascus* and *Talaromyces*. The azaphilones illustrated interesting pharmacological effects viz., anti-fungal, antimicrobial, antioxidant, antiviral, anti-inflammatory, cytotoxic, and nematicidaland activities (Osmanova et al. 2010; Gao et al. 2013). Talaraculones A (**13**) and B (**14**) (Fig. 3) were reported from the fungus *Talaromyces aculeatus* and compounds **13** and **14** illustrated α-glucosidase potential with IC_{50}: 78.6 and 22.9 µM, respectively, which are lower than acarbose (IC_{50}: 101.5 µM) (Ren et al. 2017).

Chermesinone A (**15**), isolated from the fungus *Penicillium chermesinum*, illustrated α-glucosidase effects with IC_{50}: 24.5 µM (Huang et al. 2011). In this regard, compound **15** was also reported from the

Table 1 Fungal metabolites **1–39** as α-glucosidase inhibitors

Compound	Source	α-Glucosidase activity	References
Benzomalvin A (**1**)	*Penicillium spathulatum*	IC_{50}: 383.2 μM	Valle et al. (2016)
Quinolactacins A1 (**2**), A2 (**3**); mixture	*Penicillium spathulatum*	IC_{50}: 273.3 μM	Valle et al. (2016)
Benzomalvin B (**4**)	*Penicillium spathulatum*	IC_{50}: 57.3 μM	Valle et al. (2016)
Asperphenamate (**5**)	*Penicillium spathulatum*	IC_{50}: 8.3 μM	Valle et al. (2016)
Sterenin A (**6**)	*Stereum hirsutum*	IC_{50}: 25.1 μM	Wang et al. (2014)
Sterenin B (**7**)	*Stereum hirsutum*	IC_{50}: 12.3 μM	Wang et al. (2014)
Sterenin C (**8**)	*Stereum hirsutum*	IC_{50}: 3.3 μM	Wang et al. (2014)
Sterenin K (**9**)	*Stereum hirsutum*	IC_{50}: 36.6 μM	Wang et al. (2014)
Sterenin L (**10**)	*Stereum hirsutum*	IC_{50}: 13.0 μM	Wang et al. (2014)
Sterenin M (**11**)	*Stereum hirsutum*	IC_{50}: 27.5 μM	Wang et al. (2014)
Penicidone C (**12**)	*Penicillium* sp.	IC_{50}: 51.9 μM	He et al. (2019)
Talaraculone A (**13**)	*Talaromyces aculeatus*	IC_{50}: 78.6 μM	Ren et al. (2017)
Talaraculone B (**14**)	*Talaromyces aculeatus*	IC_{50}: 22.9 μM	Ren et al. (2017)
Chermesinone A (**15**)	*Penicillium chermesinum*	IC_{50}: 24.5 μM	Huang et al. (2011)
Pinazaphilone A (**16**:)	*Penicillium* sp.	IC_{50}: 81.7 μM	Liu et al. (2015)
Pinazaphilone B (**17**)	*Penicillium* sp.	IC_{50}: 28.0 μM	Liu et al. (2015)
Sch 1385568 (**18**)	*Penicillium* sp.	IC_{50}: 16.6 μM	Liu et al. (2015)
Sch 725680 (**19**)	*Penicillium* sp.	IC_{50}: 33.8 μM	He et al. (2019)
6′-O-desmethylterphenyllin (**20**)	*Penicillium chermesinum*	IC_{50}: 2.5 μM	Huang et al. (2011)
3-hydroxy-6′-O-desmethylterphenyllin (**21**)	*Penicillium chermesinum*	IC_{50}: 4.9 μM	Huang et al. (2011)
3,3″-dihydroxy-6′-O-desmethylterphenyllin (**22**)	*Penicillium chermesinum*	IC_{50}: 0.9 μM	Huang et al. (2011)
Sarcoviolin β (**23**)	*Sarcodon leucopus*	IC_{50}: 0.58 μM	Ma et al. (2014)
Episarcoviolin β (**24**)	*Sarcodon leucopus*	IC_{50}: 1.07 μM	Ma et al. (2014)
2′,3′,5′,6′-Tetracetoxy-4,4″-dihydroxy-p-terphenyl (**25**)	*Sarcodon leucopus*	IC_{50}: 35 μM	Ma et al. (2014)
2′,3′-Diacetoxy-4,4″,5′,6′-tetrahydroxy-p-terphenyl (**26**)	*Sarcodon leucopus*	IC_{50}: 19 μM	Ma et al. (2014)
2′,3′-Diacetoxy-3,4,4″,5′,6′-pentahydroxy-p-terphenyl (**27**)	*Sarcodon leucopus*	IC_{50}: 3.3 μM	Ma et al. (2014)
Leucomelone (**28**)	*Sarcodon leucopus*	IC_{50}: 3.5 μM	Ma et al. (2014)
Bl-V (**29**)	*Sarcodon leucopus*	IC_{50}: 6.2 μM	Ma et al. (2014)
Episarcodonin α (**30**)	*Sarcodon leucopus*	IC_{50}: 3.6 μM	Ma et al. (2014)
Episarcodonin (**31**)	*Sarcodon leucopus*	IC_{50}: 4.2 μM	Ma et al. (2014)
Sarcodonin α (**32**)	*Sarcodon leucopus*	IC_{50}: 1.2 μM	Ma et al. (2014)
Concrescenin A (**33**)	*Hydnellum concrescens*	IC_{50}: 0.9 μM	Wang et al. (2014a)
Concrescenin B (**34**)	*Hydnellum concrescens*	IC_{50}: 3.1 μM	Wang et al. (2014a)
Thelephantin L (**35**)	*Hydnellum concrescens*	IC_{50}: 4.5 μM	Wang et al. (2014a)
Thelephantin I (**36**)	*Hydnellum concrescens*	IC_{50}: 18.7 μM	Wang et al. (2014a)
Thelephantin K (**37**)	*Hydnellum concrescens*	IC_{50}: 2.9 μM	Wang et al. (2014a)
Dihydroauran-tiacin dibenzoate (**3**)	*Hydnellum concrescens*	IC_{50}: 5.1 μM	Wang et al. (2014a)
Curtisian A (**39**)	*Hydnellum concrescens*	IC_{50}: 8.3 μM	Wang et al. (2014a)

Fig. 2 Structures of alkaloids **6–12**



fungus *Phomopsis* sp. (Yang et al. 2015). Pinazaphilones A (**16**: IC_{50}: 81.7 μM) and B (**17**: IC_{50}: 28.0 μM), and Sch 1385568 (**18**: IC_{50}: 16.6 μM) were produced by the fungus *Penicillium* sp. and illustrated good to moderate α-glucosidase effects (Table 1) (Liu et al. 2015a). Sch 725680 (**19**) was reported from *Penicillium* sp. (He et al. 2019) and was shown to possess α-glucosidase effects with IC_{50}: 33.8 μM.

p-Terphenyls

p-Terphenyls bearing a C-18 tricyclic or polycyclic aromatic core demonstrate a huge chemical diversity generated among these compounds by suitable changes in the middle aromatic ring or the linkages between the rings (Li et al. 2018). Over 230 p-terphenyl analogs have been reported as well as a number of isolated derivatives (Li et al. 2018). The majority of these compounds were reported from fungi (Li et al. 2018; Quang et al. 2003; Liu et al. 2004; Lee et al. 1996; Nagasawa et al. 2014). The three *p*-terphenyls **20–22** (Fig. 4) were isolated from the fungus *Penicillium chermesinum* and illustrated α-glucosidase effects with IC_{50} values of 2.5, 4.9, and 0.9 μM, respectively (Table 1). Notably, the activity of these compounds was higher than the reference genistein (IC_{50}: 9.8 μM, Huang et al. 2011). Previously, compound **20** was reported from the fungus *Penicillium raistrickii* (Belofsky et al. 1998).

p-Terphenyls **23–32** were produced by the fungus *Sarcodon leucopus* and their structures were determined via extensive NMR techniques (Ma et al. 2014). All compounds displayed α-glucosidase effects with

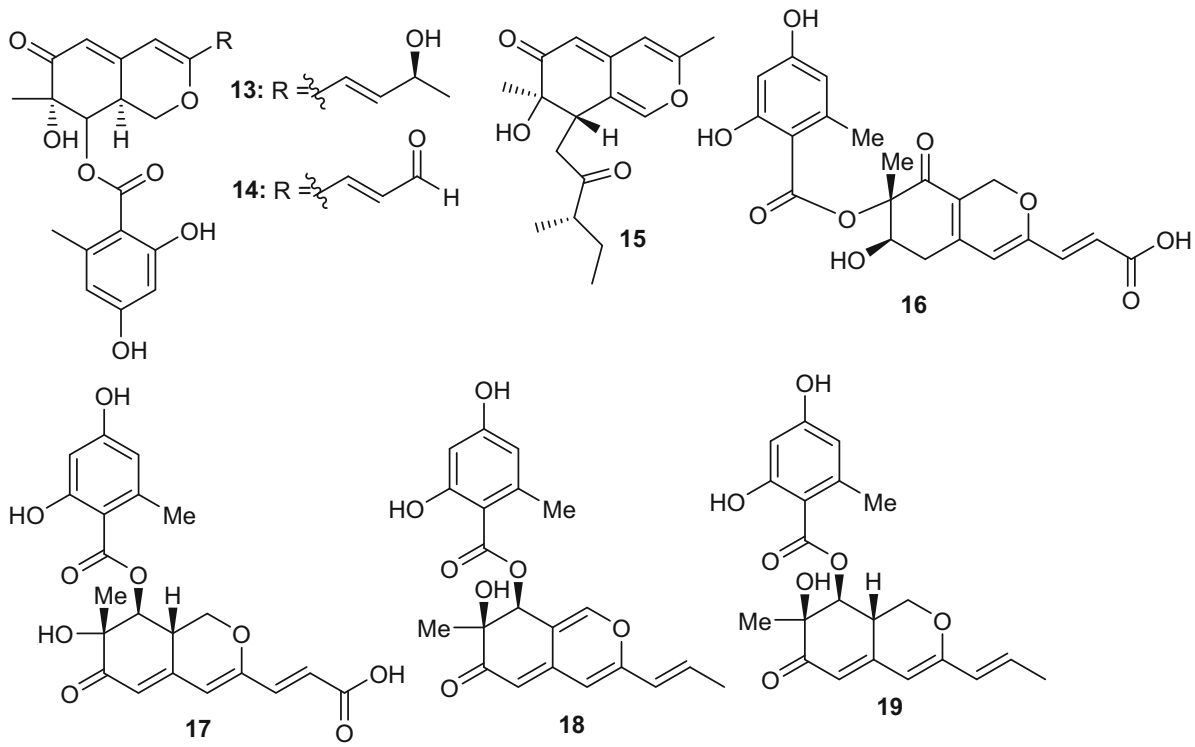


Fig. 3 Structures of azaphilones **13–19**

IC_{50} values ranging from 0.58 to 35.0 μM. Among these, sarcoviolin β (**23**) showed good and potent effects with an IC_{50}: 0.58 μM followed by an isomer of **24**. Compounds **24** and **27–32** illustrated moderate inhibition with IC_{50} values ranging from 1 to 10 μM (Table 1). On the other hand p-terphenyls **25** and **26** possess relatively weak effects with IC_{50} values of 35.0 and 19.0 μM, respectively. An SAR analysis demonstrated that the configuration at N-1β and C-2β greatly effects the α-glucosidase activity. For instance, metabolites **23** and **32** having the *cis* N-1β and C-2β displayed better activity than metabolites **24** and **30** bearing a *trans* configuration (Ma et al. 2014).

p-Terphenyl analogs viz., concrescenins A (**33**) and B (**34**), thelephantins L (**35**), I (**36**), K (**37**), compound **38**, and curtisian A (**39**) (Fig. 5) were reported from the fungus *Hydnellum concrescens* (Wang et al. 2014a). p-Terphenyl analogs **33–39** illustrated α-glucosidase effects with the IC_{50} ranging from of 0.99 to18.77 μM. Among the tested compounds, metabolite **33** (IC_{50}: 0.99 μM) possesses the strongest effects followed by metabolite **34** (IC_{50}: 3.11 μM) and **37** (IC_{50}: 2.98 μM) (Table 1). A preliminary SAR study demonstrated that the benzene core in the center of the *p*-terphenyl core enhances the α-glucosidase effects when compared to the benzoquinone ring as can be noticed by metabolites **33–35** and **37–39** displaying better activity than compound **36** (Wang et al. 2014a).

Depsides

The fungus MEXU 27095 produces the tridepsides, thielavins A (**40**), J (**41**) and K (**42**) (Fig. 6). Moreover, the activities of thielavins A (**40**: IC_{50}: 23.8 μM; K_i: 27.8 μM), J (**41**: IC_{50}: 15.8 μM; K_i: 66.2 μM), and K (**42**: IC_{50}: 22.1 μM; K_i: 22.1 μM) illustrated good *Saccharomyces cerevisieae* α-glucosidase inhibition (Table 2). Notably, the activities of these compounds were higher than that of acarbose (IC_{50}: 545 μM). Metabolites **40–42** are reported as being non-competitive inhibitors with K_i values ranging from 27.8 to 66.2 μM. Thielavin J (**41**: IC_{50}: 30.5 μM) also

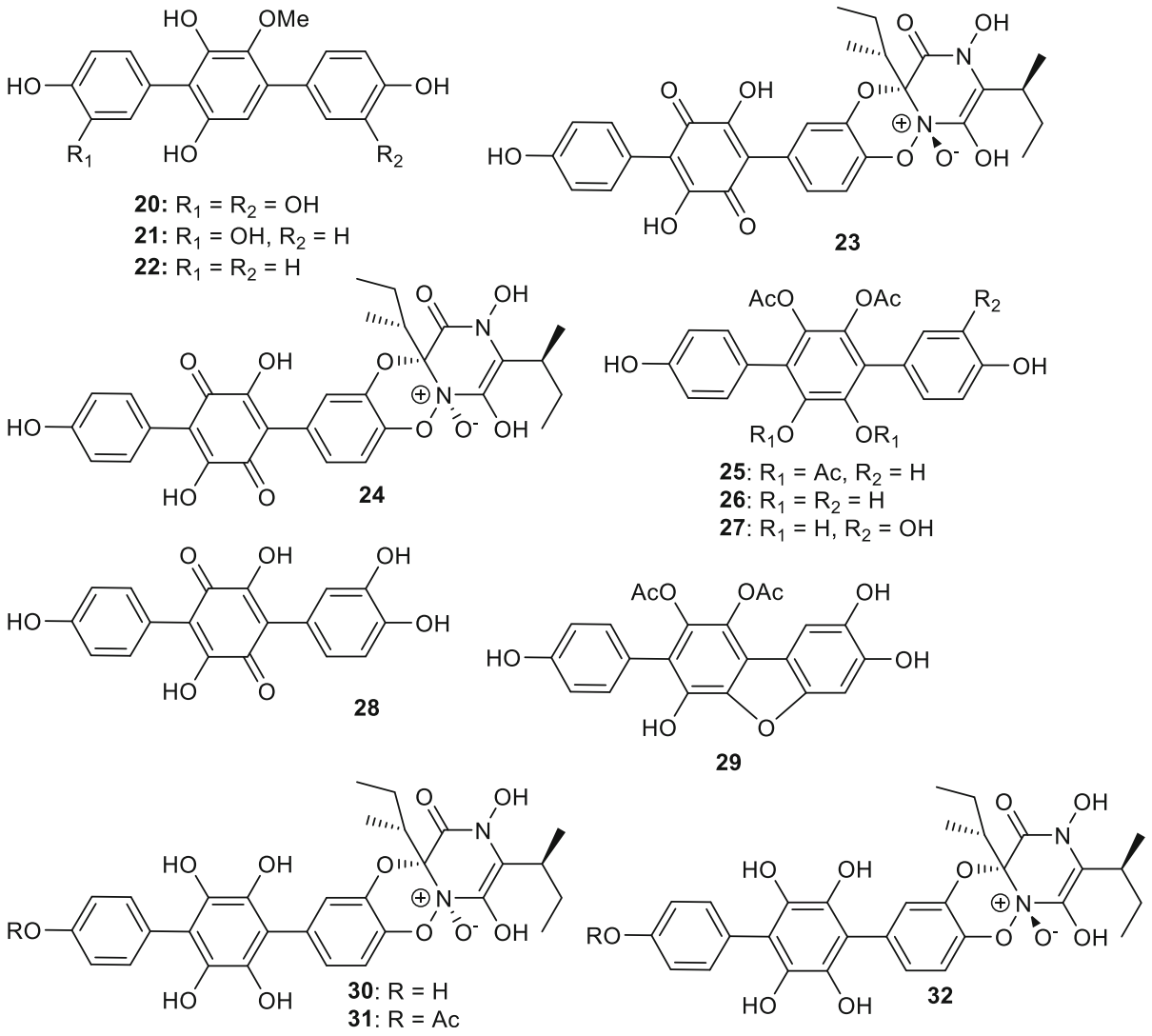


Fig. 4 Structures of p-terphenyls **20–32**

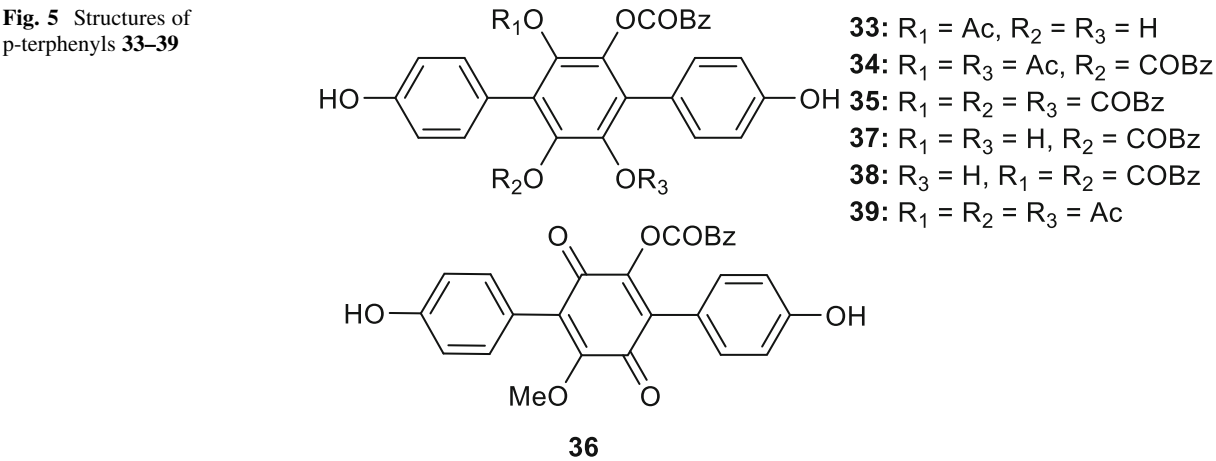
inhibited the effects of *Bacillus stearothermophilus*-based α-glucosidase (Rivera-Chávez et al. 2013).

Sterenins E-J (**43–48**), MS-13 (**49**) and **50** were reported from *Stereum hirsutum* and these compounds were all shown to possess α-glucosidase effects with IC_{50}: 3.06–72.50 μM (Table 2). Compounds **43–45** (IC_{50}: 3.06 to 7.62 μM) illustrated higher activities than compounds **46–50** indicating that the ring B carbonyl moiety substitution can enhance the activity. Moreover, compound **43** has much stronger effects than metabolite **48** and this finding confirmed that the isoprenyl group significantly affects the inhibitory activity (Wang et al. 2014). Colletotric A (**51**: IC_{50}: 36.2 μM), B (**52**: IC_{50}: 35.8 μM), and C (**53**: IC_{50}: 60.2 μM) were reported from the fungus *Phoma* sp. and showed α-glucosidase effects (Chen et al. 2019) (Table 2).

Depsidones

The depsidone talaromyone B (**54**) was reported from the fungus *Talaromyces stipitatus* (Cai et al. 2017) while purpactin A (**55**) was obtained from the fungi *T. stipitatus* (Cai et al. 2017) and *Penicillium* sp. (Tomoda et al. 1991; Nishida et al. 1991). In addition,

Fig. 5 Structures of p-terphenyls **33–39**



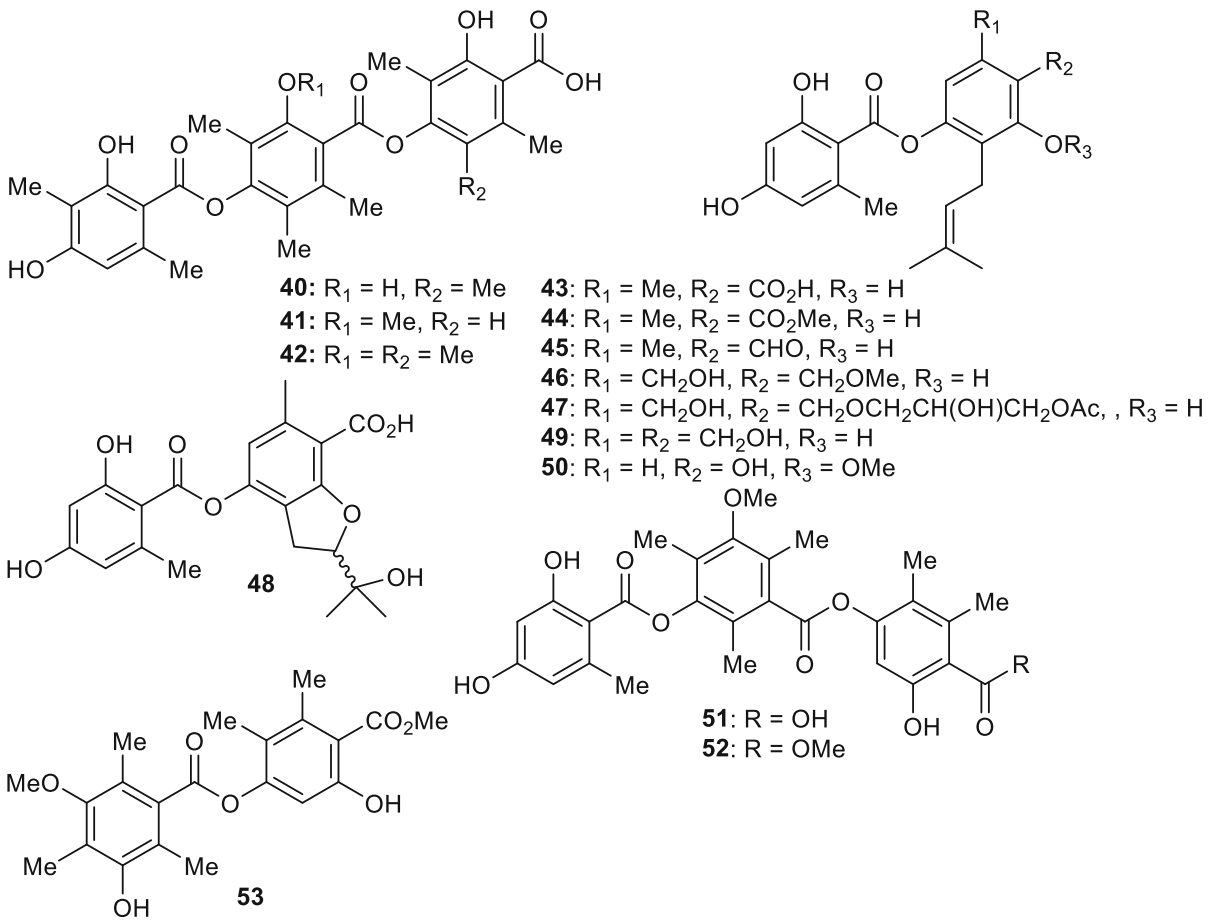


Fig. 6 Structures of p-terphenyls **40–53**

tenellic acid A (**56**) (Fig. 7) was isolated from the fungi *T. stipitatus* (Cai et al. 2017) and *Camposporium quercicola* (Wang et al. 2008) and its structure was established via NMR spectroscopic methods as well as employing the Mosher's protocol. Compounds **54–56** illustrated moderate α-glucosidase activity (Table 2)

Table 2 Fungal metabolites **40–73** as α-glucosidase inhibitors

Compd.	Source	A-Glucosidase activity	References
Thielavin A (**40**)	Fungus MEXU 27095	IC_{50}: 23.8 μM; K_i: 27.8 μM	Rivera-Chávez et al. (2013)
Thielavin J (**41**)	Fungus MEXU 27095	IC_{50}: 15.8; K_i: 66.2 μM	Rivera-Chávez et al. (2013)
Thielavin K (**42**)	Fungsu MEXU 27095	IC_{50}: 22.1 μM; K_i: 22.1 μM	Rivera-Chávez et al. (2013)
Sterenin E (**43**)	*Stereum hirsutum*	IC_{50}: 7.6 μM	Wang et al. (2014)
Sterenin F (**44**)	*Stereum hirsutum*	IC_{50}: 3.0 μM	Wang et al. (2014)
Sterenin G (**45**)	*Stereum hirsutum*	IC_{50}: 6.0 μM	Wang et al. (2014)
Sterenin H (**46**)	*Stereum hirsutum*	IC_{50}: 22.7 μM	Wang et al. (2014)
Sterenin I (**47**)	*Stereum hirsutum*	IC_{50}: 72.5 μM	Wang et al. (2014)
Sterenin J (**48**)	*Stereum hirsutum*	IC_{50}: 65.7 μM	Wang et al. (2014)
MS-13 (**49**)	*Stereum hirsutum*	IC_{50}: 23.8 μM	Wang et al. (2014)
4-Hydroxy-3-methoxy-2-(3-methylbut-2-en-1-yl)phenyl 2,4-dihydroxy-6-methylbenzoate (**50**)	*Stereum hirsutum*	IC_{50}: 14.7 μM	Wang et al. (2014)
Colletotric A (**51**)	*Phoma* sp.	IC_{50}: 36.2 μM	Chen et al. (2019)
Colletotric B (**52**)	*Phoma* sp.	IC_{50}: 35.8 μM	Chen et al. (2019)
Colletotric C (**53**)	*Phoma* sp.	IC_{50}: 60.2 μM	Chen et al. (2019)
Talaromyone B (**54**)	*Talaromyces stipitatus*	IC_{50}: 48.4 μM	Cai et al. (2017)
Purpactin A (**55**)	*Talaromyces stipitatus*	IC_{50}: 80.9 μM	Cai et al. (2017)
Tenellic acid A (**56**)	*Talaromyces stipitatus*	IC_{50}: 99.8 μM	Cai et al. (2017)
Botryorhodine E (**57**)	*Meyerozyma guilliermondii*	IC_{50}: 15.4 μM	Chen et al. (2015a)
Botryorhodine F (**58**)	*Meyerozyma guilliermondii*	IC_{50}: 9.8 μM	Chen et al. (2015a)
Botryorhodine G (**59**)	*Meyerozyma guilliermondii*	IC_{50}: 12.4 μM	Chen et al. (2015a)
	Trichoderma sp.	IC_{50}: 54.1 μM	Zhang et al. (2017)
Botryorhodine A (**60**)	*Meyerozyma guilliermondii*	IC_{50}: 13.3 μM	Chen et al. (2015a)
Botryorhodine B (**61**)	*Meyerozyma guilliermondii*	IC_{50}: 11.7 μM	Chen et al. (2015a)
Botryorhodine D (**62**)	*Meyerozyma guilliermondii*	IC_{50}: 2.1 μM	Chen et al. (2015a)
	Trichoderma sp.	IC_{50}: 10.3 μM	Zhang et al. (2017)
Botryorhodine H (**63**)	*Trichoderma* sp.	IC_{50}: 8.1 μM	Zhang et al. (2017)
Botryorhodine C (**64**)	*Trichoderma* sp.	IC_{50}: 11.2 μM	Zhang et al. (2017)
Compound **65**	*Talaromyces amestolkiae*	IC_{50}: 140.8 μM	Chen et al. (2016)
Compound **66**	*Talaromyces amestolkiae*	IC_{50}: 89.4 μM	Chen et al. (2016)
Compound **67**	*Talaromyces amestolkiae*	IC_{50}: 585.7 μM	Chen et al. (2016)
Compound **68**	*Talaromyces amestolkiae*	IC_{50}: 573.3 μM	Chen et al. (2016)

Table 2 continued

Compd.	Source	A-Glucosidase activity	References
S-(-)-5,6,8-trihydroxy-4-(1′-hydroxyethyl)isocoumarin (69)	*Talaromyces amestolkiae*	IC_{50}: 315.3 μM	Chen et al. (2016)
Sescandelin B (70)	*Talaromyces amestolkiae*	IC_{50}: 17.2 μM	Chen et al. (2016)
6-Hydroxy-4-hydroxymethyl-8-methoxy-3-methyl-isocou-marin (71)	*Talaromyces amestolkiae*	IC_{50}: 302.6 μM	Chen et al. (2016)
3,4-Dimethyl-6,8-dihydroxyisocoumarin (72)	*Talaromyces amestolkiae*	IC_{50}: 36.4 μM	Chen et al. (2016)
28 sescandelin (73)	*Talaromyces amestolkiae*	IC_{50}: 417.8 μM	Chen et al. (2016)

with IC_{50} values ranging from 48.4 to 99.8 μM (Cai et al. 2017).

Six further depsidones viz., botryorhodines E–G (**57–59**), botryorhodine A (**60**), B (**61**), D (**62**) were reported from the fungus *Meyerozyma guilliermondii* and all illustrated significant α-glucosidase potentials with IC_{50}: ranging from 2.1 to 15.4 μM (Table 2). Compound **62** was the most active with an IC_{50} value of 2.1 μM followed by compounds **58**, **61** and **59**, which is significantly lower than that of acarbose (IC_{50} = 553.7 μM). An SAR analysis suggests that the hydroxymethyl group at C-3 increases the α-glucosidase effects, whereas, the presence of a methyl group at C-3′ exerts no additional effect on the α-glucosidase inhibitory power of compounds **57–62** (Chen et al. 2015a).

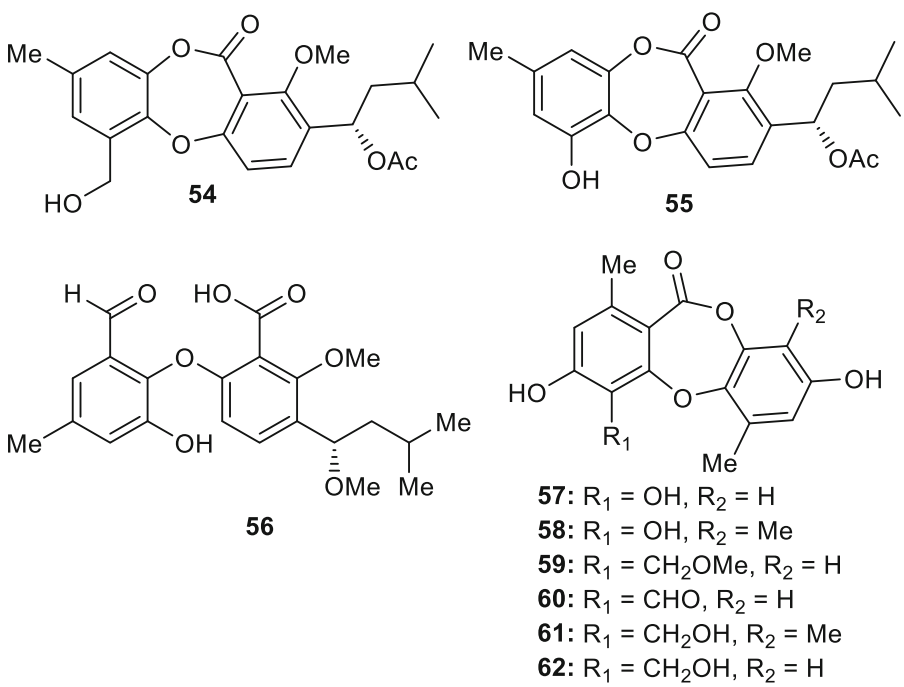
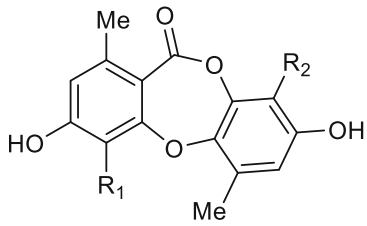


Fig. 7 Structures of depsodones **54–62**



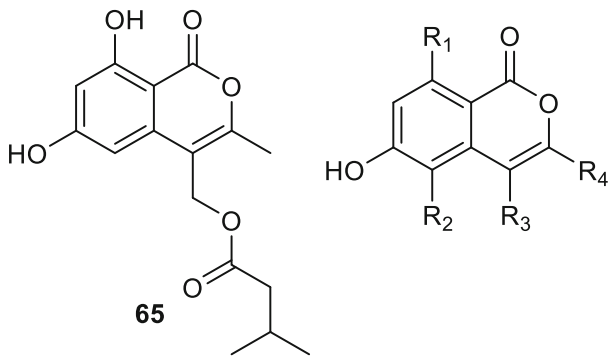
63: $R_1 = CH_2C_6H_4$-pOH, R_2 = H
64: $R_1 = CH_2OH$, R_2 = Me

Fig. 8 Structures of depsidones **63** and **64**

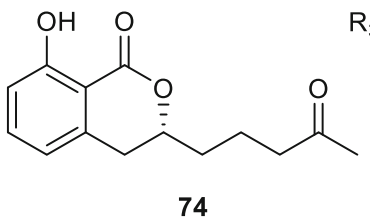
Another fungus *Trichoderma* sp. produces botryorhodines G (**59**) and H (**63**) (Fig. 8) and compound **59** possess moderate α-glucosidase effects with an IC_{50}: 54.1 μM. On the other hand, compound **63** illustrated potent α-glucosidase effects with IC_{50}: 8.1 μM and its activity was higher than the standard acarbose IC_{50}: 703.8 μM (Zhang et al. 2017). Moreover botryorhodines C (**64**) and D (**62**) possess significant α-glucosidase effects with IC_{50}: 11.2 and 10.3 μM (Zhang et al. 2017) respectively and these metabolites were reported from the fungi *Trichoderma* sp. (Zhang et al. 2017) and *Botryosphaeria rhodian* (Abdou et al. 2010). All these compounds illustrated α-glucosidase activity with IC_{50} values ranging from 8.1 to 54.1 μM (Table 2). Compared to the reference drug acarbose (IC_{50} = 703.8 μM), it can be concluded that compounds **62–64** are potent anti-diabetic depsidones. An SAR study showed that C-3 groups could affect α-glucosidase effects (compound **63** vs. **62** vs. **59**) while on the other hand the C-3′ methyl group exerts no effect on the activity (compound **64** vs. **62**) (Zhang et al. 2017).

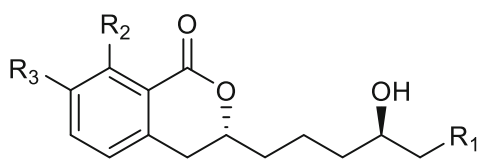
Isocoumarins

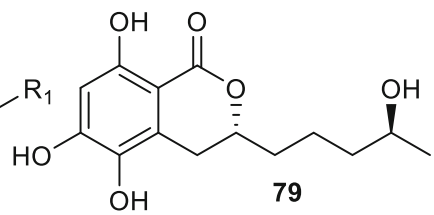
Isocoumarins are a class secondary metabolites bearing a lactone core and these compounds feature a wide range of chemical diversity with a most diverse range of biological effects. Notably, some isocoumarins have been entered into clinical trials for cancer and other diseases (Hampl et al. 2011; Yin et al. 2001; Salloum et al. 2000; Pochet et al. 2004). The fungus *Talaromyces amestolkiae* produced the library of isocoumarins (**65–79**) (Fig. 9) which were evaluated for their α-glucosidase inhibition. Isocoumarins **66**, **70**, **72** and **74** illustrated the most encouraging effects among all the tested compounds with IC_{50} values ranging from 17.2 to 89.4 μM (Table 2). Furthermore metabolites **65**, **75**, **78** and **79** are interestingly, five-



66: R_1 = OH, R_2 = OMe, R_3 = H, R_4 = Me
67: R_1 = OMe, R_2 = H, R_3 = R_4 = Me
68: R_1 = OMe, R_2 = R_4 = H, R_3 = CH(OH)Me
69: R_1 = R_2 = OH, R_3 = CH(OH)Me, R_4 = H
70: R_1 = OH, R_2 = H, R_3 = CH_2OH, R_4 = Me
71: R_1 = OMe, R_2 = H, R_3 = CH_2OH, R_4 = Me
72: R_1 = OH, R_2 = H, R_3 = R_4 = Me
73: R_1 = OH, R_2 = H, R_3 = CH(OH)Me, R_4 = H







75: R_1 = R_3 = H, R_2 = OH
76: R_1 = H, R_2 = OMe, R_3 = OH
77: R_1 = R_3 = H, R_2 = OMe
78: R_1 = R_2 = OH, R_3 = H

Fig. 9 Structures of isocoumarins **65–79**

fold more potent (IC_{50} range: 140.8 to 193.1 μM) than acarbose (IC_{50}: 958.3 μM) (Chen et al. 2016). Since metabolites **69**, **71**, **73**, **76** and **77** illustrated moderate inhibition with IC_{50} ranging from 266.3 to 431.4 μM, respectively, it may be concluded that the 4-$CH(OH)CH_3$ moiety in metabolites **68**, **69** and **73** decreases the activity level when compared with the activties with metabolites **70** and **71** bearing a 4-hydroxymethyl group. The compounds comprising an alkyl chain with the carbonyl group (as in compound **74**) appear to possess higher activity in competition with compounds **75–79** which only have an hydroxyl moiety at the corresponding position (Chen et al. 2016).

The fungus *Aspergillus* sp. produces a range of furo[3,2-*h*]isocoumarin derivatives viz., asperisocoumarins A (**80**: IC_{50}: 87.8 μM), E (**81**: IC_{50}: 52.3 μM), and F (**82**: IC_{50}: 95.6 μM) and all displayed moderated α-glucosidase effects (Table 3) (Xiao et al. 2016). Furo[3,2-*h*]isocoumarins are uncommon and few members of this group have been reported in literature (Saeed 2016; Baba et al. 1991). Asperisocoumarin E (**81**) featured an isopentenyl group having two adjacent carbonyl moieties and asperisocoumarin F (**82**) represents an isocoumarin dimer via an ether linkage (Xiao et al. 2016). Furthermore, the same fungus *Aspergillus* sp. produced other isocoumarin analogues viz., asperisocoumarins C (**83**), E (**84**), F (**85**), G (**86**), I (**87**), J (**89**) (Fig. 10) along with compound **88** and their structures were all established via extensive NMR spectroscopic techniques. It was found that metabolites **83**, **86**, **87**, and **89** illustrated significant α-glucosidase activities with IC_{50} ranging from 38.1 to 78.1 μM. Since metabolites **84** and **85** displayed only moderate inhibition (Table 3), it may be concluded that either an epoxide and/or an hydroxyl group at C-10/C-11 could enhance the α-glucosidase effects (Cai et al. 2018).

The isocoumarin 12-epicitreoisocoumarinol (**90**) is produced by the fungus *Nectria* sp., and illustrated α-glucosidase potential with IC_{50}: 343.7 μM (Cui et al. 2016). On the other hand citreoisocoumarinol (**91**) and citreoisocoumarin (**92**) (Fig. 11) were produced by the fungi *Nectria* sp. (Cui et al. 2016), *Fusarium* sp. (Ola et al. 2013) and *Penicillium* sp. (Lai et al. 1991) and display activity towards α-glucosidase with IC_{50}: 392.5 and 538.7 μM (Table 3) respectively (Cui et al. 2016). Notably, compounds **90–92** were more potent than acarbose (IC_{50} = 815.3 μM) (Cui et al. 2016). The fungus, *Aspergillus* sp. produced 6-O-demethylmonocerin (**93**: IC_{50}: 0.027 mM), (+)-monocerin (**94**; IC_{50}: 1.65 mM), fusarentin 6-methyl ether (**95**; IC_{50}: 1.19 mM) and 6,7-O-dimethyl-4*R*-hydroxy-10-epifusarentin (**96**; IC_{50}: 1.74 mM) and all were shown to possess α-glucosidase effects (Table 3). Among these metabolites, compound **93** displayed 35 times more potent inhibitory effects than acarbose (IC_{50} = 0.95 mM) (Kong et al. 2015).

β-Resorcylic acid derivatives

β-Resorcylic acid analogs have been reported from a number of natural sources and these compounds were reported to display a diverse range of biological activities viz., antimicrobial (Yang et al. 2006), antimalarial (Xu et al. 2010), cytotoxic (Buayairaksa et al. 2011) and kinases and ATPases inhibitions (Shen et al. 2015). In this regard, the fungus *Lasiodiplodia* sp. produced β-resorcylic acid analogs **97–99** (Fig. 12) and their structures were established by 1D, 2D NMR, and X-ray crystallography in addition to the Mosher protocol (Chen et al. 2015b). All the compounds were evaluated for their α-glucosidase effects and illustrated inhibition with IC_{50} values ranging from 15.2 to 24.6 μM (Table 3) and interestingly, their activities were better than the standard acarbose (IC_{50} = 368 μM) (Chen et al. 2015b). Moreover compound **100**, which was reported from the fungus *Lasiodiplodia* sp. (Chen et al. 2015b) and the yeast *Saccharomyces cerevisiae* (Xu et al. 2014), proved to be a most potent α-glucosidase inhibitor with an IC_{50}: 10.1 μM (Chen et al. 2015b).

Compound **101**, initially reported as a plant metabolite viz., from *Euphorbia splendenfs* (Lee et al. 1982) and later from the fungus *Lasiodiplodia* sp. (Chen et al. 2015b), illustrated α-glucosidase effects with IC_{50}: 32.5 μM (Chen et al. 2015b). Compound **102** was obtained from the fungus *Lasiodiplodia sp.* (Chen et al. 2015b; Aldridge et al. 1971), and compound **103** from the fungi *Lasiodiplodia sp.* (Chen et al. 2015b) as well as ZZF36 (Yang et al. 2006). Both compounds inhibited α-glucosidase activity with IC_{50}: 13.6 and 35.9 μM respectively (Chen et al. 2015b). SAR studies for compounds **97–103** demonstrated that the C-3 hydroxyl moiety in these compounds enhances the inhibitory effects (compound **99** vs. **100** and compound **101** vs. **102**)

Table 3 Fungal metabolites **74–112** as α-glucosidase inhibitors

Compd.	Source	A-Glucosidase activity	References
21,22 aspergillumarin A (**74**)	*Talaromyces amestolkiae*	IC_{50}: 38.1 μM	Chen et al. (2016)
24 aspergillumarin B (**75**)	*Talaromyces amestolkiae*	IC_{50}: 193.1 μM	Chen et al. (2016)
24penicimarin C (**76**)	*Talaromyces amestolkiae*	IC_{50}: 266.3 μM	Chen et al. (2016)
26 and penicimarin B (**77**)	*Talaromyces amestolkiae*	IC_{50}: 431.4 μM	Chen et al. (2016)
Compound **78**	*Talaromyces amestolkiae*	IC_{50}: 162.5 μM	Chen et al. (2016)
Compound **79**	*Talaromyces amestolkiae*	IC_{50}: 142.1 μM	Chen et al. (2016)
Asperisocoumarin A (**80**)	*Aspergillus* sp.	IC_{50}: 87.8 μM	Xiao et al. (2016)
Asperisocoumarin E (**81**)	*Aspergillus* sp.	IC_{50}: 52.3 μM	Xiao et al. (2016)
Asperisocoumarin F (**82**)	*Aspergillus* sp.	IC_{50}: 95.6 μM	Xiao et al. (2016)
Asperisocoumarin C (**83**)	*Aspergillus* sp.	IC_{50}: 38.1 μM	Cai et al. (2018)
Asperisocoumarin E (**84**)	*Aspergillus* sp.	IC_{50}: 158.4 μM	Cai et al. (2018)
Asperisocoumarin F (**85**)	*Aspergillus* sp.	IC_{50}: 110.3 μM	Cai et al. (2018)
Asperisocoumarin G (**86**)	*Aspergillus* sp.	IC_{50}: 40.5 μM	Cai et al. (2018)
Asperisocoumarin I (**87**)	*Aspergillus* sp.	IC_{50}: 78.1 μM	Cai et al. (2018)
3-[(R)-3,3-dichloro-2-hydroxypropyl]-8-hydroxy-6-methoxy-1H-isochromen-1-one (**88**)	*Aspergillus* sp.	IC_{50}: 102.4 μM	Cai et al. (2018)
Asperisocoumarin J (**89**)	*Aspergillus* sp.	IC_{50}: 45.1 μM	Cai et al. (2018)
12-Epicitreoisocoumarinol (**90**)	*Nectria* sp.	IC_{50}: 343.7 μM	Cui et al. (2016)
Citreoisocoumarinol (**91**)	*Nectria* sp.	IC_{50}: 392.5 μM	Cui et al. (2016)
Citreoisocoumarin (**92**)	*Nectria* sp.	IC_{50}: 538.7 μM	Cui et al. (2016)
6-O-demethylmonocerin (**93**)	*Aspergillus* sp.	IC_{50}: 0.027 mM	Kong et al. (2015)
(+)-monocerin (**94**),	*Aspergillus* sp.	IC_{50}: 1.65 mM	Kong et al. (2015)
fusarentin 6-methyl ether (**95**)	*Aspergillus* sp.	IC_{50}: 1.19 mM	Kong et al. (2015)
6,7-O-dimethyl-4R-hydroxy-10-epifusarentin (**96**)	*Aspergillus* sp.	IC_{50}: 1.74 mM	Kong et al. (2015)
(*R*)-ethyl 3,5-dihydroxy-7-(8-hydroxynonyl) benzoate (**97**)	*Lasiodiplodia sp.*	IC_{50}: 22.3 μM	Chen et al. (2015b)

Table 3 continued

Compd.	Source	A-Glucosidase activity	References
(*R,E*)-ethyl 2,4-dihydroxy-6-(8-hydroxynon-1-en-1-yl) benzoate (**98**)	*Lasiodiplodia sp.*	IC_{50}: 24.6 μM	Chen et al. (2015b)
3-Methoxy-lasicicol (**99**)	*Lasiodiplodia sp.*	IC_{50}: 15.2 μM	Chen et al. (2015b)
Lasicicol (**100**)	*Lasiodiplodia sp.*	IC_{50}: 10.1 μM	Chen et al. (2015b)
Lasiodiplodin (**101**)	*Lasiodiplodia sp.*	IC_{50}: 32.5 μM	Chen et al. (2015b)
De-O-methyllasiodiplodin (**102**)	*Lasiodiplodia sp.*	IC_{50}: 13.6 μM	Chen et al. (2015b)
(*E*)-9-etheno-lasiodiplodin (**103**)	*Lasiodiplodia sp.*	IC_{50}: 35.9 μM	Chen et al. (2015b)
Lasiodiplactone A (**104**)	*Lasiodiplodia theobromae*	IC_{50} = 367 μM	Chen et al. (2017)
Eurothiocin A (**105**)	*Eurotium rubrum*	IC_{50} = 17.1 μM	Liu et al. (2014a)
Eurothiocin B (**106**)	*Eurotium rubrum*	IC_{50} = 42.6 μM	Liu et al. (2014a)
Epicoccolide B (**107**)	*Aspergillus flavipes*	IC_{50}: 33 μM	Wang et al. (2016)
6-Demethylpenisimplicissin (**108**)	*Penicillium* sp.	IC_{50}: 9.5 μM	Liu et al. (2014b)
1″-Epihydroxydihydrovermistatin (**109**)	*Penicillium* sp.	IC_{50}: 8.0 μM	Liu et al. (2014b)
Vermistatin (**110**)	*Penicillium* sp.	IC_{50}: 29.2 μM	Liu et al. (2014b)
Hydroxyvermistatin (**111**)	*Penicillium* sp.	IC_{50}: 20.3 μM	Liu et al. (2014b)
(+)-Geodin (**112**)		IC_{50} of 0.12 mM	Wang et al. (2018)

(Table 3). Furthermore, when comparing the activity of compound **97** and **102**, it may be assumed that the aliphatic macrocyclic acid system is also necessary for the activity (Chen et al. 2015b). Another 12-membered ring system comprising a β-resorcylic acid analog, lasiodiplactone A (**104**), reported from the fungus *Lasiodiplodia theobromae* comprises an interesting and unique 12/6/6/5 tetracyclic system. Compound **104** inhibited α-glucosidase with an IC_{50}: 29.4 μM which is better than the clinical acarbose (IC_{50} = 367 μM) (Chen et al. 2017).

Benzofurans

The fungus *Eurotium rubrum* SH-823, produced the benzofuran analogs eurothiocin A (**105**; IC_{50} = 17.1 μM) and B (**106**; IC_{50} = 42.6 μM) (Fig. 13), which inhibited the α-glucosidase activity as illustrated in Table 4. It is worth mentioning that both compounds exhibited considerably lower IC_{50} values compared to the standard drug acarbose (IC_{50} = 376.7 μM), which makes them interesting candidates for further studies (Liu et al. 2014a). In addition, epicoccolide B (**107**) was produce by the fungi *Aspergillus flavipes* (Wang et al. 2016) and *Epicoccum* sp. (Talontsi et al. 2013) and this compound inhibited α–glucosidase with an IC_{50} of 33 μM (Wang et al.

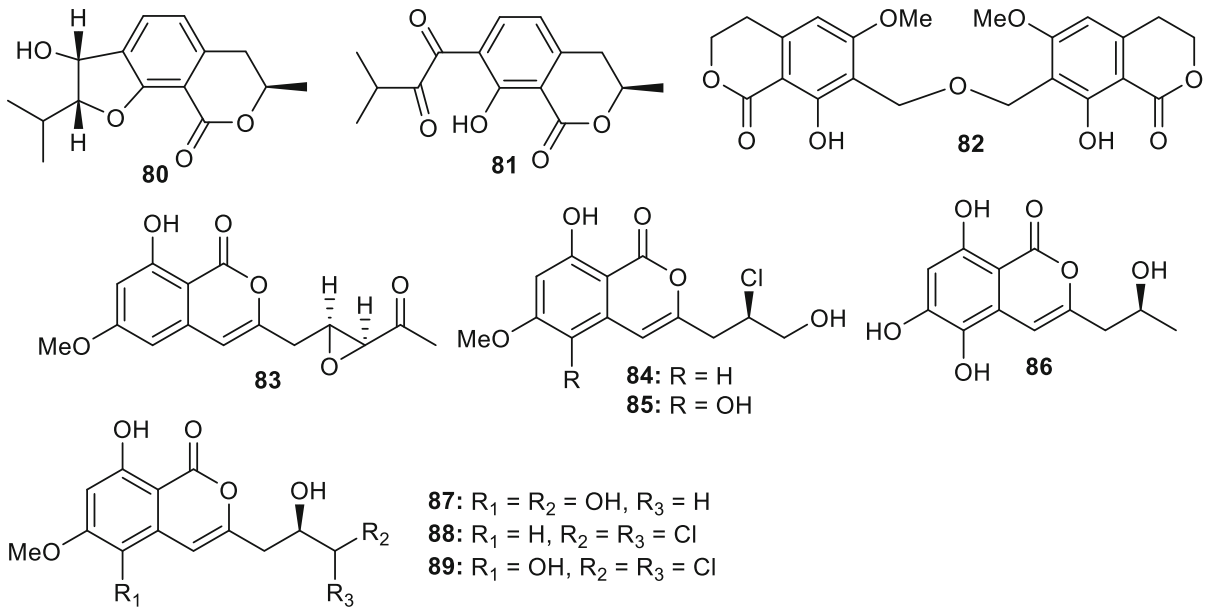


Fig. 10 Structures of isocoumarins **80–89**

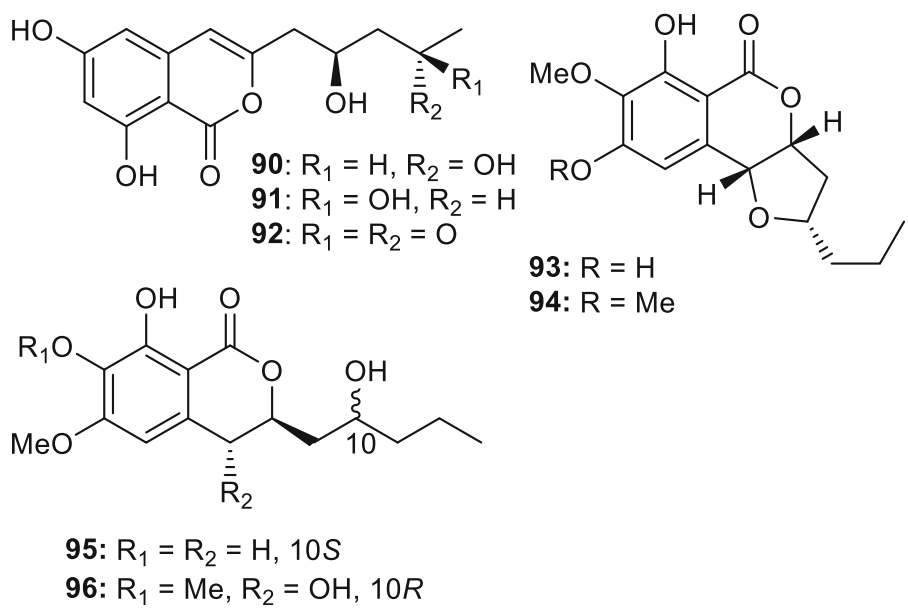


Fig. 11 Structures of isocoumarins **90–96**

2016). In addition, kinetic studies demonstrated that benzofuran **107** acted as a noncompetitive inhibitor with K_i values of 2.5/7.2 μM, and thus have been identified as displaying mixed behavior (Wang et al. 2016).

Benzofuran analogs, 6-demethylpenisimplicissin (**108**), 1″-epihydroxydihydrovermistatin (**109**), vermistatin (**110**) and hydroxyvermistatin (**111**) (Fig. 14) were obtained from *Penicillium* sp. and tested for their anti-α-glucosidase effects. The results revealed that metabolites **108** (IC_{50}: 9.5 μM) and **109** (IC_{50}: 8.0 μM) illustrated significant activity while the α-

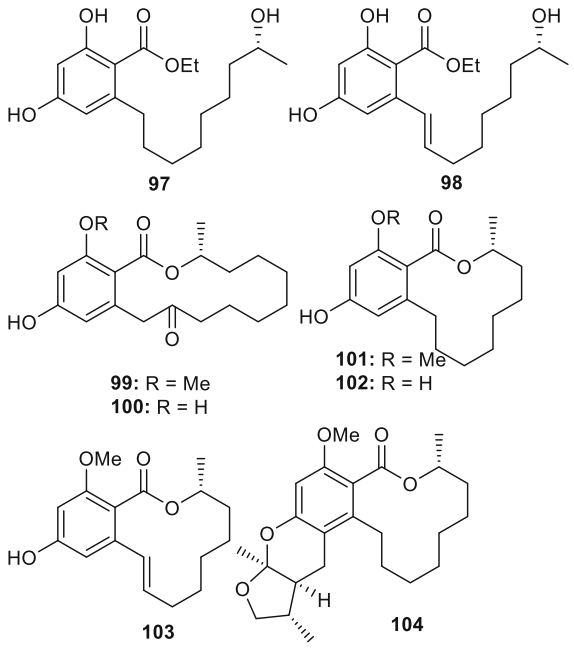


Fig. 12 Structures of β-resorcylic acid analogs **97–104**

glucosidase inhibition capacity of compounds **110** (IC_{50}: 29.2 μM) and **111** (IC_{50}: 20.3 μM) (Table 4) were lower, but still higher that the reference resveratrol (IC_{50} = 31.2 μM) (Liu et al. 2014b). (+)-Geodin (**112**), which is a biosynthetically a polyketide derived compound (Askenazi et al. 2003; Couch and Gaucher 2004; Sutherland, et al. 2001), was reported from the fungus *Penicillium chrysogenum* (Wang et al. 2018) along with the fungus *Aspergillus* sp. (Hargreaves et al. 2002), illustrated excellent α-glucosidase effects with an IC_{50} of 0.12 mM (Wang et al. 2018).

Quinones and xanthones

Emodin (**113**) is reported from various plant families (Izhaki 2002) as well as various fungal species viz *Penicillium* sp. (Shibata and Udagawa 1963; Natori et al. 1965; Ghosh et al. 1977), *Aspergillus* sp. Yamazaki et al. 1971; Wells et al. 1975; Anke et al. 1980; Wang et al. 2016), *Cladosporium fulvum* (Agosti et al. 1962), and *Penicilliopsis clavariaeformis* (Shibata et al. 1957). Emodin (**113**) illustrated quite reasonable α-glucosidase effects IC_{50}: 19 μM and kinetic studies demonstrated that compound **113** (Fig. 15) was a noncompetitive inhibitor with a K_i value of 0.79 μM (Wang et al. 2016). On the other hand the fungus *Alternaria* sp. produced the tetrahydroanthraquinone analogs, alterporriol S (**114**), alterporriol T (**115**) and anthraquinone **116** (Chen et al. 2014). Quinone **115** (IC_{50}: 7.2 μM) illustrated significant α-glucosidase effects being higher than the positive control genistein (IC_{50} = 13.6 μM). In this regard it is interesting to note that metabolites **114** (IC_{50} = 72.0 μM) and **116** (IC_{50} = 83.5 μM) displayed weaker activity (Table 4) (Chen et al. 2014).

The xanthone derivatives (+)- and (−)-ascomlactone A (**117a** and **117b**) (Fig. 16) are produced by the fungus *Ascomycota* sp. and their structures were established based on spectroscopic methods. The activity studies revealed that as a racemic mixture, these metabolites inhibited the activity of α-glucosidase with an IC_{50} value of 36.1 μM. On the other hand, and interestingly, the pure enantiomer, (−)-ascomlactone A (**117b**) illustrated better inhibition with an IC_{50} value of 27.9 μM, whereas, the enantiomer (+)-ascomlactone A (**117a**) demonstrated slightly weaker inhibition (IC_{50} = 63.7 μM). When compared to the activity of acarbose (IC_{50} = 477.0 μM), both pure enatiomers as well as the racemate is more potent (Liu et al. 2017). Chrysoxanthone (**118**) was obtained from the fungus *Penicillium chrysogenum* and illustrated α-glucosidase effects with an IC_{50} of 0.04 mM (Wang et al. 2018).

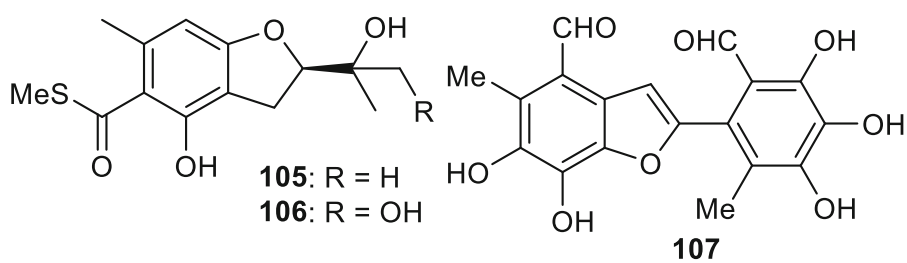


Fig. 13 Structures of benzofurans **105–107**

Table 4 Fungal metabolites **113–128** as α-glucosidase inhibitors

Compd.	Source	A-Glucosidase activity	References
Emodin (**113**)	*Aspergillus flavipes*	IC_{50}: 19 μM; K_i: 0.79 μM	Wang et al. (2016)
Alterporriol S (**114**)	*Alternaria* sp.	IC_{50} = 72.0 μM	Chen et al. (2014)
Alterporriol T (**115**)	*Alternaria* sp.	IC_{50}: 7.2 μM	Chen et al. (2014)
Macrosporin (**116**)	*Alternaria* sp.	IC_{50} = 83.5 μM	Chen et al. (2014)
(+)-Ascomlactone A (**117a**)	*Ascomycota* sp.	IC_{50} = 63.7 μM	Liu et al. (2017)
(−)-Ascomlactone A (**117b**)	*Ascomycota* sp.	IC_{50} = 27.9 μM	Liu et al. (2017)
Chrysoxanthone (**118**)	*Penicillium chrysogenum*	IC_{50} = 0.04 mM	Wang et al. (2018)
Daldinione B (**119**)	*Daldinia eschscholtzii*	IC_{50} = 38 μM	Liao et al. (2019)
Daldinione C (**120**)	*Daldinia eschscholtzii*	IC_{50} = 155 μM	Liao et al. (2019)
Daldinione D (**121**)	*Daldinia eschscholtzii*	IC_{50} = 35 μM	Liao et al. (2019)
4*R*-(O)-Methylsclerone (**122**)	*Daldinia eschscholtzii*	IC_{50} = 90 μM	Liao et al. (2019)
Isosclerone (**123**)	*Daldinia eschscholtzii*	IC_{50} = 70 μM	Liao et al. (2019)
(−)-cis-(3R*,4S*)-3,4,8-trihydroxy-6,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**124**)	*Daldinia eschscholtzii*	IC_{50} = 21 μM	Liao et al. (2019)
7-Hydroxy-5-methoxy-2,3-dimethylchromone (**125**)	*Daldinia eschscholtzii*	IC_{50} = 13 μM	Liao et al. (2019)
5-Methoxy-2-propylchromone (**126**)	*Daldinia eschscholtzii*	IC_{50} = 84 μM	Liao et al. (2019)
7-Ethyl-8-hydroxy-6-methoxy-2,3-dimethylchromone (**127**)	*Daldinia eschscholtzii*	IC_{50} = 100 μM	Liao et al. (2019)
2,3-Dihydro-5-methoxy-2-methylchromen-4-one (**128**)	*Daldinia eschscholtzii*	IC_{50} = 15 μM	Liao et al. (2019)

Tetralone and chromone derivatives

The fungus *Daldinia eschscholtzii* produced a small library of tetralones viz., daldiniones B–D (**119–121**) and tetralones **122–124** (Fig. 17) and their structures were established by NMR, GIAO based NMR and ECD spectroscopic methods. All these compounds illustrated α-glucosidase effects with IC_{50} values ranging from 21 to 155 μM (Table 5). Among these compounds, metabolite **124** was the most active (IC_{50}: 21 μM) followed by compounds **121** (IC_{50}: 35 μM) and **119** (IC_{50}: 38 μM) (Liao et al. 2019). Moreover, *Daldinia eschscholtzii* also produced the chromone analogs, **125–128,** which were also tested for their α-glucosidase effects. All these compounds inhibited α-glucosidase with IC_{50}: ranging from 13 to 100 μM (Table 5). Notably, chromone analogs **125** (IC_{50}: 13 μM) and **128** (IC_{50}: 15 μM) proved to be the most active metabolites among the tested chromones (Liao et al. 2019).

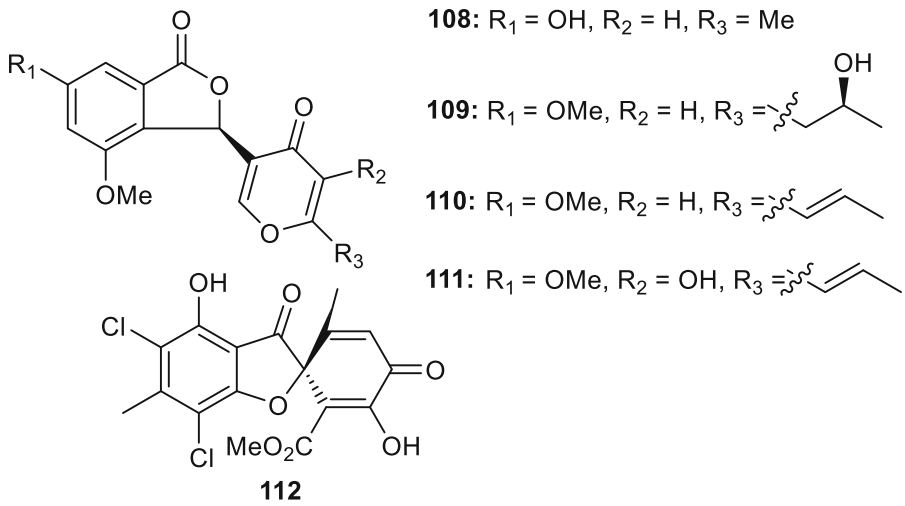
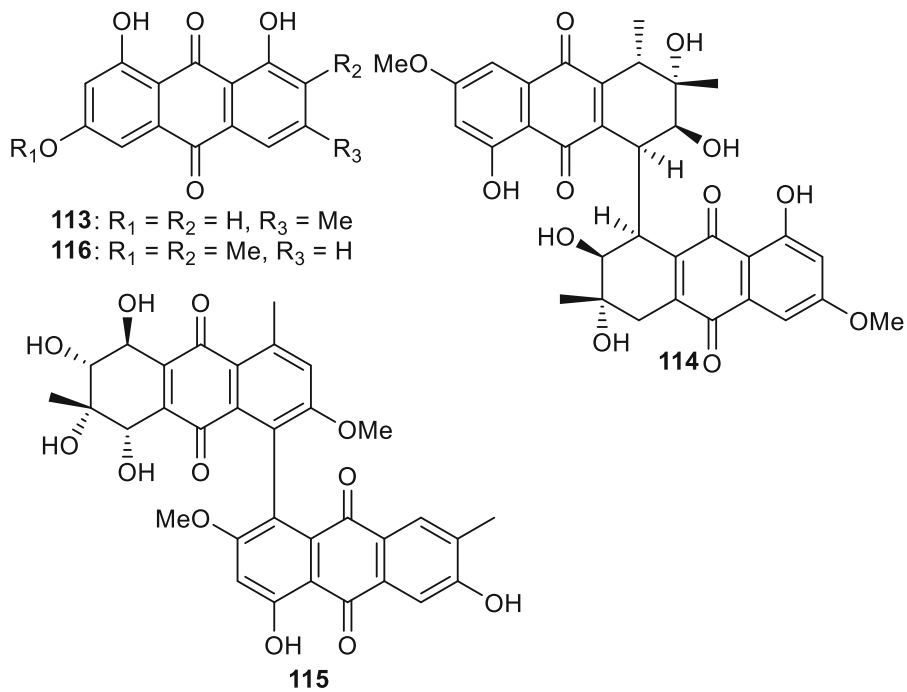


Fig. 14 Structures of benzofurans **108–112**

Fig. 15 Structures of quinones **113–116**



Butenolides

The fungus *Aspergillus terreus* produces (±)-asperteretals D (**129**) and E (**130**), flavipesolides B (**131**) and C (**132**), butyrolactones I (**133**) and II (**134**), butanolide **135** and aspernolide A (**136**) (Fig. 18). All these metabolites illustrated α-glucosidase inhibition with IC_{50} values ranging from 7.6 to 85.1 μM (Table 5). Moreover, compound **132** proved to be the most potent since it displayed the lowest IC_{50} value of 7.63 μM. Both enantiomerically pure isomers of compound **129** also exerted significant inhibition of the enzyme with IC_{50} values of 8.65 μM [(+)-**129**) and 9.98 μM [(−)-**129**] (Sun et al. 2018a). It has been reported that (+)- and (−)-**129** are methanolysis artifacts of asperteretal E (Capon 2020; Sun et al. 2018b).

The fungus *A. terreus* furthermore produced (±)-asperteretones A-D (**137a/b–140a/b**) (Fig. 19), and

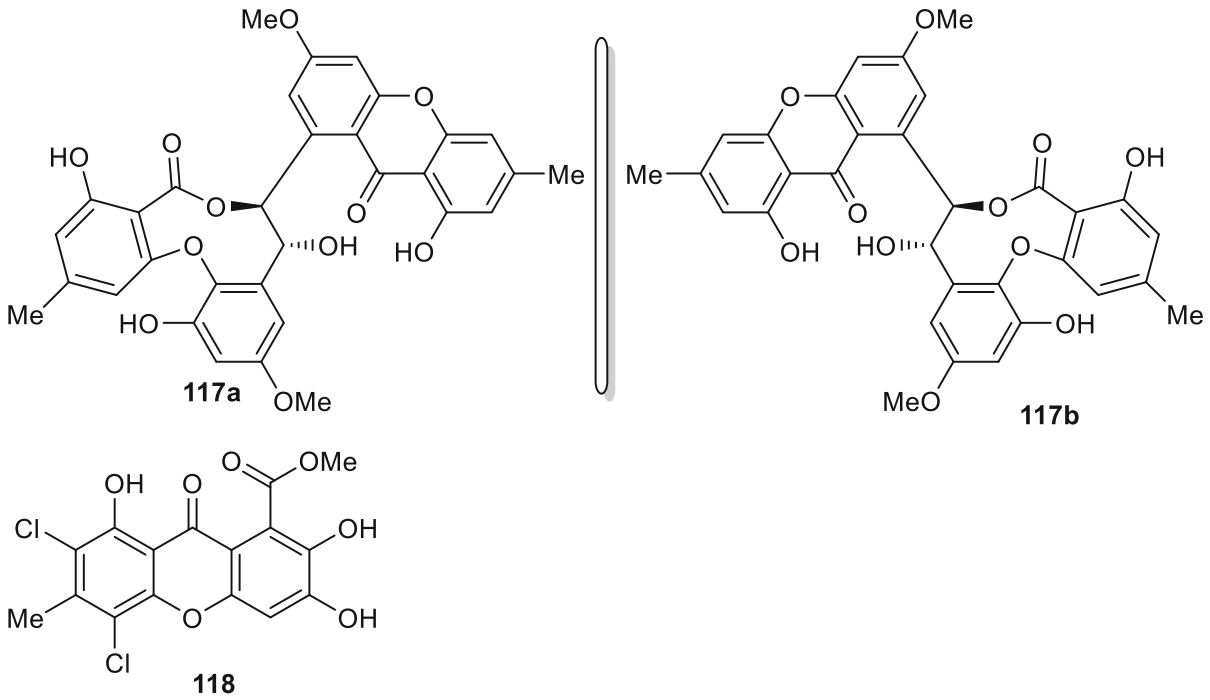


Fig. 16 Structures of quinones xanthones **117a,b** and **118**

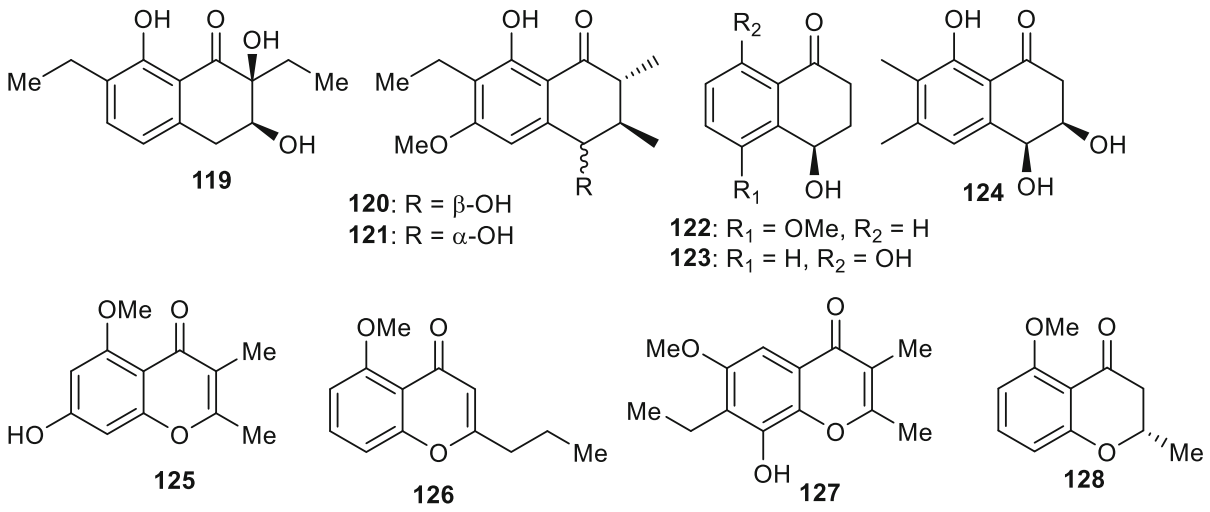


Fig. 17 Structures of tetralone and chromone derivatives **119–128**

the racemate, asperteretone E (**141**) and all these metabolites demonstrated α-glucosidase inhibition with IC_{50} values ranging from 15.7 to 53.1 μM (Table 6). Butanolide **140a** (IC_{50}: 15.7 μM) was the most active while **138a** (IC_{50}: 17.3 μM)**, 138b** (IC_{50}: 19.2 μM) and **140b** (IC_{50}: 18.9 μM) also displayed comparable inhibitory potential. Although the other compounds showed moderate activity, their inhibition values were higher than the reference drug acarbose (IC_{50} = 154.7 μM) (Liu et al. 2018a). Notably, it was postulated that all enantiomers illustrated would most likely demonstrate similar α-glucosidase effects, suggesting that chirality may play a negligible role on their potential activities.

Table 5 Fungal metabolites **129–152** as α-glucosidase inhibitors

Compd.	Source	A-Glucosidase activity	References
(-)-Asperteretal D (**129**)	*Aspergillus terreus*	IC_{50} = 9.9 μM	Sun et al. (2018a)
(+)-Asperteretal D (**129**)	*Aspergillus terreus*	IC_{50} = 8.6 μM	Sun et al. (2018a)
Asperteretal E (**130**)	*Aspergillus terreus*	IC_{50} = 13.3 μM	Sun et al. (2018a)
Flavipesolide B (**131**)	*Aspergillus terreus*	IC_{50} = 10.3 μM	Sun et al. (2018a)
Flavipesolide C (**132**)	*Aspergillus terreus*	IC_{50} = 7.63 μM	Sun et al. (2018a)
Butyrolactone I (**133**)	*Aspergillus terreus*	IC_{50} = 14.1 μM	Sun et al. (2018a)
Butyrolactone II (**134**)	*Aspergillus terreus*	IC_{50} = 85.3 μM	Sun et al. (2018a)
5-[(3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-yl)-methyl]-3-hydroxy-4-(4-hydroxyphenyl)-2(5H)-furanone (135)	*Aspergillus terreus*	IC_{50} = 11.6 μM	Sun et al. (2018a)
Aspernolide A (**136**)	*Aspergillus terreus*	IC_{50} = 47.3 μM	Sun et al. (2018a)
(-)-Asperteretones A (**137a**)	*Aspergillus terreus*	IC_{50} = 45.4 μM	Liu et al. (2018a)
(+)-Asperteretones A (**137b**)	*Aspergillus terreus*	IC_{50} = 53.1 μM	Liu et al. (2018a)
(-)-Asperteretones B (**138a**)	*Aspergillus terreus*	IC_{50} = 17.3 μM	Liu et al. (2018a)
(+)-Asperteretones B (**138b**)	*Aspergillus terreus*	IC_{50} = 19.2 μM	Liu et al. (2018a)
(-)-Asperteretones C (**139a**)	*Aspergillus terreus*	IC_{50} = 52.2 μM	Liu et al. (2018a)
(+)-Asperteretones C (**139b**)	*Aspergillus terreus*	IC_{50} = 49.8 μM	Liu et al. (2018a)
(-)-Asperteretones C (**140a**)	*Aspergillus terreus*	IC_{50} = 15.7 μM	Liu et al. (2018a)
(+)-Asperteretones C (**140b**)	*Aspergillus terreus*	IC_{50} = 18.9 μM	Liu et al. (2018a)
Asperteretone E (**141**)	*Aspergillus terreus*	IC_{50} = 48.9 μM	Liu et al. (2018a)
(R,E)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-((2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-yl)methylene) furan-2(5H)-one (**142**)	*Aspergillus terreus*	IC_{50} = 24.8 μM	Sun et al. (2018b)
Rubrolide S (**143**)	*Aspergillus terreus*	IC_{50} = 1.2 μM; *Ki*: 1.42 μM	Sun et al. (2018b)
Avipesolide A (**144**);	*Aspergillus flavipes*	IC_{50}: 44 μM; K_i: 2.4 μM	Wang et al. (2016)
Avipesolide B (**145**);	*Aspergillus flavipes*	IC_{50}: 57 μM; K_i: 3.4 μM	Wang et al. (2016)
Avipesolide C (**146**);	*Aspergillus flavipes*	IC_{50}: 95 μM; K_i: 9.2 μM	Wang et al. (2016)
5-[(3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-yl)methyl]-3-hydroxy-4-(4-hydroxyphenyl)-2(5H)furanone (147)	*Aspergillus flavipes*	IC_{50}: 34 μM; K_i: 0.43 μM	Wang et al. (2016)

Table 5 continued

Compd.	Source	A-Glucosidase activity	References
Pulvinone P (**148**)	*Aspergillus flavipes*	IC_{50}: 0.079 mM	Zhang et al. (2016a)
Pulvinone Q (**149**)	*Aspergillus flavipes*	IC_{50}: 0.022 mM	Zhang et al. (2016a)
Methybutyrolactone III (**150**):	*Aspergillus flavipes*	IC_{50}: 0.016 mM	Zhang et al. (2016a)
Flavipesin B (**151**):	*Aspergillus flavipes*	IC_{50}: 0.385 mM	Zhang et al. (2016a)
Versicolactone G (**152**)	*Aspergillus terreus*	IC_{50} = 154.7 μ	Liu et al. (2018b)

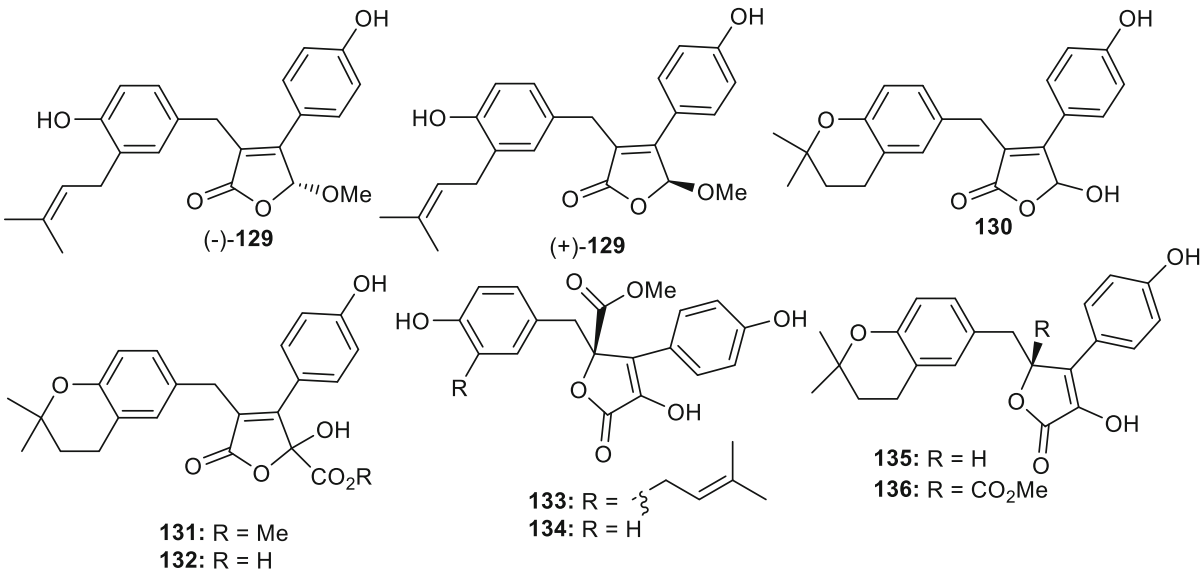


Fig. 18 Structures of butanolides **129–136**

Further butenolides, compound **142** and rubrolide S (**143**) (Fig. 20) were obtained from the fungus *A. terreus* and demonstrated α-glucosidase effects with IC_{50} values of 24.8 and 1.2 μM, respectively. Additional enzyme kinetic studies were performed with compound **143**, which revealed that it is an anticompetitive inhibitor with a *K*i value of 1.42 μM (Sun et al. 2018b). Another fungus varietal of *Aspergillus* sp., viz., *Aspergillus flavipes* produced antidiabetic avipesolides A–C (**144–146**) and butanolide **147** and these compounds inhibit α-glucosidase with IC_{50} values ranging from 34 to 95 μM (Table 6). Appropriate enzyme kinetic studies have also been carried out which revealed that compound **147** (K_i: 0.43 μM) is a noncompetitive inhibitor while compounds **144–146** were demonstrated to be more competitive (K_i: 2.5, 3.4, and 9.2 μM respectively) (Wang et al. 2016).

Pulvinones have been reported from various fungi and illustrated interesting biological effects (Bernier et al. 2007; Xu et al. 2013). Pulvinones viz., pulvinone P (**148**: IC_{50}: 0.079 mM) and Q (**149**: IC_{50}: 0.022 mM) were reported from *A. flavipes* and illustrated significant α-glucosidase inhibition (Zhang

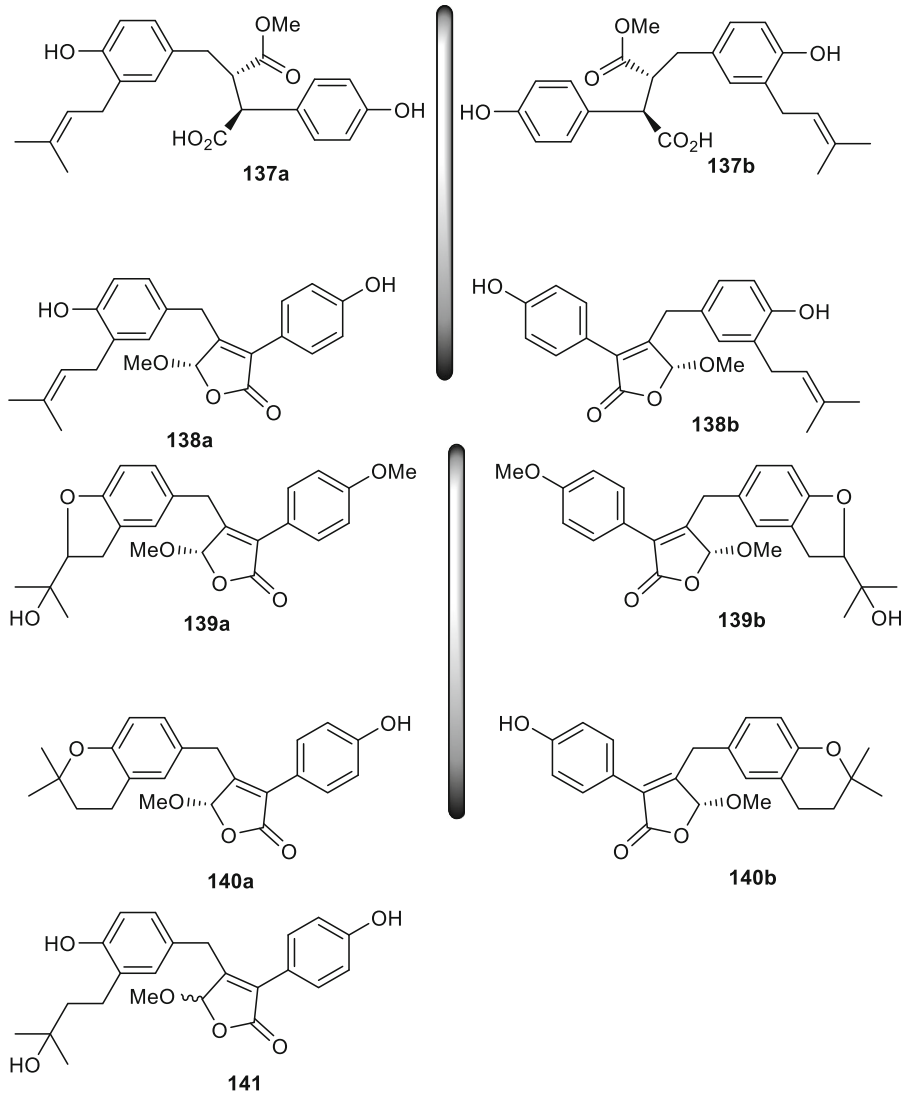


Fig. 19 Structures of butanolides **137–141**

et al. 2016a). Methybutyrolactone III (**150**: IC_{50}: 0.016 mM) and flavipesin B (**151**: IC_{50}: 0.385 mM) (Fig. 21) were obtained from *A. flavipes* and all were shown to possess significant α-glucosidase inhibition (Table 6) when compared to the standard drug acarbose (IC_{50} = 0.685 mM) (Zhang et al. 2016a). A butenolide analog, versicolactone G (**152**) was obtained from the fungus *Aspergillus terreus* and showed inhibitory potential towards α-glucosidase (IC_{50} = 104.8 µM) and under the same conditions this compound was more potent than the standard acarbose (IC_{50} = 154.7 µM) (Liu et al. 2018b).

Diphenyl ether and benzophenone derivatives

Neogeodin hydrate (**153**) (Zhang et al. 2016a; Jongrungruangchok et al. 2013) and methyl dichloroasterrate (**154**) (Liu et al. 2015b ; Zhang et al. 2016a) were produced by various *Aspergillus* sp. and illustrated α-glucosidase effects with IC_{50}: 1.47 mM and 1.45 mM respectively (Zhang et al. 2016a). 2,4-Dichloroasterric acid (**155**) along with benzophenones 3-de-O-methylsulochrin (**156**) and compound **157** (Fig. 22) were also produced by *Aspergillus* sp. (Zhang et al. 2016a). All these compounds possess good α-glucosidase inhibition with IC_{50} values

Table 6 Fungal metabolites **153–189** as α-glucosidase inhibitors

Compd.	Source	α-Glucosidase activity	References
Neogeodin hydrate (**153**),	*Aspergillus flavipes*	IC_{50}: 1.47 mM	Zhang et al. (2016a)
	Aspergillus flavipes	IC_{50}: 55 μM	Wang et al. (2016)
Methyl dichloroasterrate (**154**),	*Aspergillus flavipes*	IC_{50}: 1.45 mM	Zhang et al. (2016a)
	Aspergillus flavipes	IC_{50}: 90 μM; K_i: 2.8 μM	Wang et al. (2016)
2,4-Dichloroasterric acid (**155**)	*Aspergillus flavipes*	IC_{50}: 0.091 mM	Zhang et al. (2016a)
3-de-O-methylsulochrin (**156**)	*Aspergillus flavipes*	IC_{50}: 0.19 mM	Zhang et al. (2016a)
2-(3,5-Dichloro-2,6-dihydroxy-4-methylbenzoyl)-5-hydroxy-3-methoxybenzoic acid (**157**)	*Aspergillus flavipes*	IC_{50}: 0.042 mM	Zhang et al. (2016a)
Monomethylosoic acid (**158**)	*Aspergillus flavipes*	IC_{50}: 9.9 μM	Wang et al. (2016)
Chrysines B (**159**)	*Penicillium chrysogenum*	IC_{50}: 0.35 mM	Wang et al. (2018)
Chrysines C (**160**)	*Penicillium chrysogenum*	IC_{50}: 0.20 mM	Wang et al. (2018)
Methyl-3′-methoxy-3,5-dichloroasterric acid (**161**)	*Penicillium chrysogenum*	IC_{50}: 0.15 mM	Wang et al. (2018)
Methyl chloroasterrate (**162**)	*Penicillium chrysogenum*	IC_{50}: 0.14 mM	Wang et al. (2018)
Mono-chlorosulochrin (**163**)	*Penicillium chrysogenum*	IC_{50}: 0.14 mM	Wang et al. (2018)
Compound **164**	*Aspergillus flavus*	IC_{50}: 165.2 μM	Wu et al. (2018)
Compound **165**	*Aspergillus flavus*	IC_{50}: 129.9 μM	Wu et al. (2018)
Peniciaculin A (**166**)	*Aspergillus flavus*	IC_{50}: 1.5 μM	Wu et al. (2018)
Expansol D (**167**)	*Aspergillus flavus*	IC_{50}: 2.3 μM	Wu et al. (2018)
Dichloroorcinol (**168**)	*Penicillium chrysogenum*	IC_{50}: 0.16 mM	Wang et al. (2018)
Daldinione E (**169**)	*Daldinia eschscholtzii*	IC_{50}: 54 μM	Liao et al. (2019)
Bacillisporin A (**170**)	*Penicillium aculeatum*	IC_{50}: 95.8 μM	Huang et al. (2017)
Bacillisporin B (**171**)	*Penicillium aculeatum*	IC_{50}: 33.5 μM	Huang et al. (2017)
6′-Methyl-[1,1′-biphenyl]-3,3′,4′,5-tetraol (**172**)	*Penicillium* sp.	IC_{50}: 2.2 μM	Liu et al. (2015)
(±)-Penifupyrone (**173**)	*Penicillium* sp.	IC_{50} = 14.4 μM	Liu et al. (2015)
Flaviphenalenone B (**174**)	*Aspergillus flavipes*	IC_{50}: 94.9 μM)	Zhang et al. (2016b)

Table 6 continued

Compd.	Source	α-Glucosidase activity	References
Flaviphenalenone C (**175**)	*Aspergillus flavipes*	IC_{50}: 78.9 μM	Zhang et al. (2016b)
Cryptosporioptide (**176**)	*Cryptosporiopsis* sp.	IC_{50}: 50.5 μM	Tousif et al. (2014)
Cryptosporioptide A (**177**)	*Cryptosporiopsis* sp.	IC_{50}: 44.9 μM	Tousif et al. (2014)
Cryptosporioptide B (**178**)	*Cryptosporiopsis* sp.	IC_{50}: 41.2 μM	Tousif et al. (2014)
Compound **179**	*Aspergillus flavus*	IC_{50}: 4.5 μM	Wu et al. (2018)
Compound **180**	*Aspergillus flavus*	IC_{50}: 3.1 μM	Wu et al. (2018)
Aecilodepsipeptide A (**181**)	*Paecilomyces formosus*	IC_{50}: 74.2 μg/mL	Bilal et al. (2018)
YW3548 (**182**)	*Paecilomyces formosus*	IC_{50}: 61.8 μg/mL	Bilal et al. (2018)
Nectriacid A (**183**)	*Nectria* sp.	IC_{50} = 121.8 μM	Cui et al. (2016)
Nectriacid B (**184**)	*Nectria* sp.	IC_{50} = 23.5 μM	Cui et al. (2016)
Nectriacid C (**185**)	*Nectria* sp.	IC_{50} = 42.3 μM	Cui et al. (2016)
Helicascolide A (**186**)	*Daldinia eschscholtzii*	IC_{50}: 16 μM),	Liao et al. (2019)
Helicascolide B (**187**)	*Daldinia eschscholtzii*	IC_{50}: 31 μM	Liao et al. (2019)
Helicascolide D (**188**)	*Daldinia eschscholtzii*	IC_{50}: 20 μM	Liao et al. (2019)
Helicascolide E (**189**)	*Daldinia eschscholtzii*	IC_{50}: 240 μM	Liao et al. (2019)

ranging from 0.042 to 1.47 mM (Table 6). Among these tested metabolites, compounds **157** (IC_{50}: 0.042 mM) was the most active followed by **155** (IC_{50}: 0.091 mM) and their effects were higher than acarbose (IC_{50}: 0.685 mM) (Zhang et al. 2016a). In another investigation of the fungus *A. flavipes*, compounds **153** and **154** along with monomethylosoic acid (**158**) were also isolated (Wang et al. 2016). Compounds **153** (IC_{50}: 55 μM) and **154** (IC_{50}: 90 μM) along with monomethylosoic acid (**158**; IC_{50}: 9.9 μM) inhibited α-glucosidase while a corresponding kinetic study revealed that compound **154** is a noncompetitive inhibitor with K_i: 2.8 μM (Wang et al. 2016).

The fungus *Penicillium chrysogenum* produced diphenl ethers, chrysines B (**159**), C (**160**), compound **161**, and methyl chloroasterrate (**162**), together with benzophenone, mono-chlorosulochrin (**163**) (Fig. 23). The group demonstrated that all these compounds illustrated α-glucosidase effects with IC_{50}: ranging from 0.15 mM to 0.35 mM (Table 6). Most of the compounds were more potent than the standard acarbose with an IC_{50} of 0.28 mM (Wang et al. 2018). The fungus *Aspergillus flavus* produced compounds **164–167** whose structures were established via spectroscopic techniques. Compounds **166** and **167** exhibited significant inhibition potential with IC_{50} values of 1.5, and 2.3 μM, respectively. Furthermore,

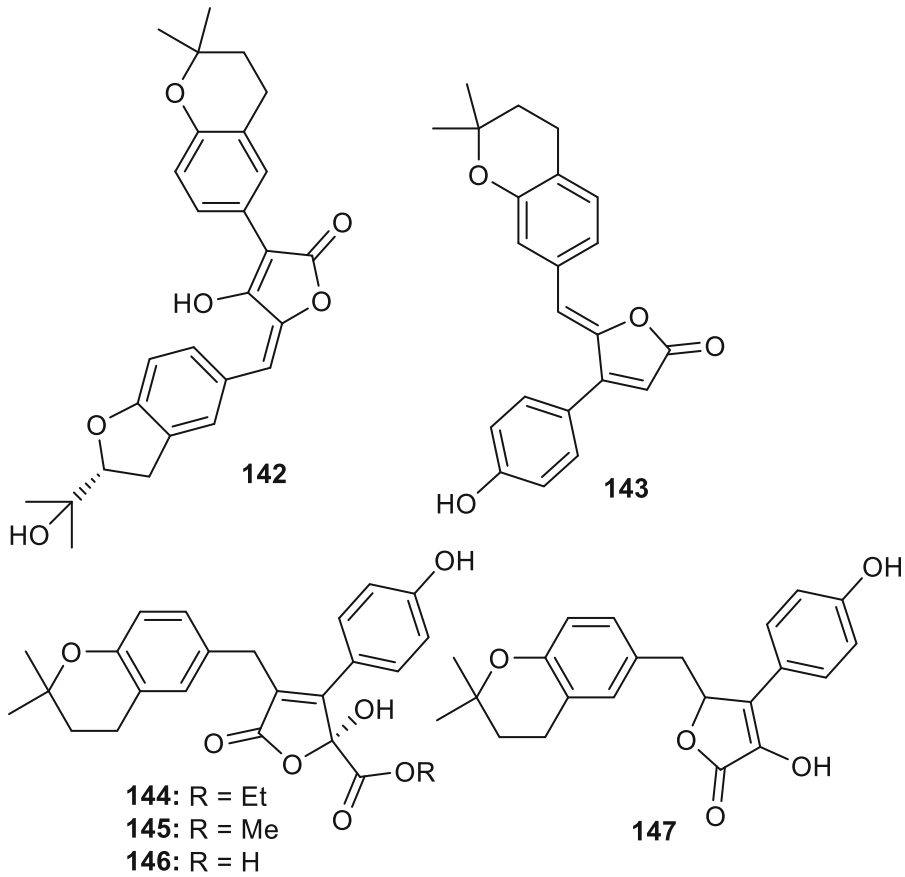


Fig. 20 Structures of butanolides **142–147**

metabolites **164** and **165** were only moderately active with IC_{50} values of 165 and 129 μM, respectively. However, their effects were higher than acarbose which had an IC_{50}: 840.2 μM) (Wu et al. 2018).

Miscellaneous

The fungus *Penicillium chrysogenum* produces dichloroorcinol (**168**) (Fig. 24) which demonstrated good α-glucosidase effects with an IC_{50}: 0.16 mM (Wang et al. 2018). Daldinione E (**169**: IC_{50}: 54 μM) was obtained from the fungus *Daldinia eschscholtzii* and illustrated α-glucosidase effects (Liao et al. 2019). In another investigation, bacillisporin A (**170**: IC_{50}: 95.8 μM) and bacillisporin B (**171**: IC_{50}: 33.5 μM) were isolated from the fungus *Penicillium aculeatum* and both substances inhibited α-glucosidase activity (Huang et al. 2017; Lin et al. 2008). The fungus *Penicillium* sp. produced compound **172** (IC_{50}: 2.2 μM) and (±)-penifupyrone (**173**: IC_{50} = 14.4 μM) and both compounds inhibited α-glucosidase (Liu et al. 2015a). Flaviphenalenones B (**174**: IC_{50}: 94.9 μM) and C (**175**: IC_{50}: 78.9 μM) were isolated from the fungus *Aspergillus flavipes* and illustrated anti-α-glucosidase effects (Table 6). Moreover, these compounds demonstrated a greater potency than that of the acarbose (IC_{50}: 685 μM) but were less effective than quercetin (IC_{50}: 14.5 μM) (Zhang et al. 2016b).

Cryptosporioptide (**176**: IC_{50}: 50.5 μM) along with cryptosporioptide A (**177**: IC_{50}: 44.9 μM) and B (**178**: IC_{50}: 41.2.5 μM) (Fig. 25) were obtained from the fungus *Cryptosporiopsis* sp. and all three compounds inhibited α-glucosidase with comparable activity to the standard acarbose with an IC_{50} value of 38.2 μM (Tousif et al. 2014). The fungus *Aspergillus flavus* furthermore produced compounds **179** and **180** which exhibited significant potential with IC_{50} values of 4.5 and 3.1 μM, respectively. Interestingly the effects of

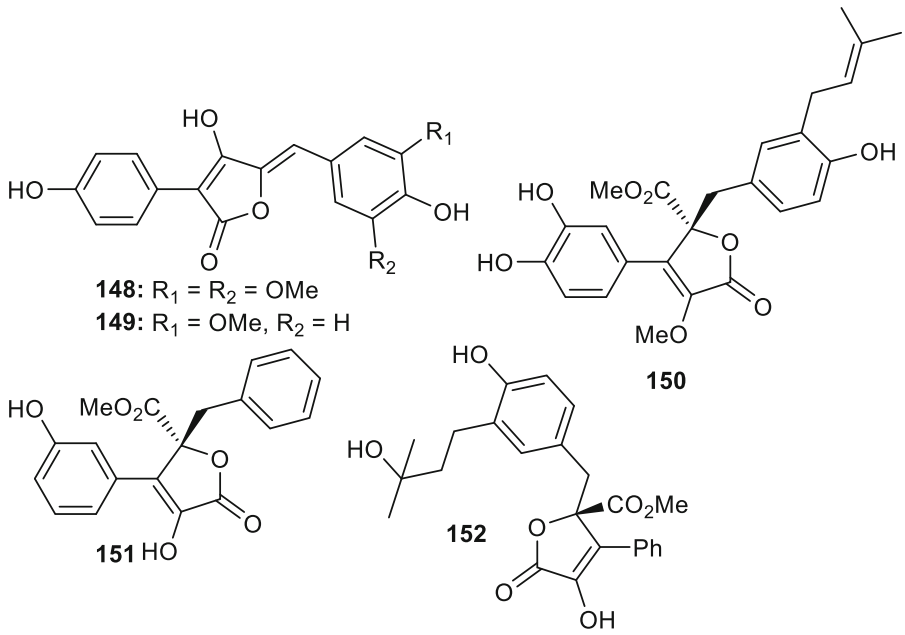
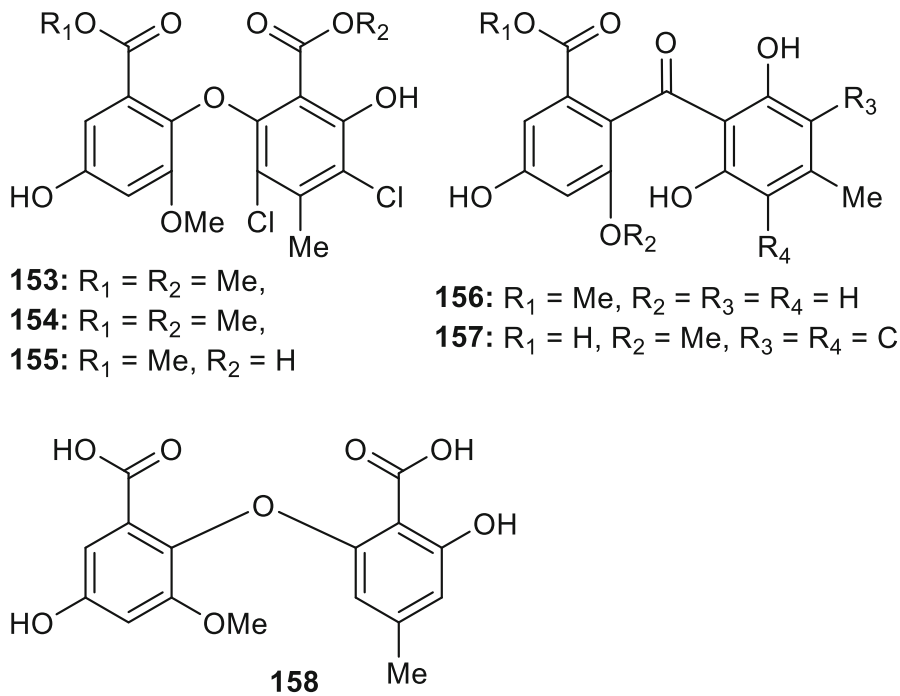


Fig. 21 Structures of butanolides **148–152**

Fig. 22 Structures of butanolides **153–158**



these compounds were higher than the reference compound acarbose IC_{50}: 840.2 μM) (Wu et al. 2018). Aecilodepsipeptide A (**181**: IC_{50}: 74.2 μg/mL) and YW3548 (**182**: IC_{50}: 61.8 μg/mL) were obtained from the fungus *Paecilomyces formosus* and illustrated good anti-α-glucosidase effects (Bilal et al. 2018). The polyketides, nectriacids A-C (**183–185**) were isolated from the fungus *Nectria* sp. In this regard polyketides **184** (IC_{50} = 23.5 μM) and **185** (IC_{50} = 42.3 μM) illustrated rather good α-glucosidase

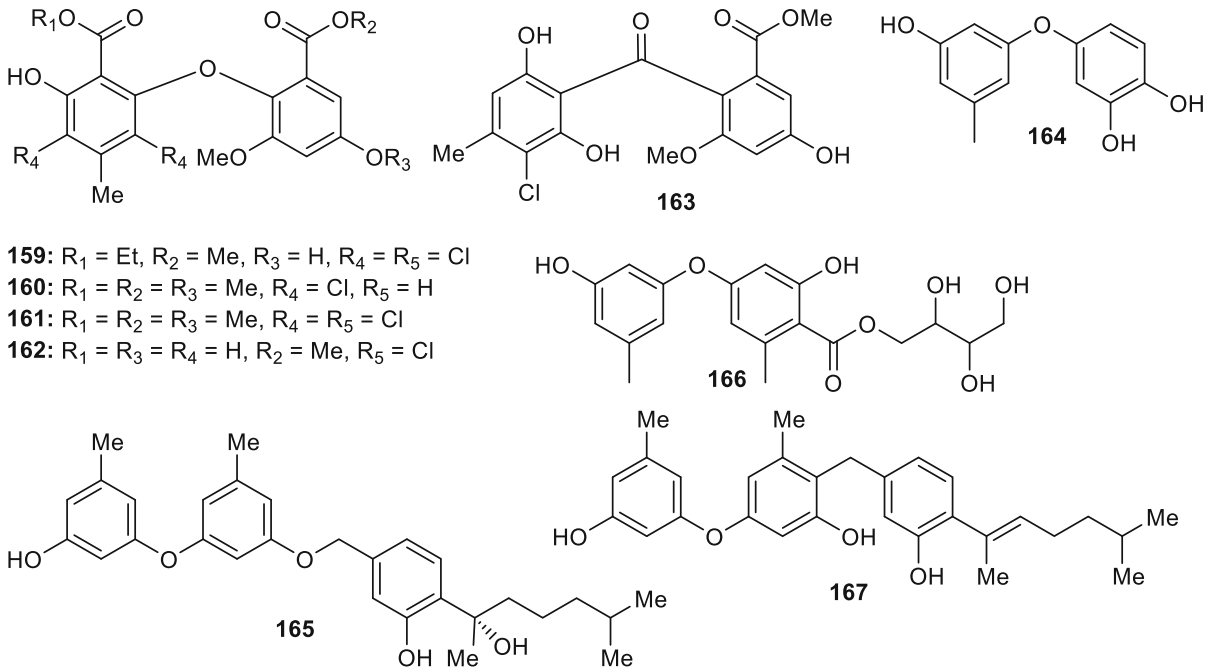


Fig. 23 Structures of butanolides **159–167**

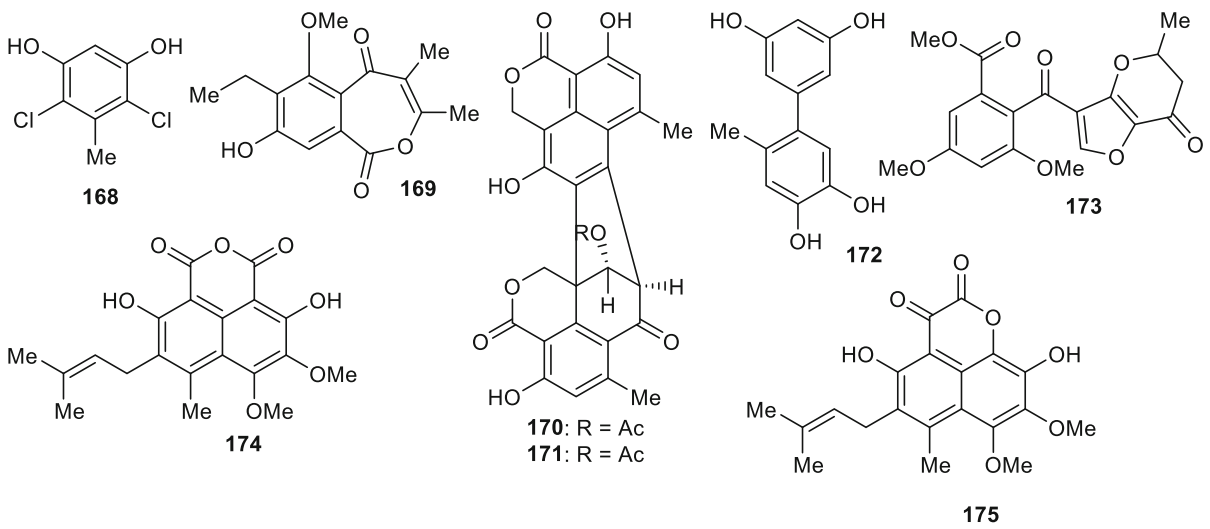


Fig. 24 Structures of butanolides **168–175**

effects which were higher than acarbose (IC_{50} = 815.3 μM). On the other hand nectriacid A (**183**) also possessed good α-glucosidase effects with IC_{50} = 121.8 μM (Cui et al. 2016).

Helicascolides A (**186**: IC_{50}: 16 μM), B (**187**: IC_{50}: 31 μM), D (**188**: IC_{50}: 20 μM), and E (**189**: IC_{50}: 240 μM) (Fig. 26) are all produced by the fungus *Daldinia eschscholtzii* and these isolated compounds illustrated excellent α-glucosidase effects (Table 7). Compound **186** was the most potent followed by compound **188** while metabolite **189** was the least active. The activity difference between compounds **188** and **189** indicated that it was indeed the acetyl group at C-8 that was responsible for the reduced activity (Liao et al. 2019). Polyketides viz., aspergones A (**190**), B (**191**), E (**192**), J (**193**), K (**194**), N-Q

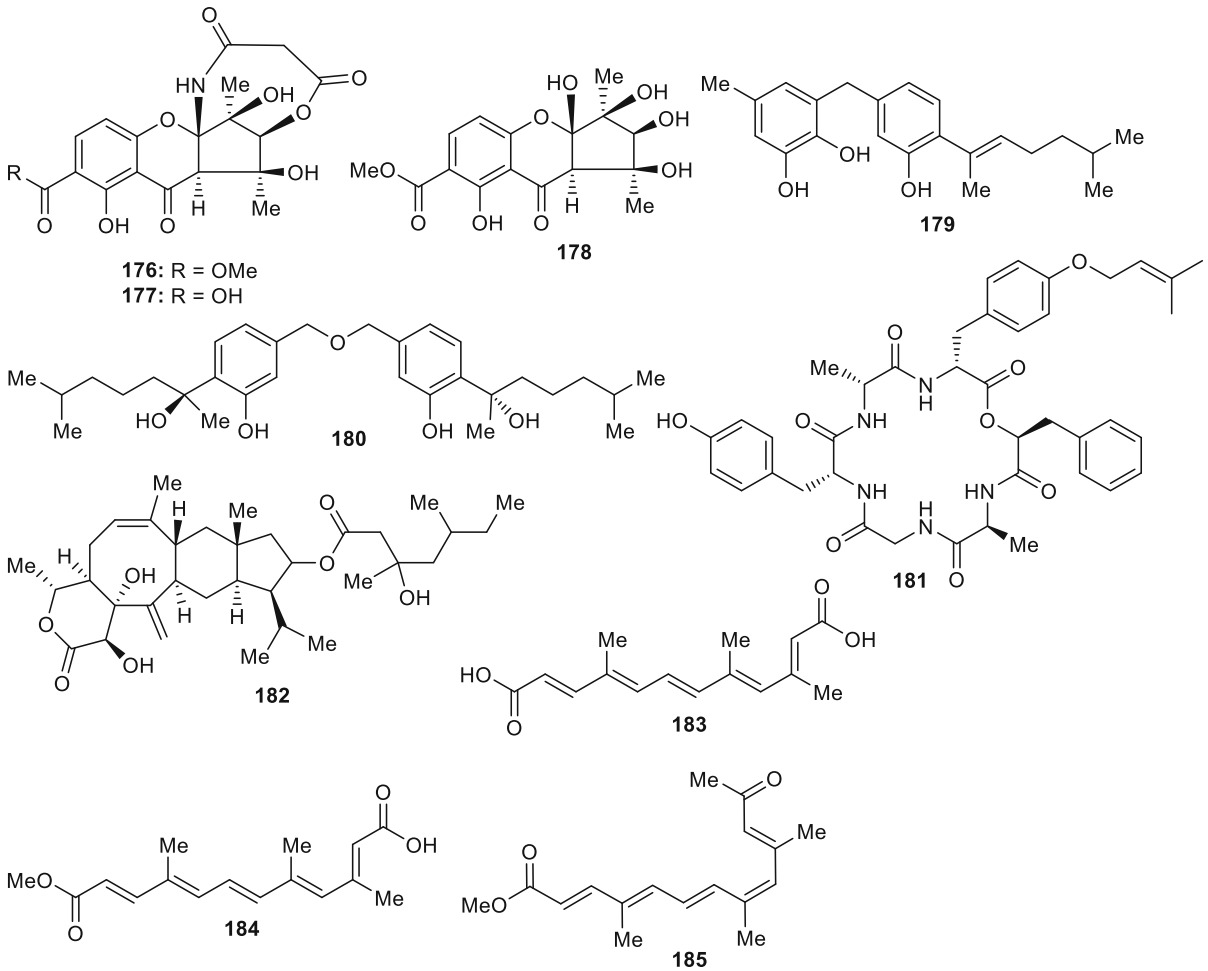


Fig. 25 Structures of butanolides **176–185**

(**195–198**) were isolated from the fungus *Aspergillus* sp. and all these compounds inhibited α-glucosidase with IC_{50} values ranging from 1.30 to 2.37 mM (Table 7). Moreover all the compounds were less effective than acarbose (IC_{50}: 0.95 mM) (Kong et al. 2015). The fungus *Penicillium expansum* produced expansolides C (**199**) and D (**200**). An epimeric mixture of compounds **199** and **200** (2:1) potentially inhibited α-glucosidase (IC_{50} = 0.50 mM) and thus was more potent than acarbose (IC_{50} = 1.90 mM) (Ying et al. 2017).

The fungus *Ganoderma lucidum* produces nor-triterpenoids, (**201**), D (**202**), E (**203**) (Fig. 27). Metabolite **202** exerted potent α-glucosidase effects among these compounds, with an IC_{50} value of 41.7 μM, followed by metabolites **201** (IC_{50} = 81.8 μM) and **203** (IC_{50} = 91.3 μM). All these compounds were more potent than acarbose (IC_{50}: 669.7 μM) (Zhao et al. 2015). A pair of enantiomers: (+)-1-hydroxyboivinianic acid (**204a**), (−)-1-hydroxyboivinianic acid (**204b**) along with 7-deoxy-7,14-didehydrosydonol (**205**) were separated from the fungus *Aspergillus versicolor* and evaluated for their α-glucosidase inhibition. Metabolite **205** (IC_{50}: 7.5 μM) was the most potent inhibitor when compared with the activity of acarbose (IC_{50} = 350 μM). On the other hand compounds (+)-**204** (IC_{50}: 120.3 μM) and (−)-**204** (IC_{50}: 113.3 μM) are reported as moderate inhibitors (Cui et al. 2018).

The fungus *Setosphaeria rostrata* produced thiodiketopiperazine, exserohilone (**206**) (Fig. 28) and possess α-glucosidase activity with an IC_{50} value of 82 μg/mL (Centko et al. 2017). Moreover, asperpanoid A (**207**) was obtained from *Aspergillus* sp. and

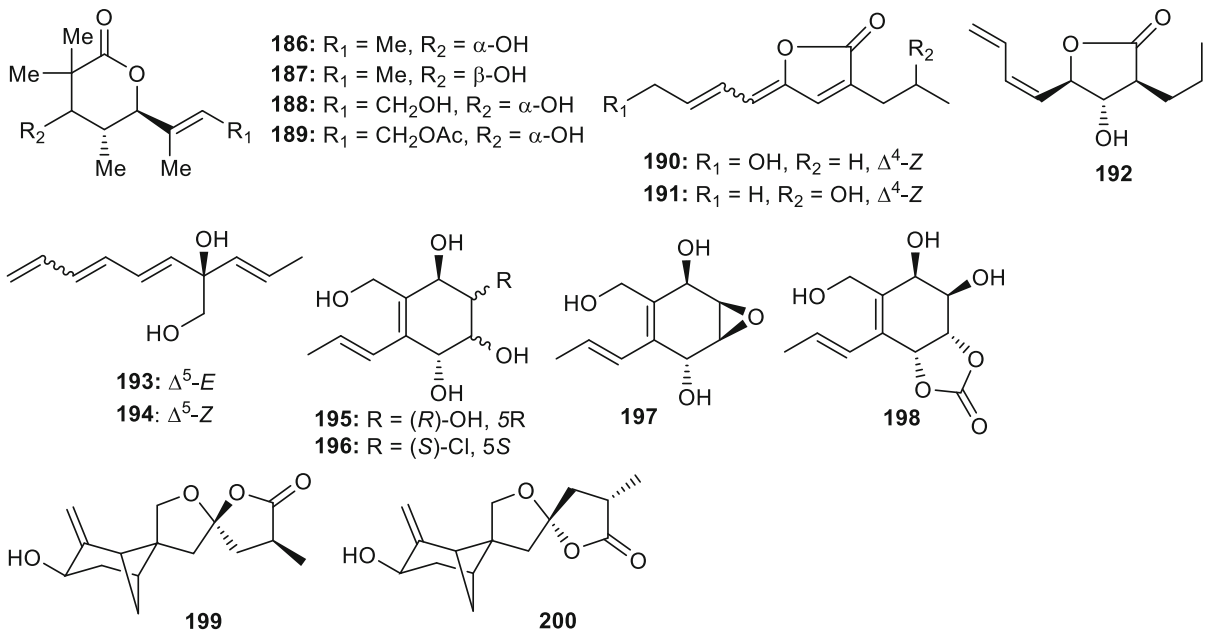


Fig. 26 Structures of butanolides **186–200**

possesses α-glucosidase activity with IC_{50}: 12.4 μM (Cai et al. 2019). The fungus *Zasmidium* sp. produced tripalmitin (**208**: IC_{50}: 3.75 μM) which illustrated potent α-glucosidase activity (Lopéz et al. 2019). Metabolites dothiorelone K (**209**: IC_{50}: 22 μg/mL), L (**210**: IC_{50}: 77.9 μg/mL), and I (**211**: IC_{50}: 5.4 μg/mL) were reported from the fungus *Dothiorella* sp. and illustrated α-glucosidase effects (Zheng et al. 2019).

Conclusion

Fungi are known as prolific producers of diverse secondary metabolites. Fungal metabolites range from simple small molecules to more complex systems viz., proteins and polypeptides with a wide range of biological activities. Since the scurge of diabetes has increased worldwide, it is estimated that by 2040, the number of diabetic people will increase to 642 million around the globe. There is thus a critical need to find new antidiabetic drugs with less side effects. In spite of the fact that drug treatment for diabetes has improved over the last decade, drug resistance too has become an important issue in diabetic drug discovery and consequently new and improved strategies will have to be sought. One such strategy would be to either inhibit or decrease the manufacture of glucose in the small intestine. α-Glucosidase inhibitors can reduce the digestion of carbohydrates and thus could be considered as one of the most effective strategies to reduce post-prandial hyperglycemia. α-Glucosidase inhibitors are thus an important group of therapeutic agents to treat diabetes which currently comprises of three drugs viz., acarbose, miglitol, and voglibose (Derosa and Maffioli 2012). Numberous studies have been conducted to analyze the clinical efficacy and safety of acarbose, miglitol, and voglibose α-glucosidase with respect to glycemic control, atherosclerosis, and inflammation. It has been reported that these three α-glucosidase inhibitors are considered to be safe and effective both in monotherapy as well as in combination with additional anti-diabetic drugs (Dash et al. 2018; Derosa and Maffioli 2012).

In this context, the last decade has been noted to be a most fruitful period in isolating low molecular weight antidiabetic compounds from fungi. During this decade (2010 to 2019), more than 200 natural products have been isolated from various fungal sources and screened for their α-glucosidase inhibitory activity. Among the alkaloids, compound **8** exhibited an IC_{50} value of 3.3 μM, which showed that the pyrolidine-2-one system coupled with a phenolic function are important functional groups for the development of antidiabetic drugs. Moreover, among

Table 7 Fungal metabolites **190–211** as α-glucosidase inhibitors

Compd.	Source	A-Glucosidase activity	References
Aspergone A (**190**)	*Aspergillus* sp.	IC_{50} = 2.36 mM	Kong et al. (2015)
Aspergone B (**191**)	*Aspergillus* sp.	IC_{50} = 1.65 mM	Kong et al. (2015)
Aspergone E (**192**)	*Aspergillus* sp.	IC_{50} = 1.30 mM	Kong et al. (2015)
Aspergone J (**193**)	*Aspergillus* sp.	IC_{50} = 2.37 mM	Kong et al. (2015)
Aspergone K (**194**)	*Aspergillus* sp.	IC_{50} = 2.70 mM	Kong et al. (2015)
Aspergone N (**195**)	*Aspergillus* sp.	IC_{50} = 1.36 mM	Kong et al. (2015)
Aspergone O (**196**)	*Aspergillus* sp.	IC_{50} = 1.54 mM	Kong et al. (2015)
Aspergone P (**197**)	*Aspergillus* sp.	IC_{50} = 2.21 mM	Kong et al. (2015)
Aspergone Q (**198**)	*Aspergillus* sp.	IC_{50} = 2.26 mM	Kong et al. (2015)
Expansolide C (**199**)	*Penicillium expansum*	IC_{50} = 0.50 mM (mixture of 199 and 200)	Ying et al. (2017)
Expansolide D (**200**)	*Penicillium expansum*		Ying et al. (2017)
Ganoderlactone B (**201**)	*Ganoderma lucidum*	IC_{50}: 81.8 μM	Zhao et al. (2015)
Ganoderlactone D (**202**)	*Ganoderma lucidum*	IC_{50}: 41.7 μM	Zhao et al. (2015)
Ganoderlactone E (**203**)	*Ganoderma lucidum*	IC_{50}: 91.3 μM	Zhao et al. (2015)
(+)-1-Hydroxyboivinianic acid (**204a**)	*Aspergillus versicolor*	IC_{50}: 120.3 μM	Cui et al. (2018)
(−)-1-Hydroxyboivinianic acid (**204b**)	*Aspergillus versicolor*	IC_{50}: 113.3 μM	Cui et al. (2018)
7-Deoxy-7,14-didehydrosydonol (**205**)	*Aspergillus versicolor*	IC_{50}: 7.5 μM	Cui et al. (2018)
exserohilone (**206**)	*Setosphaeria rostrata*	IC_{50}:82 μg/mL	Centko et al. (2017)
Asperpanoid A (**207**)	*Aspergillus* sp.	IC_{50}: 12.4 μM	Cai et al. (2019)
Tripalmitin (**208**)	*Zasmidium* sp.	IC_{50}: 3.75 μM	Lopéz et al. (2019)
Dothiorelone K (**209**)	*Dothiorella* sp.	IC_{50}: 22 μg/mL	Zheng et al. (2019)
Dothiorelone L (**210**)	*Dothiorella* sp.	IC_{50}: 77.9 μg/mL	Zheng et al. (2019)
Dothiorelone I (**211**)	*Dothiorella* sp.	IC_{50}: 5.4 μg/mL	Zheng et al. (2019)

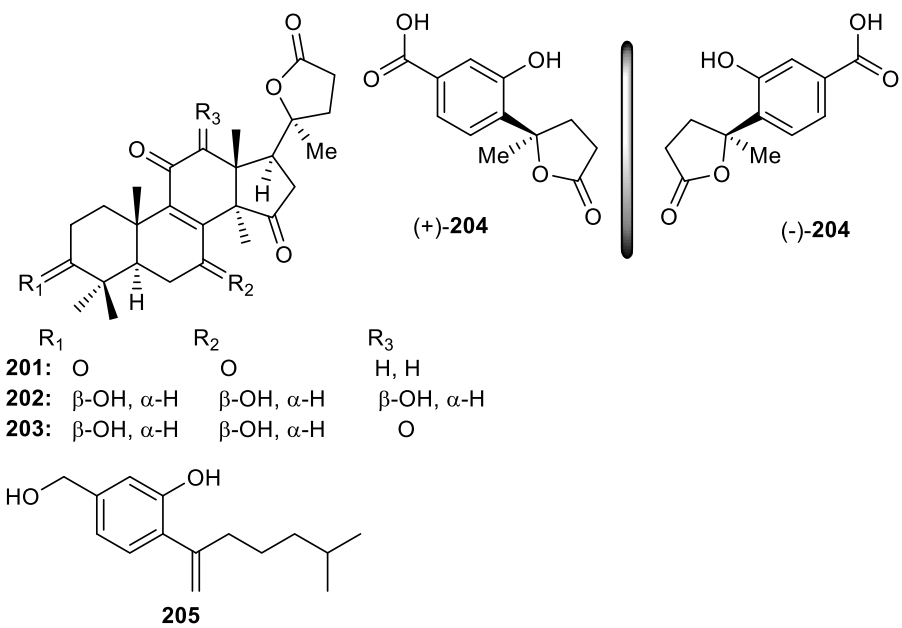


Fig. 27 Structures of butanolides **201–205**

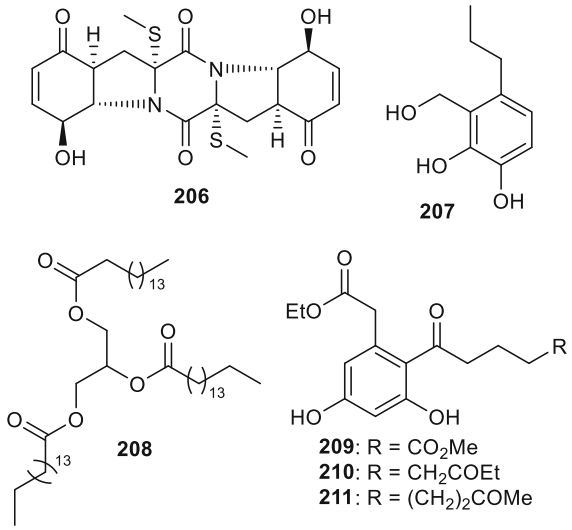


Fig. 28 Structures of butanolides **206–211**

p-terphenyls as α-glucosidase inhibitors, sarcoviolin β (**23**, IC_{50} = 0.58 μM), 3,3″-dihydroxy-6′-O-desmethylterphenyllin (**22**, IC_{50} = 0.9 μM) and concrescenin A (**33**, IC_{50}: 0.9 μM) were found to be the most potent α-glucosidase inibitors. Depsides **43–45** showed α-glucosidase inibiton with IC_{50}: 3–7.6 μM, and thus offer their strong candidature to be studied further for development as antidiabetic drugs. Among the depsidones, botryorhodine D (**62**, IC_{50} = 2.1 μM) has been identified as a potential α-glucosidase inhibitor. Since two more depsides (**63** and **64**) also showed significant inhibtion, this fact revealed that the dioxipanone system is important and is also supported by other functional groups attached at C-3 to improve the α-glucosidase activity. A reasonable number (25) of isocoumarins have been idetified from various fungi as α-glucosidase inhibitors. Notably compound **93** (IC_{50}: 0.027 mM) was found to be 35 fold more potent than the standard drug acarbose which indicated that a substituted tetrahydrofuran system might be playing a key role in the inhibitory activity. Among the benzofurans, 6-demethylpenisimplicissin (**108**, IC_{50}: 9.5 μM) and 1″-epihydroxydihydrovermistatin (**109**, IC_{50}: 8.0 μM) have also shown their potential as antidiabetic drug candidates. However, among the few quinone exmples, only compound **115** (IC_{50} = 7.2 μM) exerted potential inhibition of α-glucosidase being higher than the positive control genistein (IC_{50} = 13.6 μM), whereas, chromone analogs **125** (IC_{50}: 13 μM) and **128** (IC_{50}: 15 μM) proved to be the most active metabolites. Butanolide polyketides are another major class identified as antidiabetic fungal metabolites. A total of 29 compounds forming this group were isolated from various fungi during the last decade and almost all showed remarkable α-glucosidase inhibitory activity. Rubrolide S (**143,** IC_{50} = 1.2 μM) with a *K*i value of 1.42 μM has been identified as the most potent inhibitor. Further studies on this compound may lead to the development of a new and novel antidiabetic agent. Among the diphenyl ether dervatives, peniciaculin A (**166**, IC_{50}: 1.5 μM) and expansol D (**167**, IC_{50}: 2.3 μM) showed their potential as future drug candidates to treat diabetes mellitus. Other than these metabolites, 6′-Methyl-[1,1′-biphenyl]-3,3′,4′,5-tetraol (**172**, IC_{50}: 2.2 μM), meroterpenoids **179** (IC_{50}: 4.5 μM) and **180** (IC_{50}: 3.1 μM), sesquiterpenoid; 7-deoxy-7,14-didehydrosydonol (**205**, IC_{50}: 7.5 μM), tripalmitin (**208**, IC_{50}: 3.75 μM) and dothiorelone I (**211**, IC_{50}: 5.4 μg/mL) are also considered as powerful candidates as α-glucosidase inhibitors. The above information clearly demonstrates that fungi are one of the most vital sources of novel substances with diverse structural features, which can be further explored as new and noval antidiabetic agents.

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