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α-Glucosidase inhibitors isolated from medicinal plants

Zhenhua Yin [a], Wei Zhang [a], Fajin Feng [a,b], Yong Zhang [a], Wenyi Kang [a,*]

[a] *Huanghe Science and Technology College, Zhengzhou 450063, China*
[b] *College of Chemistry and Chemical Engineering, Guizhou University, Guiyang 550025, China*

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Abstract

Objective: α-Glucosidase inhibitors can be used as a new class of antidiabetic drug. By competitively inhibiting glycosidase activity, these inhibitors help to prevent the fast breakdown of sugars and thereby control the blood sugar level. This study provides a wealth of information about α-glucosidase inhibitors isolated from medicinal plants; this knowledge will be useful in finding more potent antidiabetic candidates from the natural resources for the clinical development of antidiabetic therapeutics.
Results: 411 compounds exhibiting α-glucosidase inhibitory activity were summarized and isolated them from medicinal plants. The compound classes isolated include: terpenes (61) from 14 genus, alkaloids (37) from 11 genus, quinines (49) from 4 genus, flavonoids (103) from 24 genus, phenols (37) from 9 genus, phenylpropanoids (73) from 20 genus, sterides (8) from 5 genus, and other types of compounds (43).
Conclusion: Compounds with α-glucosidase inhibitory activity are abundant in nature and can be obtained from several sources. They have high α-glucosidase inhibitory potential, and can be clinically developed for treating diabetes mellitus.

Keywords: α-Glucosidase inhibitor; Inhibitory activity; Medicinal plants

1. Introduction

Diabetes mellitus is a well-known metabolic disorder, which is characterized by an abnormal postprandial increase of blood glucose level. The control of postprandial hyperglycemia is believed to be important in the treatment of diabetes mellitus. α-Glucosidase secreted from intestinal chorionic epithelium is responsible for the degradation of carbohydrates. In the 1980s, α-glucosidase (EC 3.2.1.20) inhibitors became a new class of antidiabetic drug. α-Glucosidase inhibitors slow down the process of digestion and absorption of carbohydrates by competitively blocking the activity of glucosidase. Consequently, the peak concentration of postprandial blood glucose is reduced and the blood sugar level comes under control. α-Glucosidase inhibitors can offer several advantages and has been recommend by the *Third Asia-Pacific Region Diabetes Treatment Guidelines* as the first-line of treatment for lowering postprandial hyperglycemia [1].

α-Glucosidase inhibitors fall under the third category of oral hypoglycemic agents [2]. Several α-glucosidase inhibitors, such as acarbose and voglibose obtained from natural sources, can effectively control blood glucose levels after food intake and have been used clinically in the treatment of diabetes mellitus [3]. Only a few α-glucosidase inhibitors are commercially available. All of them contain sugar moieties and their synthesis involves tedious multistep procedures. Moreover, clinically they have been associated with serious gastrointestinal side effects. Therefore, it is necessary to search for alternatives that can display α-glucosidase inhibitory activity but without side reactions. In recent years, projects undertaken to discover potent non-sugar based α-glucosidase inhibitors from natural sources have received tremendous attention because of the highly abundant compounds in nature and their promising biological activities [4].

* Corresponding author at: Huanghe Science and Technology College, Zhengzhou 450063, China.
E-mail address: kangweny@hotmail.com (W. Kang).
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2. Research development

2.1. α-Glucosidase inhibitory compounds from medicinal plants

α-Glucosidase inhibitors were isolated from natural resources including microorganisms and medicinal plants. A review of literature reveals that α-glucosidase enzyme from yeast, rat intestine, and mouse intestine have been widely used for pharmacological screenings. In addition, coffee-glucosidase, amylase mammal glucosidase, rat intestinal isomaltase, α-glucosidase type IV from *Bacillus stearothermophilus*, and glucosidase II from rat liver microsomes have been used as the sources of enzymes for enzyme inhibition assays. Acarbose has been frequently used as positive control in screenings, and a few researchers have also applied genistein, quercitrin, and 1-deoxynojirinmycin as positive controls. On the basis of literatures published worldwide, we have summarized a list of 411 natural products isolated from medicinal plants that showed α-glucosidase inhibitory activity. Structurally these natural product inhibitors incorporate terpene, alkaloid, quinine, flavonoid, phenol, phenylpropanoid, and steride frameworks rich in organic acid, ester, alcohol, and allyl functional groups. A majority of the compounds reported contain flavonoid, terpene, and phenylpropanoid ring structures.

2.2. Terpenes

Sixty-one terpenoids isolated from plants have shown α-glucosidase inhibitory activity. Compound 1 was isolated from the methanol extracts of stem and bark of *Fagara tessmannii* (Rutaceae). It showed strong inhibitory activity with an IC_{50} value of 7.6 μmol/L [5]. Compounds 2–4 were isolated from *Luculia pinceana* Hook using bioactivity-guided method. The IC_{50} values reported for these compounds were 18.48, 3.30, and 2.88 μg/mL, respectively. Compound 2 (K_i = 3.36 μg/mL) showed competitive inhibitory profile for α-glucosidase activity and the profile closely resembled the inhibitory activity of acarbose, which was used as positive control. The inhibitory activity of compounds 3 and 4 fitted the profile of a non-competitive inhibition model with K_i values—195.04 and 3.36 μg/mL, respectively [6].

Triterpenoid saponins (5–11) and (IC_{50} = 23.1, 65.5, 15.2, 78.5, 59.7, 98.2, and 85.2 μmol/L, respectively), isolated from the roots of *Gypsophila oldhamiana*, showed stronger inhibitory potency than acarbose (388.0 ± 9.6 μmol/L) [7]. Triterpenoid saponins (12–13) (IC_{50} = 908.5 and 819.7 μmol/L, respectively), isolated from the leaves of *Acanthopanax senticosus*, showed higher inhibition compared with acarbose (788.6 ± 53.66 μmol/L) [8].

Three abietane diterpenoids (14–16) were isolated from methanol extract of *Plectranthus madagascariensis* and exhibited α-glucosidase inhibitory activity with IC_{50} values of 274.9 ± 12.3, 108.2 ± 1.3, and 142.7 ± 1.4 μmol/L, respectively [9].

Phytochemical investigation of antihyperglycemic extract from the rhizomes of *Hedychium spicatum* led to the isolation of diterpenes (17–25). Compounds 17–24 displayed varying degree of intestinal α-glucosidase inhibitory potentials. The presence of α,β-unsaturated γ-lactone (17–19) and furan (20–23) ring system was essential to inhibit α-glucosidase activity because the absence of these structural motifs in 25 rendered the compound inactive. Hydroxy group at C-16 in the lactone ring (18) strongly increased enzyme inhibitory potential in comparison with methoxy group [10].

Compounds (25*S*)-5α-furastan-3β,22,26-triol (26) and gitogenin (27) isolated from the plant of *Tribulus longipetalus* showed decent α-glucosidase inhibitory activity with IC_{50} values, i.e., 33.5 ± 0.22 and 37.2 ± 0.18 μmol/L, respectively, compared with acarbose (IC_{50} value = 38.3 ± 0.12 μmol/L) [11].

D-Galactopyranosyl harpagoside (28), 8-*O*-feruloyl harpagide (29), 8-*O*-(coumaroyl)harpagide (30), and ninpogenin (31) isolated from the roots of *Scrophularia ningpoensis* exhibited moderate α-glucosidase inhibitory activity (IC_{50} = 2.16 ± 0.13, 3.02 ± 0.16, 3.09 ± 0.16, and 1.54 ± 0.31 mmol/L, respectively) compared with acarbose (IC_{50} = 0.37 ± 0.01 mM) [12].

Octanordammarane triterpene—3β,15*a*-dihydroxymansumbinol (32) and A-ring contracted oleanane triterpenoid—2-formyl-(A)1–19*a*-hydroxy-1-norolean-2,12-dien-28-oic acid (33), ursolic acid (34), and sesquiterpene glucoside (35–38) were isolated from the root extract of *Rosa rugosa*. The IC_{50} values recorded for compounds 32–36 were 40.03 ± 3.25%, 32.39 ± 5.40%, 31.96 ± 4.47%, 28.26 ± 5.83%, and 28.63 ± 2.51%, respectively; the inhibitory sucrose activity was moderate for these compounds compared with that of acarbose (50.96 ± 2.97%). Compounds 37 and 38 showed weak inhibitory activity with IC_{50} values of 13.98 ± 2.92% and 12.51 ± 4.06%, respectively [13].

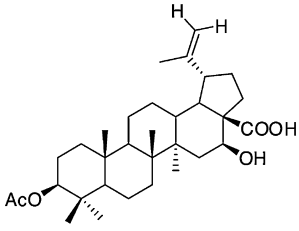
Compounds 39–44 (IC_{50} = 38.0 ± 0.2, 315.8 ± 0.2, 355.5 ± 0.9, 318.5 ± 0.3, 305.3 ± 1.0, and 231.3 ± 0.1 μmol/L, respectively) were isolated from the entire plant extract of *Phlomis stewartii* and showed α-glucosidase inhibitory activity with acarbose (IC_{50} = 38.0 ± 0.1 μmol/L) [14].

Six triterpenesaponins, including one new glinoside C (45), were isolated from the aerial parts of *Glinus oppositifolius* and the five known constituents included 3-*O*-(β-*D*-xylopyranosyl)-spergulagenin A (46), spergulacin (47), spergulin A (48), spergulacin A (49), and spergulin B (50). Among them, compound 45 exhibited the greatest inhibitory potency toward α-glucosidase with IC_{50} of 127 ± 30 μmol/L and demonstrated an inhibitory profile similar to that of a mixed-type inhibitor (K_i = 157.9 μmol/L). Compounds 46–50 (IC_{50} = 1654 ± 170, 628 ± 80, 143 ± 20, 694 ± 60, and 1783 ± 290 μmol/L) demonstrated weaker inhibitory activity toward α-glucosidase compared with acarbose (IC_{50} = 15 ± 3 μmol/L) [15].

Compounds 51–52 isolated from the ethanolic extract of the stem and the bark of *Uncaria laevigata* showed potent α-glucosidase inhibitory activity with IC_{50} values of 16 ± 2.2 and 49 ± 3.7 μmol/L, respectively, as compared with that of genistein ($IC_{50} = 36 \pm 1.5$ μmol/L), acting as positive control. Compound 52 was found to be a non-competitive α-glucosidase inhibitor ($K_i = 28$ μmol/L) [16].

2β,3β,22a-Trihydroxy-lup-20(29)-ene (53), 3β-hydroxy-2-carbonyl-lupan-29-oic acid (54), and six other known compounds, namely 2,3-seco-lup-20(29)-en-2,3-dioic-2-methylate (55), 3β,30-dihydroxy-lup-20(29)-en-2-one (56), 3β,30-dihydroxy-olean-12-ene (57), oleanic acid (58), 7a,21a-dihydroxy-D:A-friedo-oleanane-3-one (59), and salasone C (60), were isolated from the roots of *Salacia hainanensis*. Compounds 53–58 and 60 showed much stronger α-glucosidase inhibitory activity ($IC_{50} = 3.2 \pm 0.1$, 0.7 ± 0.1, 6.8 ± 0.4, 2.5 ± 0.2, 3.3 ± 0.1, 3.8 ± 0.2, and 1.9 ± 0.3 μmol/L) than acarbose ($IC_{50} = 10.2 \pm 0.1$ μmol/L), while compound 59 displayed weak inhibitory activity ($IC_{50} = 24.5 \pm 0.2$ μmol/L) [17].

Sesquiterpene lactone caleins C (61) isolated from the active aqueous extract of *Brickellia cavanillesii* inhibited the activity of α-glucosidase with $IC_{50} = 0.28$ mmol/L vs. 1.7 mmol/L for acarbose and exhibited the profile of mixed-type inhibitors with K_i value = 1.91 mmol/L. Docking analysis predicted that the compound binds to the enzyme at its catalytic site [18].



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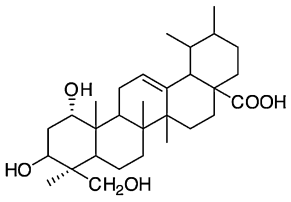

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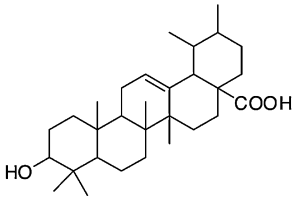

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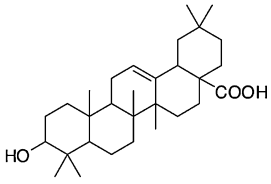

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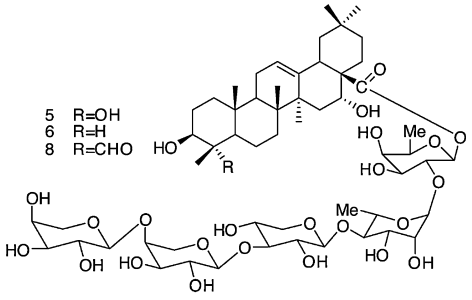

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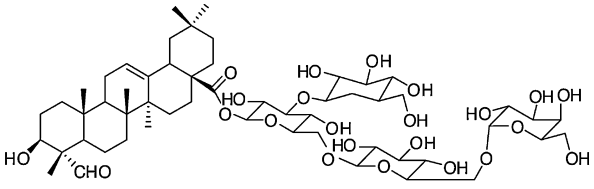

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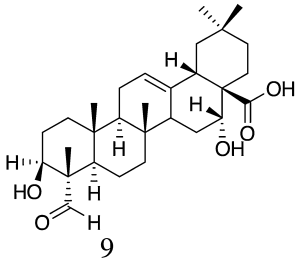

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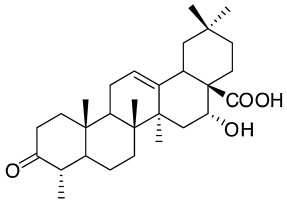

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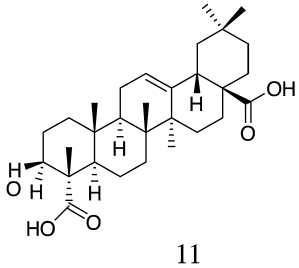

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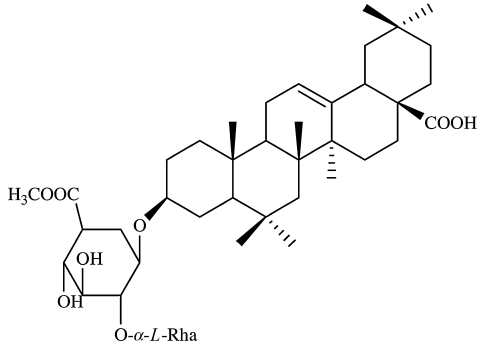

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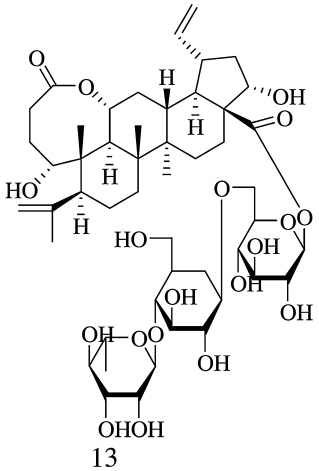

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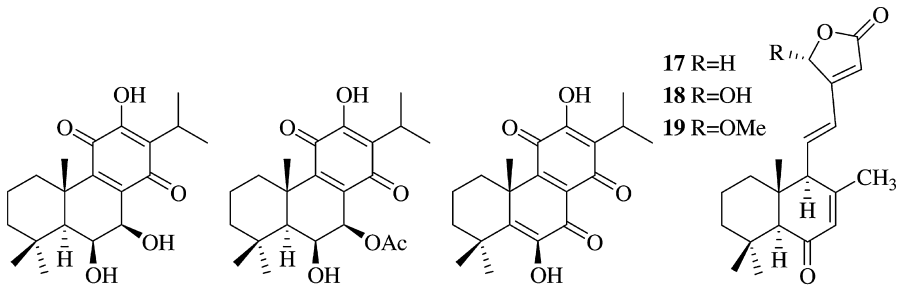

14 15 16 17, 18, 19

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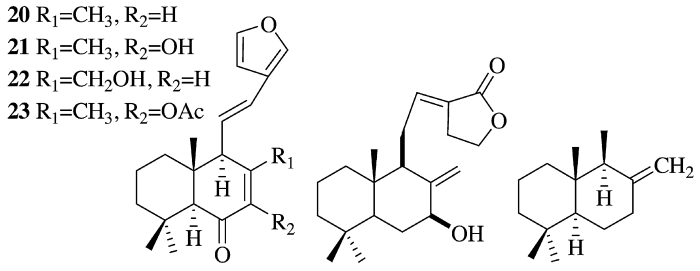
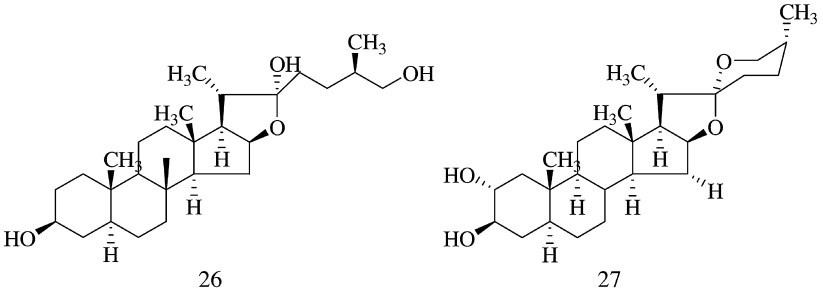
18 R=OH
19 R=OMe



20 R_1=CH_3, R_2=H
21 R_1=CH_3, R_2=OH
22 R_1=CH_2OH, R_2=H
23 R_1=CH_3, R_2=OAc

20, 21, 22, 23 24 25



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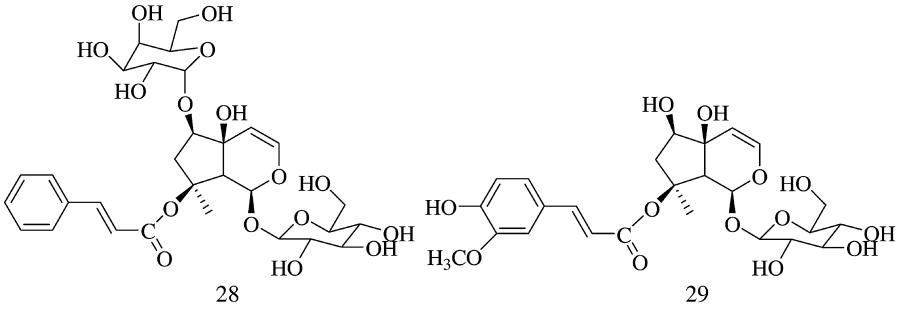

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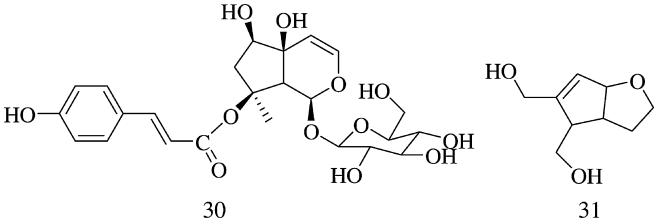

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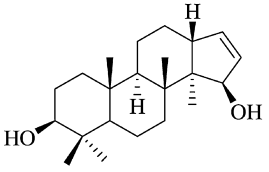

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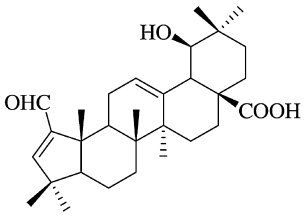

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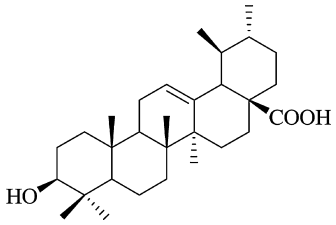

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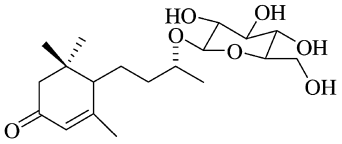

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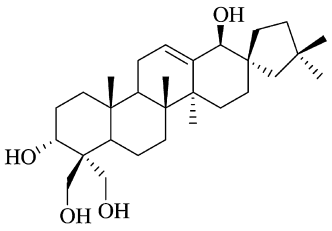

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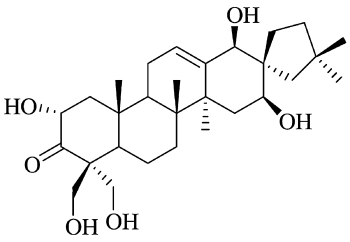

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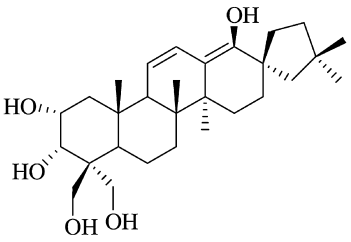

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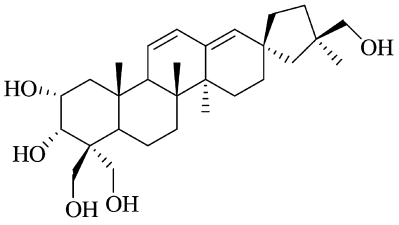

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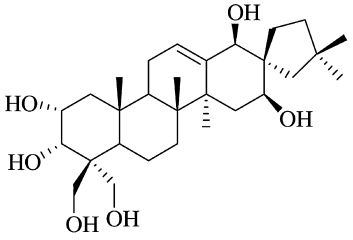

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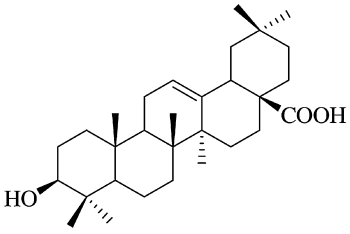

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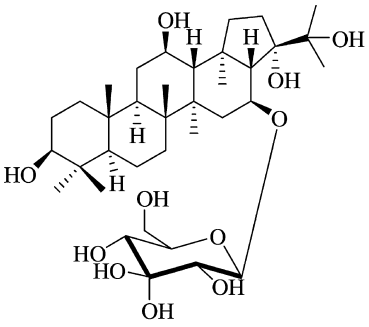

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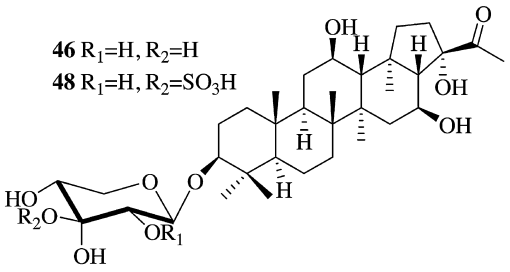
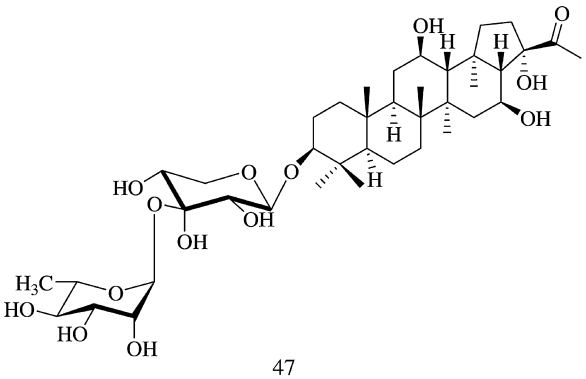


46 R_1=H, R_2=H
48 R_1=H, R_2=SO_3H

46, 48



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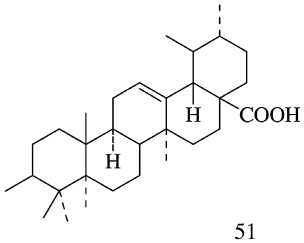

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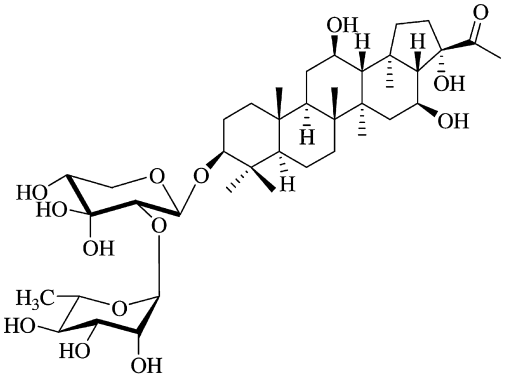

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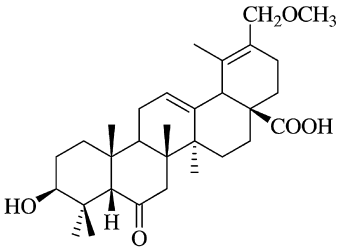

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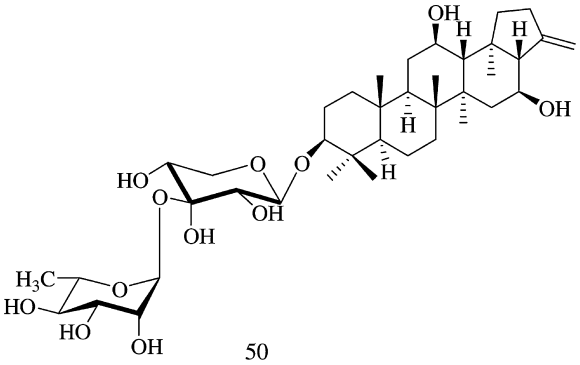

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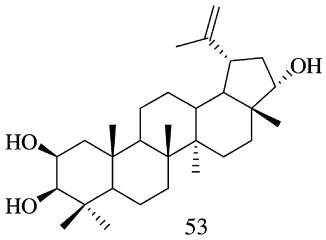

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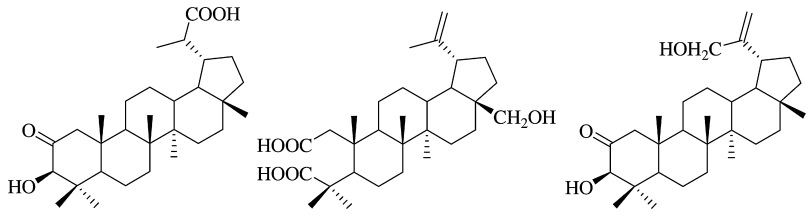
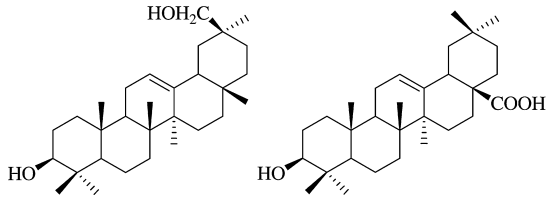
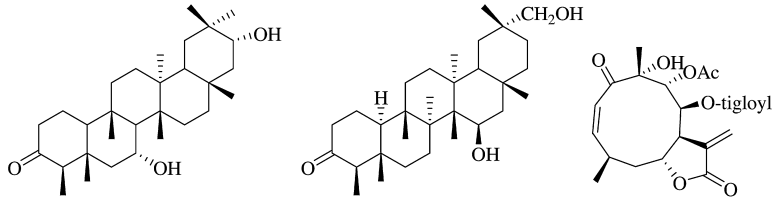






2.3. Alkaloids

Herein, we present a total of 37 alkaloids, which have been tested for α-glucosidase inhibitory activity. Two compounds 62–63 were isolated from the methanol extract of the leaves of *Adhatoda vasica* Nees (Acanthaceae). Both these compounds potently inhibited rat intestinal α-glucosidase activity (IC_{50} = 125 and 250 μmol/L, respectively), and they were both competitive inhibitors (K_i = 82 and 183 μmol/L, respectively) [19]. Another ten compounds were isolated from Campanulaceae *Lobelia* species. Among them, compound 64 was isolated from the methanol extract of *Lobelia sessilifolia* and compounds 65–73 isolated from *Adenophora* were homonojirimycin analogs. Compounds 64–66, 69, and 70 showed inhibitory activity to a certain degree toward mouse α-glucosidase, rat sucrase, maltase, and isomaltase, and among them, compounds 64 and 70 exhibited the best inhibitory activity. The IC_{50} values of all the compounds were lower than 10 μmol/L. Compounds 67–68 showed strong inhibitory activity toward glucosidase present in coffee (IC_{50} = 6.4 and 0.71 μmol/L) [20].

The strong α-glucosidase inhibitors deoxynojirimycin (DNJ) (72) and (2*R*,3*R*,4*R*,5*R*)2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP) (73) were isolated from many plants such as *Adenophora* [20,21], *Moraceae* [22,23], *Commelina communis* L. [23,24], and *Hyacinthus orientalis* [23]. Pharmacological activity studies have determined that DNJ in addition to causing lowering of blood sugar level, also possesses antiviral and other important biological activities; however its glucosidase inhibitory activity is particularly dominant. DNJ has been approved clinically for treating diabetic nephropathy and has been recognized internationally as the only zero harm antidiabetic agent currently available in the market.

Three alkaloids named piperumbellactams A–C (74–76), isolated from the branches of *Piper umbellatum*, showed moderate α-glucosidase inhibition with reported IC_{50} values—98.07 ± 0.44, 43.80 ± 0.56, and 29.64 ± 0.46 μmol/L, respectively [25].

Three acridones (77–79), isolated from the stem and bark of *Oriciopsis glaberrima* ENGL, showed potent inhibitory activity against α-glucosidase (IC_{50} = 56 ± 5.4, 34.05 ± 17, and 17 ± 1 μmol/L, respectively) [26].

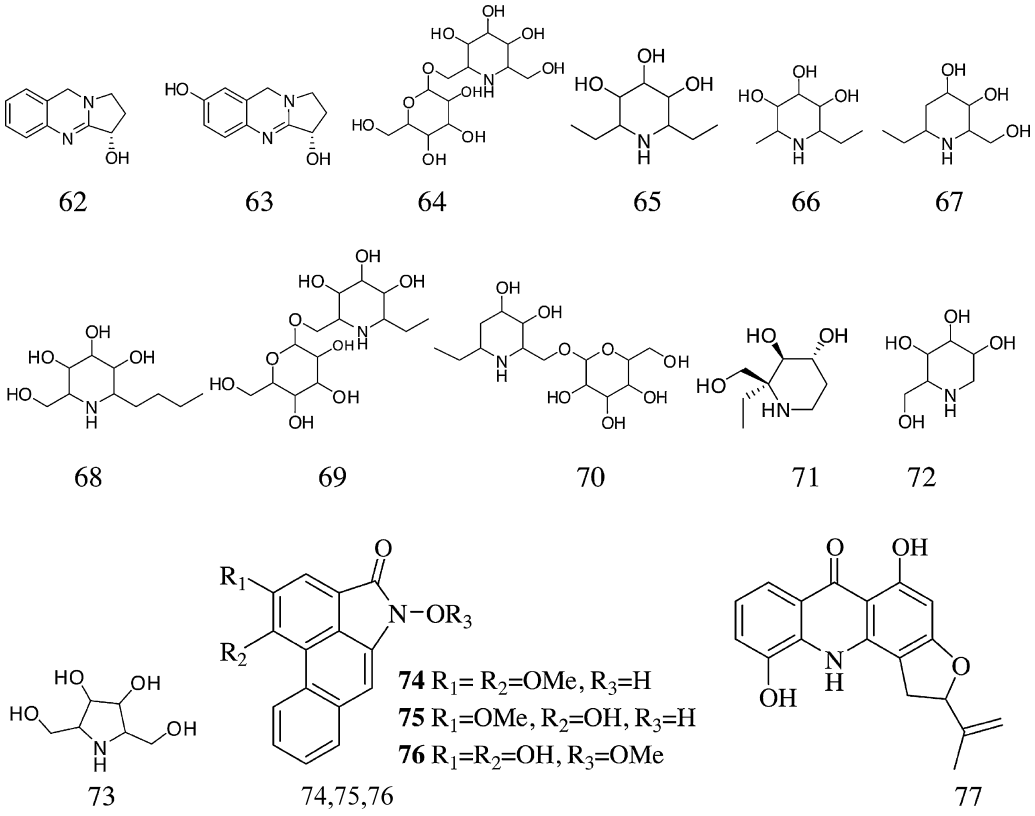
Compound 80, isolated from the ethanol extract of *Buthus martensii* Karsch, showed potent inhibitory activity against α-glucosidase with an IC_{50} value of 24 μmol/L. A Lineweaver–Burk plot indicated uncompetitive mechanism of inhibition (K_i = 16.1 μmol/L) [27].

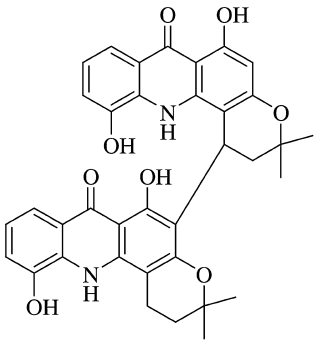
Two new phenylpropanoyl amides, namely chaplupyrrolidones A (81) and B (82), were isolated from the leaf extract of *Piper sarmentosum*. Compound 82 (IC_{50} = 430 μmol/L) revealed strong potent α-glucosidase inhibitory activity and was 18-fold more active than its demethylated congener 81 (IC_{50} = 7820 μmol/L). Kinetic evaluation studies indicated that 82 inhibited α-glucosidase in a non-competitive manner (K_i = 1.04 mmol/L) [28].

Two new dimeric carbazole alkaloids, i.e., bisgerayafoline D (83) and bismahanimbinol (84), along with four known alkaloids, i.e., bispyrayafoline (85), *O*-methyl mahanine (86), *O*-methyl mukonal (87), and mahanine (88), were obtained from the fruit pulp of *Murraya koenigii*. Compounds 83–88 ($IC_{50} = 38.7 \pm 0.4$, 51.3 ± 0.3, 29.1 ± 0.2, 46.1 ± 0.3, 77.5 ± 0.5, and 21.4 ± 0.4 μmol/L, respectively) showed moderate α-glucosidase inhibitory activity compared with acarbose ($IC_{50} = 15.2 \pm 0.6$ μmol/L) [29].

Four pyrole alkaloids, i.e., plicatanins A–D (89–92, respectively), were isolated from *Chrozophora plicata*, and showed inhibitory activity against yeast α-glucosidase with IC_{50} values—202.3 ± 0.33, 178.62 ± 0.78, 27.85 ± 0.75, and 57.15 ± 0.44 μmol/L, respectively; compound 91 showed the strongest inhibitory activity, which was stronger than that of acarbose ($IC_{50} = 38.25 \pm 0.12$ μmol/L) [30].

Six alkaloids, namely 1-DNJ (93), fagomine (94), cytidine (95), 2-(1′,2′,3′,4′-tetrahydroxybutyl)-5-(2″,3″,4″-trihydroxybutyl)-pyrazine (96), 2-(1′,2′,3′,4′-tetrahydroxybutyl)-6-(2″,3″,4″-trihydroxybutyl)-pyrazine (97), and 2-(1′,2′,3′,4′-tetrahydroxybutyl)-5-(1″,2″,3″,4″-tetrahydroxybutyl)-pyrazine (98), were isolated from the leaves of *Morus atropurpurea*. The six compounds ($IC_{50} = 40.0$, 65.0, 2.5, 1.9, 2.0, and 7.2 mmol/L, respectively) displayed potential inhibitory activity against α-glucosidase. The inhibitory potency of compounds 95–98 was stronger than that of acarbose ($IC_{50} = 9.25$ mmol/L) [31].





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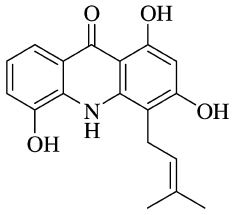

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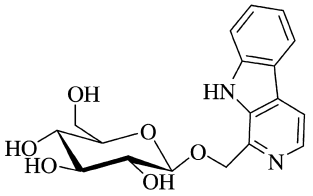

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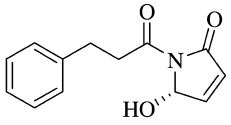

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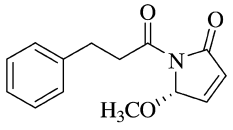

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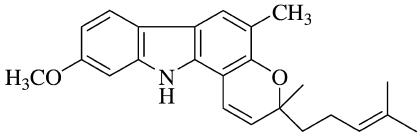

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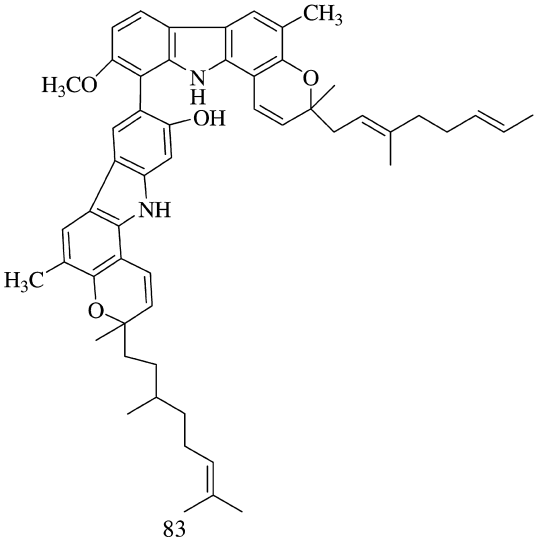

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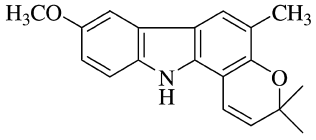

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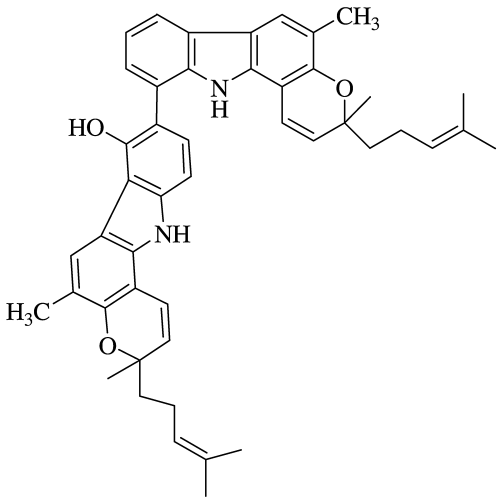

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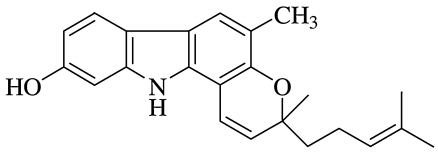

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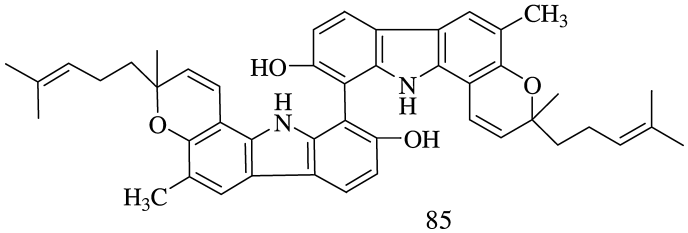

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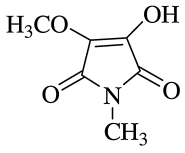

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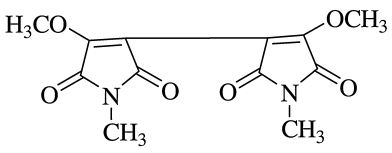

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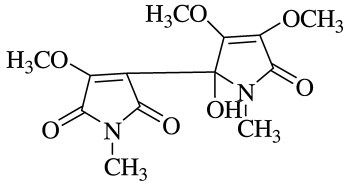

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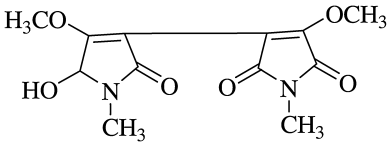

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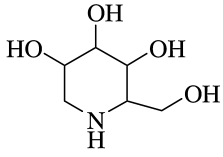

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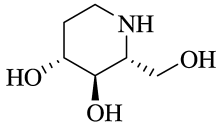

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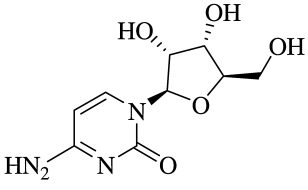

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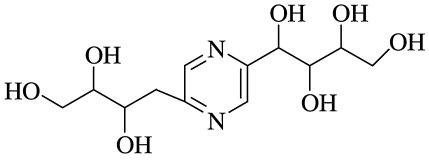

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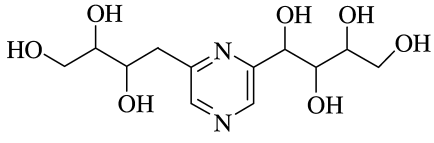

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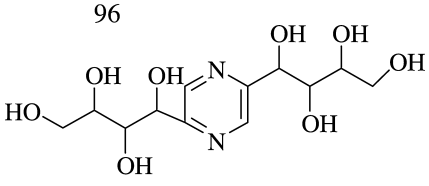


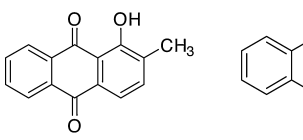
98

2.4. Quinones

A total of 49 quinones isolated from plants are presented. Eight quinones (99–106) inhibited the activity of α-glucosidase; seven of these compounds were anthraxquinones. Compounds 99–101, isolated from the rhizome extract of *Rubia cordifolia* L., showed high inhibitory activity. Furthermore, compounds 99 and 100 showed competitive inhibition (K_i = 25.0 and 11.26 μg/mL, respectively), but compound 101 showed a non-competitive inhibitory profile (K_i = 3.33 μg/mL) [32]. Four compounds (103–106) were isolated from Himalayan rhubarb *Rheum emodi* by Indian researchers. These quinones showed inhibitory activity against yeast as well as mammalian α-glucosidase; compound 106 showed the strongest inhibitory activity [33]. Compound 102 was obtained from the methanolic extract of *F. tessmannii* (IC_{50} = 900 μmol/L) [5].

Seven new xanthone glycosides (107–113) were isolated from the *n*-butanol extract of *Swertia bimaculata* along with six known compounds (114–119). Compounds 109, 110, and 113 exhibited more potent α-glucosidase inhibitory activity (IC_{50} = 142 ± 17, 136 ± 14, and 258 ± 19 μmol/L, respectively) compared with acarbose (IC_{50} = 426 ± 45 μmol/L). Compounds 107, 111, 112, 115, and 117–119 weakly inhibited α-glucosidase activity (IC_{50} = 442 ± 47, 417 ± 32, 478 ± 32, 578 ± 39, 389 ± 23, 765 ± 54, and 679 ± 58 μmol/L, respectively) compared with acarbose. The IC_{50} values of compounds 108, 114, and 116 were more than 1000 μmol/L [34].

Two new xanthones, 1,8-dihydroxy-3-methoxy-xanthone 7-*O*-[α-*L*-rhamnopyranosyl(1→2)-β-*D*-glucopyranoside] (120) and 1,8-dihydroxy-3-methoxyxanthone 7-*O*-[α-*L*-rhamnopyranosyl (1→3)-α-*L*-rhamno-pyranosyl (1→2)-β-*D*-xylo-pyranoside] (121), together with 26 known xanthones (122–147) were isolated from the aqueous ethanol extract of the traditional Chinese herb *Swertia mussotii*. Compounds 120–121, 124–130, and 133–147 (IC_{50} = 75.8 ± 1.3, 84.5 ± 1.2, 133.7 ± 3.0, 394.9 ± 2.0, 115.0 ± 2.4, 83.8 ± 1.2, 31.1 ± 0.2, 13.0 ± 0.2, 140.4 ± 0.8, 5.42 ± 0.07, 107.8 ± 0.1, 142.1 ± 0.2, 30.6 ± 0.1, 5.3 ± 0.1, 77.4 ± 0.1, 65.8 ± 0.1, 71.2 ± 0.2, 17.6 ± 0.1, 31.8 ± 0.1, 7.09 ± 0.08, 18.0 ± 0.1, 82.2 ± 0.2, 40.1 ± 0.1, and 75.8 ± 0.11 μmol/L, respectively) had moderate α-glucosidase inhibitory activity compared with acarbose (IC_{50} = 39.6 ± 0.1 μmol/L). Compounds 122–123 and 131–132 had weak α-glucosidase inhibitiory activity (IC_{50} > 500 μmol/L). The results indicated that compound 137 was the best inhibitor of the lot, while the *O*-glycosylated xanthones were poor α-glycosidase inhibitors [35].



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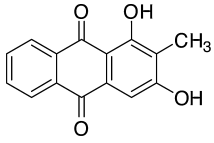

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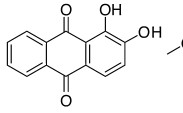

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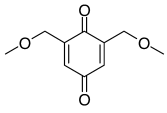

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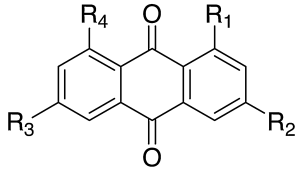
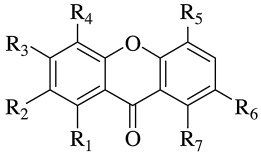
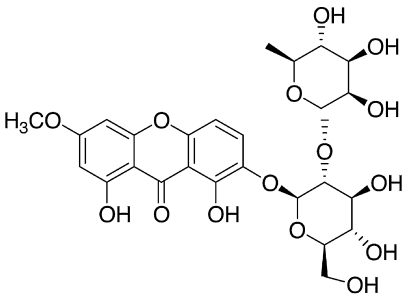


103 R_1=OH, R_2=Me, R_3=H, R_4=OH
104 R_1=OH, R_2=Me, R_3=OMe, R_4=OH
105 R_1=OH, R_2=Me, R_3=OH, R_4=OH
106 R_1=OH, R_2=Me, R_3=H, R_4=*O*-β-*D*-glucopyranoside

103, 104, 105, 106



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
107	O-glc(6-1)-xyl	OMe	OMe	OMe	OMe	H	OH
108	OH	OMe	OMe	OMe	OMe	H	O-glc(6-1)-xyl
109	O-glc(6-1)-xyl	H	OMe	OMe	OMe	H	OH
110	OH	H	OMe	OMe	OMe	H	OH
111	O-glc(6-1)-xyl	H	OH	OMe	OMe	H	OH
112	O-glc(6-1)-glc	H	OH	OMe	OMe	H	OH
113	O-glc(4-1)-glc	H	OH	OMe	OMe	H	OH
114	OH	H	O-glc	OMe	OMe	H	H
115	O-glc	H	OH	OMe	OMe	H	OH
116	OH	H	O-glc	H	OMe	H	OH
117	OH	H	OMe	H	OH	H	O-glc
118	OH	H	OMe	H	H	O-xyl(2-1)-rha	OH
119	OH	H	OH	H	OH	H	O-glc



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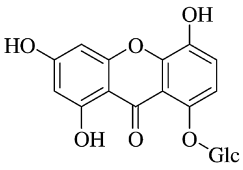

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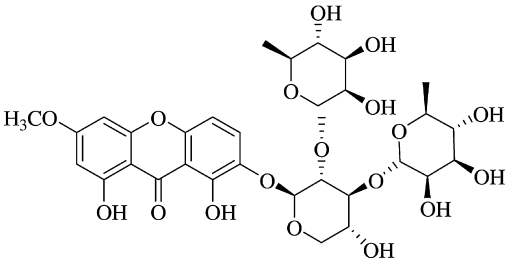

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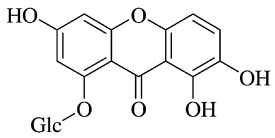

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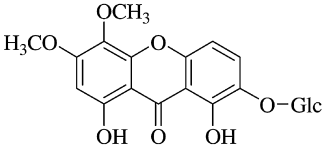

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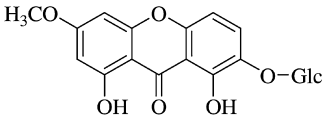

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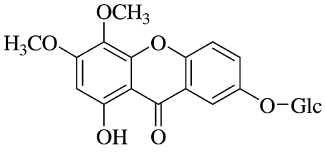

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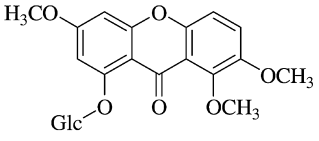

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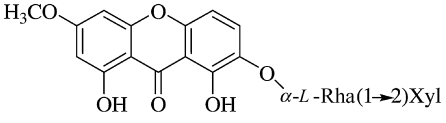

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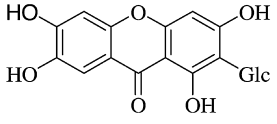

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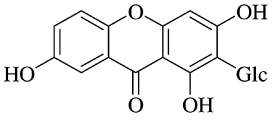

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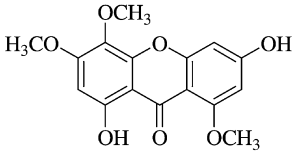

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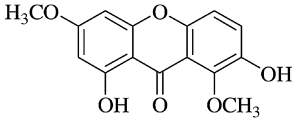

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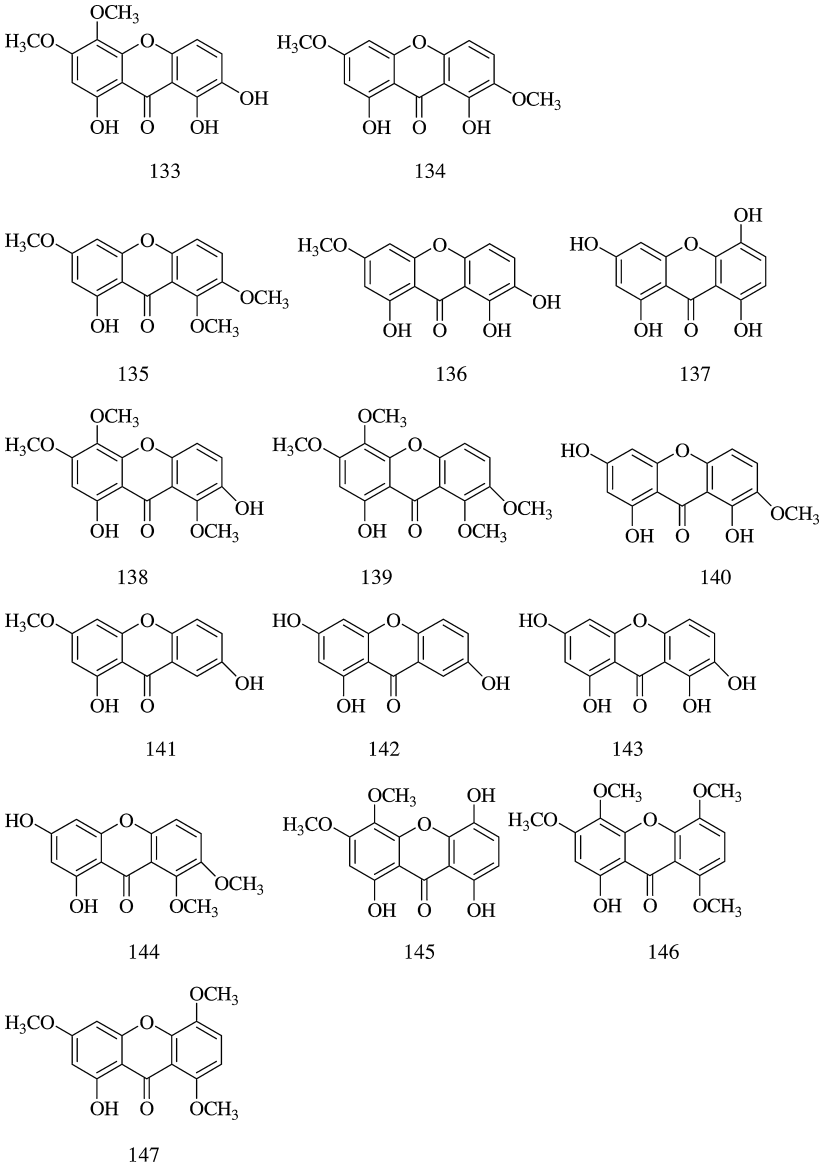


2.5. Flavonoids

Flavonoids are widely distributed in plants and therapeutically they have shown great promise as anticancer, antiviral, antioxidant, antibacterial, and anti-inflammatory agents. Recent studies have determined that flavonoid compounds can be very effective in inhibiting α-glucosidase activity [36]. A total of 103 flavonoids reported in the literature showed glycosidase inhibitory activity; these include xanthones, flavanones, flavans, anthocyamins, chalcones, and other structural motifs.

Aloeresin A (148) isolated from the methanol extract of Chinese aloes demonstrated significant α-glucosidase inhibitory activity (IC_{50} = 11.94 and 2.16 mmol/L) against rat intestinal sucrase and maltase, respectively [37]. Two acylated flavonoids 149 and 150 were isolated from *Machilus philippinensis* and demonstrated IC_{50} values of 6.10 and 1.00 μmol/L against *B. stearothermophilus* type IV α-glucosidase, respectively [38].

Xanthones (151–158) isolated from the root of *Cudrania tricuspidata* possessed highly potent α-glucosidase inhibition properties with IC_{50} values less than 100 μmol/L for most compounds. Mechanistic analysis showed that xanthones adopted mixed inhibition strategy (K_i = 31.7, 8.9, 7.4, 5.8, 15.7, 7.0, and 12.4 μmol/L). Structure–activity relationship (SAR) studies have determined that alkylation at C-4 can reduce their inhibitory potential [39]. Two xanthones (159–160) (IC_{50} = 96.1 and 158 μg/mL, respectively), isolated from the aqueous extract of *Anemarrhenae Rhizoma*, showed far lower inhibitory effects on mouse intestinal α-glucosidase than acarbose (IC_{50} = 2.39 μg/mL) [40].

Thirteen compounds (161–173) could inhibit yeast α-glucosidase. Among them, the IC_{50} values of 161–168 were lower than 50 μmol/L (IC_{50} = 8, 4, 8, 20, 20, 30, 40, and 50 μmol/L, respectively). Inhibition kinetic studies on compounds 161, 163, 164, 167,

and 168 determined that they tend to follow mixed inhibition kinetics with inhibitory strategy adopted more toward non-competitive inhibitors (K_i = 6.2, 3.2, 13.0, 47.0, and 41.0 μmol/L, respectively) [41].

Quercetin (161) isolated from the aqueous extract of *Matricaria recutita* L. [40,42], the leaf extracts of *Eucommia ulmoides* [43], and *Forsythia suspensa* (Thunb) Vahl. [44] have been reported to possess high inhibitory effects against glucosidase. The IC_{50} values against yeast α-glucosidase, rat intestinal sucrose, and amylase were 8.86 μg/mL [44], 216 μmol/L, and 71 μmol/L [42], respectively; the K_i value against yeast α-glucosidase was 8.5 μmol/L [43].

Genistein (174) was an isoflavone, which is a well-known constituent of soybean. Recently, it has also been isolated from the fermentation broths of *Streptomyces* sp. and was shown to be a reversible, slow binding, and non-competitive inhibitor of yeast glucosidase with a K_i value of 0.057 μmol/L and IC_{50} value of 50 μmol/L [45].

Two potent compounds, i.e., apigenin (175) and luteolin (176), were isolated from hot water extract of *M. recutita* L. The inhibitory percentages reported for rat intestinal maltase were 18.0% and 24.3%, respectively, and that reported for rat intestinal sucrase were 35.3% and 14.9%, respectively [42].

Isoquercitrin (177), swertisin (178), vitexin (179), and isorhamnetin-3-*O*-rutinoside (180) showed high inhibitory activity against α-glucosidase obtained from rat intestine. Their IC_{50} values were 0.24, 0.37, 0.42, and 0.51 mmol/L, respectively [24]. Eleven flavonoid glycosides (181–187) with α-glucosidase inhibitory activity were identified from the aerial parts of *C. ommunis*.

Four flavonoids, including a flavonoid glycoside (188) and two flavan compounds (189–190) besides quercetin (161), isolated from the *E. ulmoide*s leaf extract showed inhibitory activity against α-glucosidase from yeast, and the IC_{50} for both 188 and 189 was 0.25 μmol/L [43].

Three flavonoids (191–193), isolated from *Derris scandens* Benth, showed strong rat intestinal α-glucosidase inhibitory activity (IC_{50} = 45.17, 34.74, and 33.93 μg/mL respectively) [46]. Compounds 194 and 195 found from the rhizome extract of Himalayan rhubarb *R. emodi* displayed inhibitory activity against mild yeast and mammalian intestinal α-glucosidase [33]. Researchers from Japan reported that a quercetin glycoside (196) from the leaves of Devil tree (*Alstonia scholaris*) exhibited inhibitory potency against sucrase and maltase with IC_{50} values = 17.2 and 1.96 mmol/L, respectively [47].

Seven triprenylated flavonols (197–203), isolated from the roots of *Dorstenia psilurus*, exhibited high inhibitory activity against α-glucosidase. Compound 197, with three unmodified prenyl groups, was the most active (IC_{50} = 4.13 mM), while compound 202, with only one unmodified prenyl group, was the least active (IC_{50} = 43.95 μmol/L). Thus, we may infer that α-glucosidase inhibitory activity increases with the increase in the number of prenyl groups in the structure [22].

Green tea is rich in flavonol compounds—mostly catechins. Recently, Italian scholar Alessandra Gamberucci has revisited these compounds for evaluating their enzyme inhibitory activities with a view to develop these compounds as a potential antidiabetic and antiviral agents. He used 4-methylumbelliferyl glucoside and 4-nitrophenyl glucoside as substrates to investigate the effects of tea polyphenols (204–208) on glucosidase II activity in rat liver microsomes and found that all of them showed potent enzyme inhibitory activity. Compound GCG (204) showed the strongest inhibitory activity (IC_{50} = 3.702 μmol/L, K_i = 2.545 μmol/L), which was almost similar to the inhibitory activity of a widely used glucosidase inhibitor *N*-butyldeoxynojirimycin (NBDJ) (IC_{50} = 3.268 μmol/L, K_i = 2.247 μmol/L). Moreover, the mechanism of inhibition was concentration dependent and non-competitive in nature. In addition, the IC_{50} and K_i values of the compounds 199–202 and 205–208 with similar structure as that of GCG were less than 100 μmol/L, and thus could be regarded as strong glucosidase inhibitors [48]. Two compounds 209–210 with catechin structure were isolated from Nepalese medicinal herb Pakhanbhed (*Bergenia ciliata*, Haw.) and showed inhibitory activity against rat intestinal sucrase and maltase [49]. Much lately, (+)-catechin (211), (−)-epicatechin (212), and two procyanidin (213–214) isolated from *Toona sinensis* (Meliaceae) showed high α-glucosidase inhibitory activity (IC_{50} = 190.7, 189.0, 111.0, and 89.0 μmol/L, respectively) [50].

Seven flavonoids were isolated from the ethylacetate and water layer fractions of the entire plant *Crossostephium chinense* (L.). Five out of the seven compounds (215–219) had inhibitory activity against α-glucosidase (IC_{50} = 146.28 ± 12.44, 246.26 ± 8.73, 74.06 ± 3.83, 42.19 ± 5.25, and 136.20 ± 25.73 μmol/L, respectively) compared with acarbose (IC_{50} = 489.25 ± 38.55 μmol/L). Their inhibition kinetic data indicated competitive inhibition [51].

(+)-Afzelechin (220) isolated from the Rhizomes of *Bergenia ligulata* showed an ID_{50} (50% inhibition dose) value of 0.13 μmol/L [52]. Compounds 221–223 (IC_{50} = 56.06 ± 2.56, 32.21 ± 1.38, and 20.50 ± 1.62 μmol/L, respectively) were isolated from the methanol extracts of the air-dried roots of *Ferula mongolica* and exhibited significant α-glucosidase inhibitory activity [53].

Three known compounds, quercetin-3,6,7-trimethyl ether (224), isovitexin-4′-methyl ether (225), isovitexin (226), and a new compound acaetin-6-C-(6″-acetyl-β-*D*-glucopyranoside)-8-C-α-*L*-arabinopyranoside (227), were obtained from *Achillea fragrantissima*. Among them, compound 227 (IC_{50} = 1.5 ± 0.09 mg/mL) exhibited the highest α-glucosidase inhibitory activity in a concentration-dependent manner, followed by compound 224 (IC_{50} = 14.5 ± 0.89 mg/mL). The potent inhibitory activity of compound 227 may be attributed to the presence of two sugar residues; a di-glycoside is supposed to exert stronger competitive inhibitory action against the target enzyme. However, compounds 225 and 226 (IC_{50} = 83.57 ± 0.59 and 34.37 ± 1.09 mg/mL, respectively) were relatively less active. All the tested compounds were more potent than acarbose (224 ± 2.31 mg/mL) [54].

Acacetin (228) and quercetin (161) isolated from the aerial parts of *B. cavanillesii* significantly inhibited yeast α-glucosidase activity (IC_{50} = 0.16 and 0.53 mmol/L, respectively, vs. 1.7 mmol/L for acarbose). Kinetic analysis revealed that compound 228 behaved as a mixed-type inhibitor with a K_i value of 0.41 mmol/L [18].

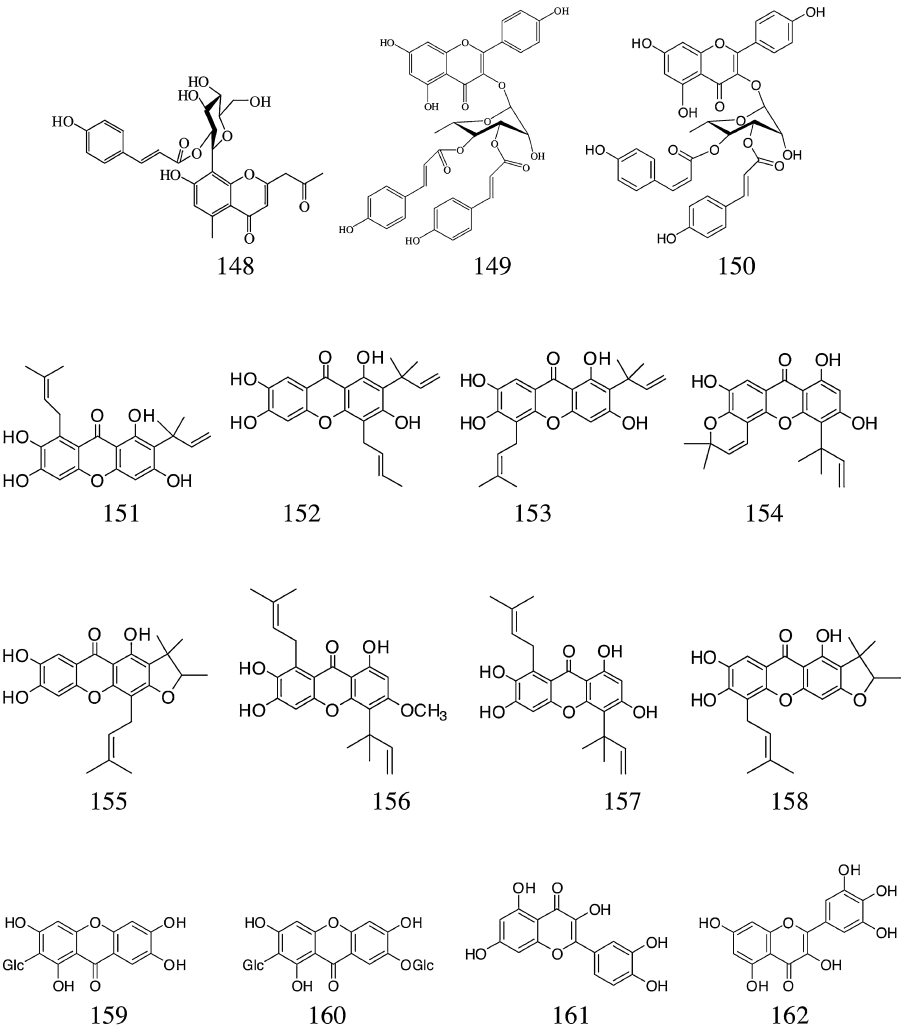
Four new compounds, i.e., aquilarisinin (229), aquilarisin (230), hypolaetin 5-*O*-*β*-*D*-glucuronopyranoside (231), and aquilarixanthone (232) (IC_{50} = 273.7 ± 39.8, 634.7 ± 45.7, 298.9 ± 27.9, and 678.1 ± 137.4 μmol/L, respectively), and four known compounds, i.e., mangiferin (233), iriflophenone 2-*O*-*α*-*L*-rhamnopyranoside (234), iriflophenone 3-C-*β*-*D*-glucoside (235), and iriflophenone 3,5-C-*β*-*D*-diglucopyranoside (236) (IC_{50} = 299.7 ± 42.3, 366.7 ± 27.0, 404.7 ± 27.7, and 454.4 ± 24.0 μmol/L, respectively), were isolated from 70% aqueous ethanolic leaf extracts of *Aquilaria sinensis* (Lour.) Gilg b. and showed more significant *α*-glucosidase inhibitory activity than acarbose (IC_{50} = 576.2 ± 58.5 μmol/L) [55].

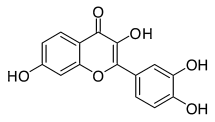
(2*R*)-3*α*,7,4′-Trihydroxy-5-methoxy-8-(*γ*,*γ*-dimethylallyl)-flavanone (237), isoxanthohumol (238), norkurarinone (239), kurarinone (240), (2*S*)-2′-methoxy-kurarinone (241), kushenol T (242), norkurarinol (243), kuraridin (244), and formononetin (245) isolated from the dried stem and bark of *Sophora flavescens* had moderate but less significant *α*-glucosidase inhibitory effects (IC_{50} = 107.8 ± 5.7, 86.9 ± 6.1, 17.7 ± 2.6, 14.5 ± 1.3, 14.0 ± 1.2, 16.7 ± 2.1, 18.0 ± 1.5, 3.6 ± 0.8, and 119.6 ± 9.4 μmol/L, respectively) than acarbose (IC_{50} = 2.9 ± 0.2 μmol/L) [56].

Three flavonoid glycosides vitexin (246), isovitexin (184), and isorhamnetin 3-*O*-*β*-*D*-rutinoside (180) obtained from *Microctis folium* exerted satisfactory *α*-glucosidase inhibitory effects (IC_{50} = 244.0, 266.2, and 275.4 μmol/L, respectively) compared with acarbose (IC_{50} = 1007 μmol/L) [57].

Two flavonoid compounds plicatanoside (247) and apigenin-5-*O*-*β*-*D*-glucopyranoside (248), isolated from *C. plicata*, showed inhibitory activity against yeast *α*-glucosidase (IC_{50} = 111.23 ± 0.65 and 287.12 ± 0.75 μmol/L, respectively), but the inhibition is not as strong as that of acarbose (IC_{50} = 38.25 ± 0.12 μmol/L) [30].

Coryfolin (249) and daidzein (250) isolated from *Psoralea corylifolia* displayed slightly weaker *α*-glucosidase inhibitory activity (IC_{50} = 45.73 and 49.44 mmol/L, respectively) than acarbose (IC_{50} = 38.25 ± 0.12 mmol/L) [58].

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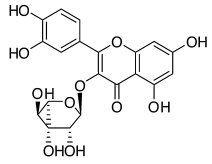
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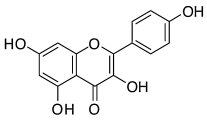
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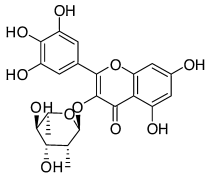
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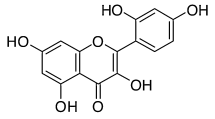
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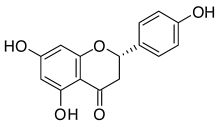
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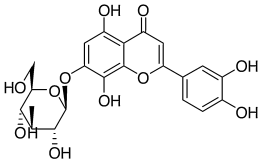
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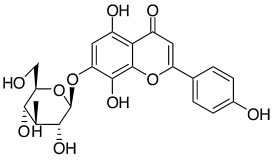
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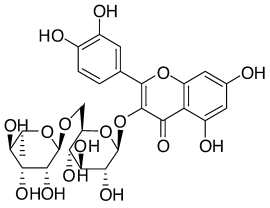
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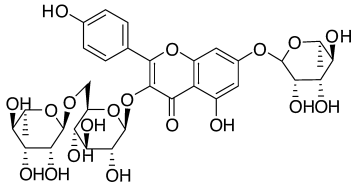
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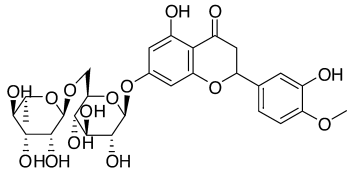
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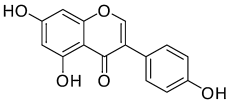
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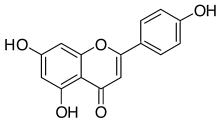
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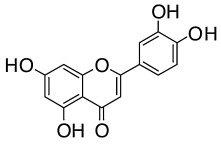
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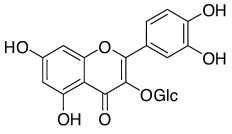
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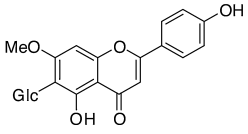
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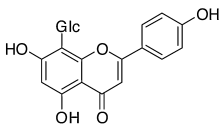
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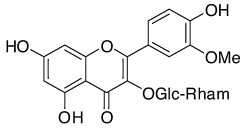
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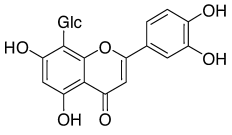
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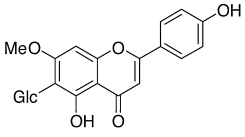
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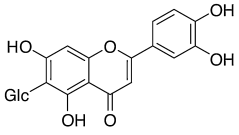
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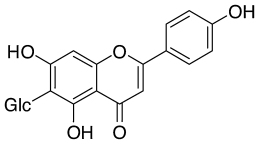
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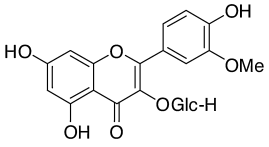
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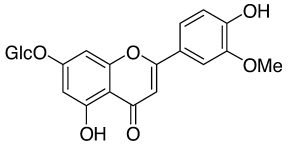
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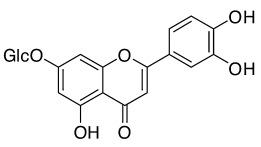
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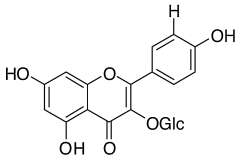

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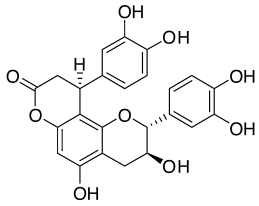

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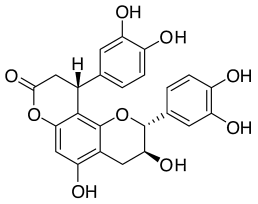

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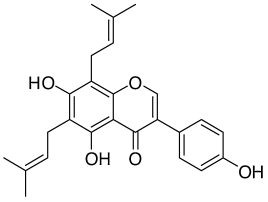

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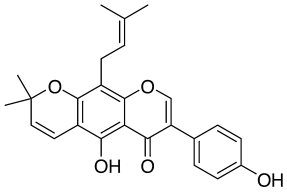

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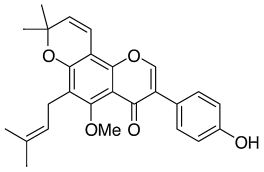

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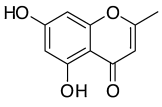

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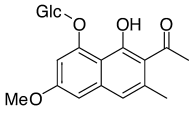

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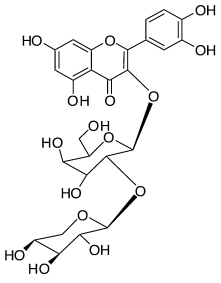

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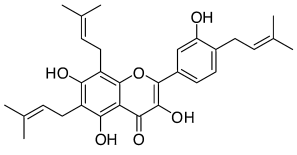

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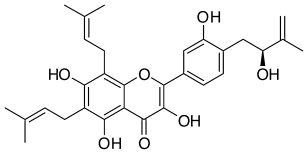

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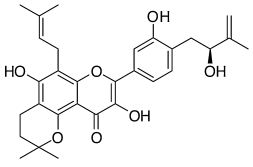

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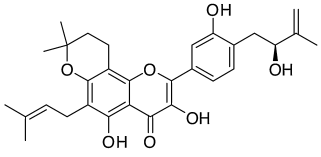

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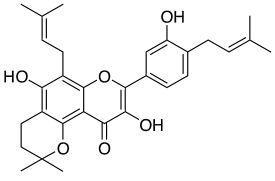

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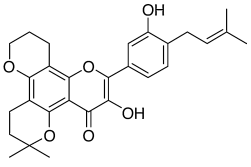

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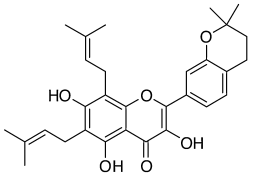

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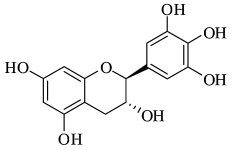

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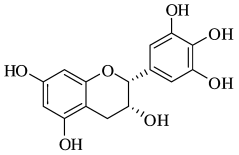

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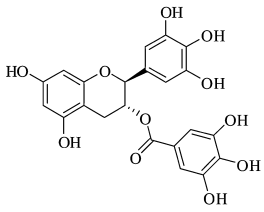

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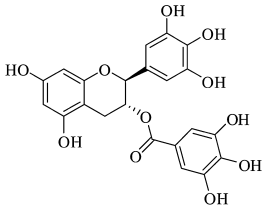

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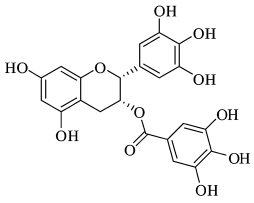

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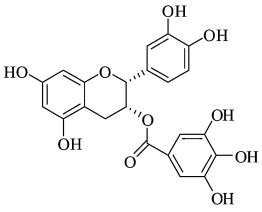

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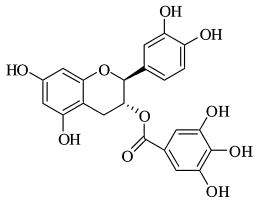

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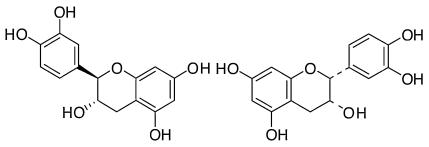
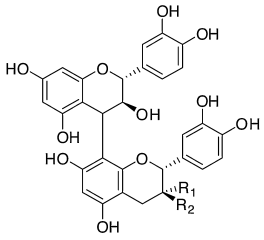
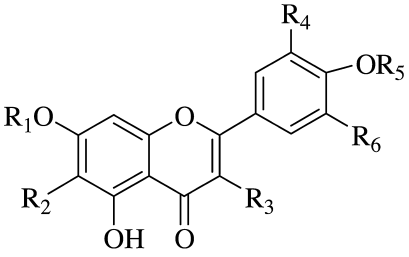


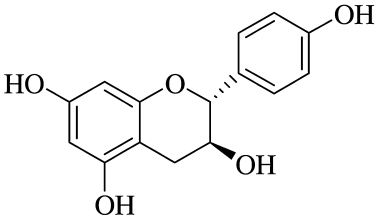
211 212



213 R_1=H, R_2=OH
214 R_1=OH, R_2=H



215 R_1=H, R_2=OMe, R_3=H, R_4=H, R_5=H, R_6=H
216 R_1 =H, R_2=H, R_3=H, R_4=OMe, R_5=H, R_6=H
217 R_1=Me, R_2=OMe, R_3=OMe, R_4=OH, R_5=H, R_6=H
218 R_1=H,R_2=H,R_3=H,R_4=OMe, R_5=H, R_6=OH
219 R_1=H,R_2=OMe, R_3=OMe, R_4=OH, R_5=H, R_6=H



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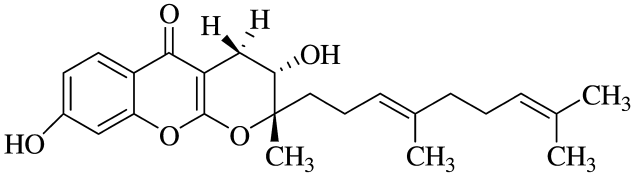

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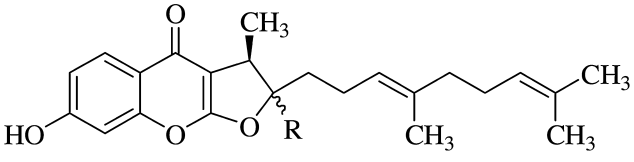
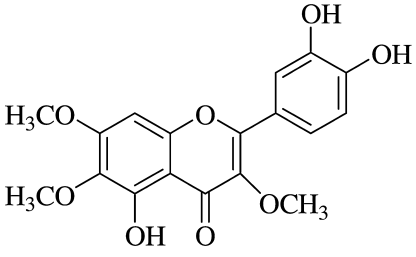


222 R=α-CH_3 , 223 R=β-CH_3



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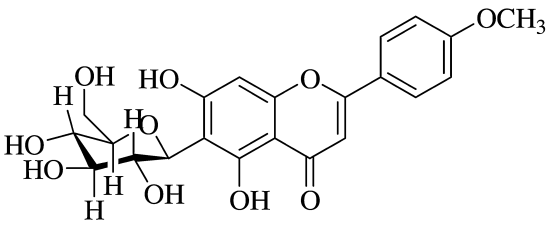

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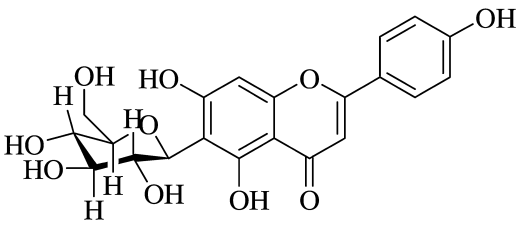

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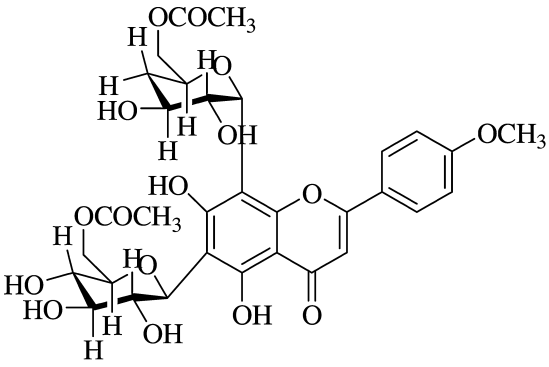

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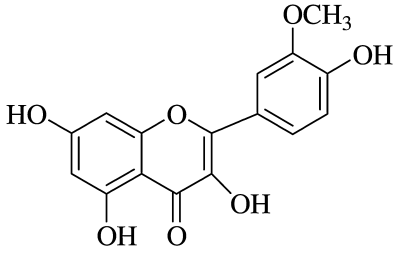

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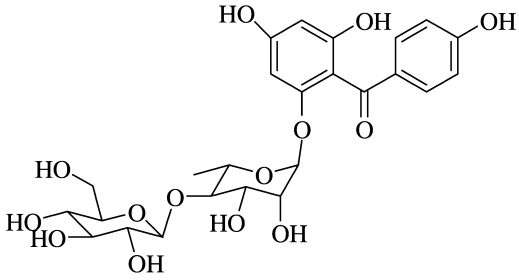

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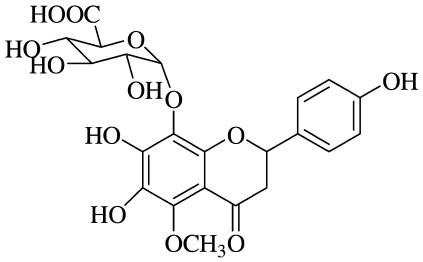

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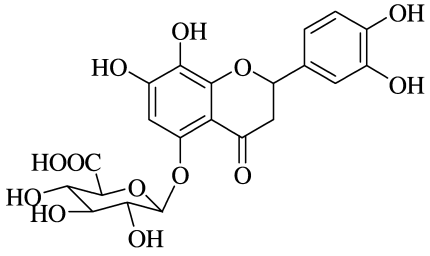

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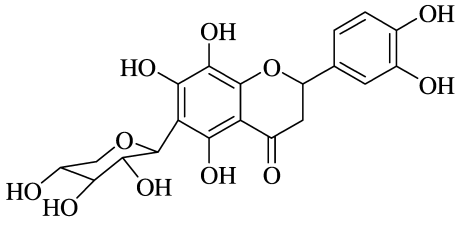

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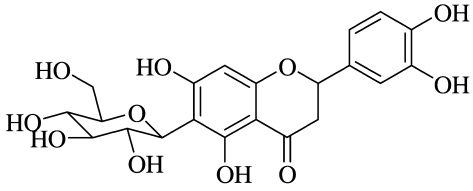

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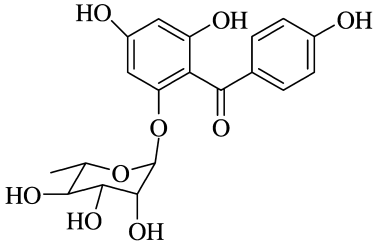

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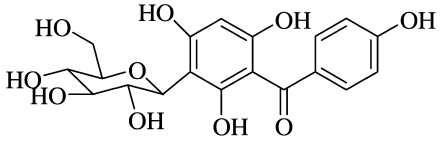

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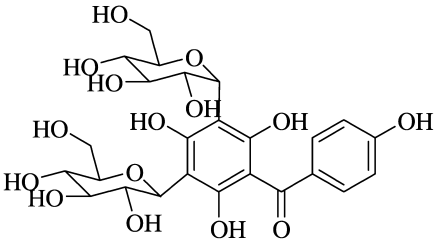

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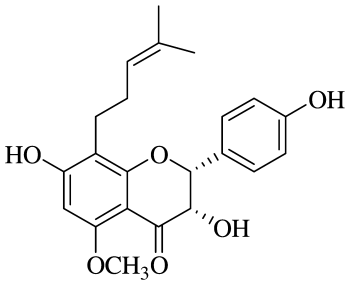

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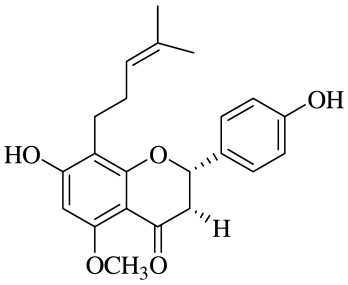

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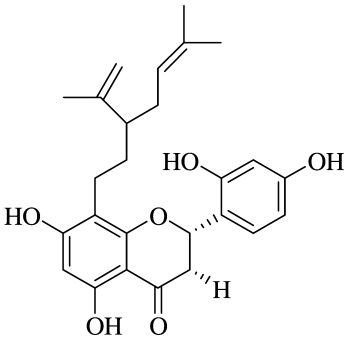

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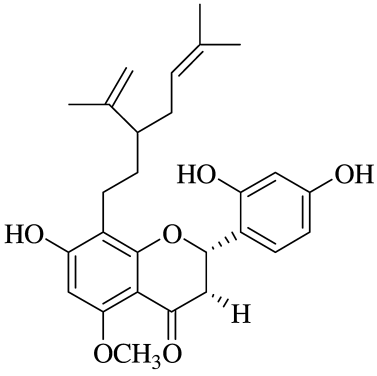

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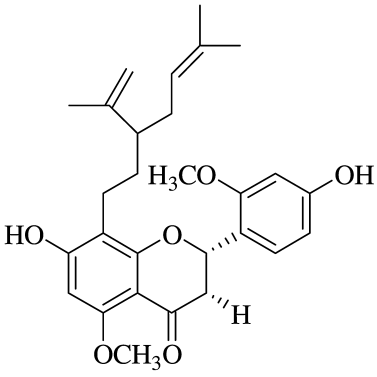

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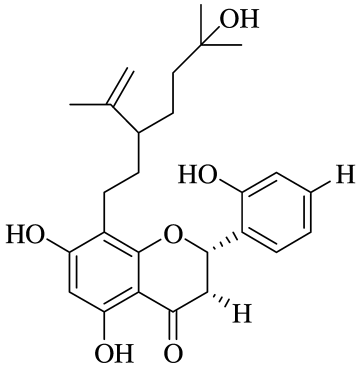

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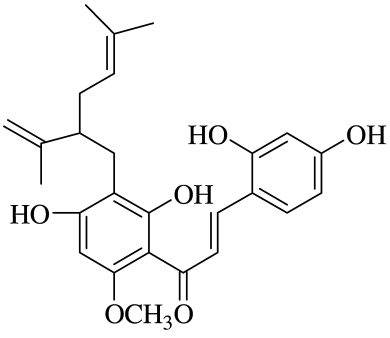

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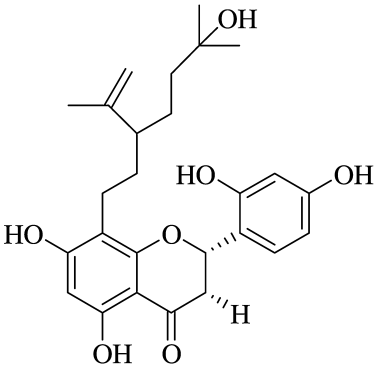

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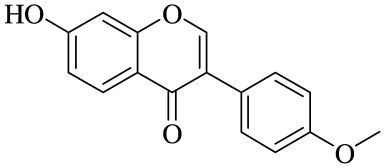

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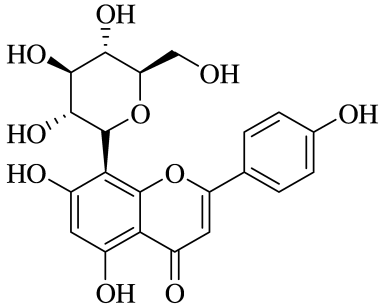

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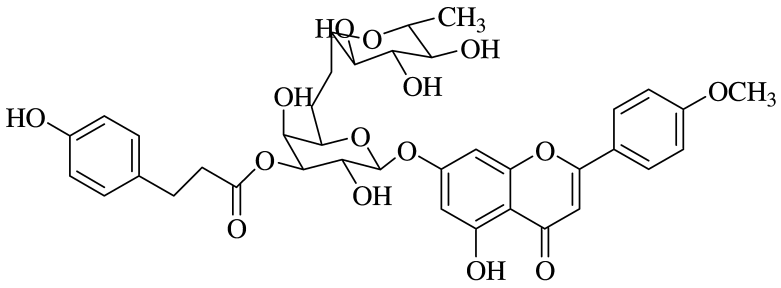

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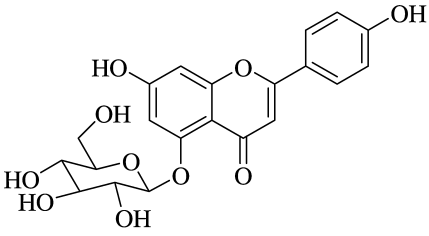

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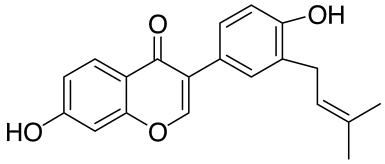

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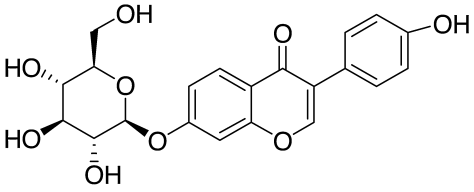


250

2.6. Phenols

Thirty-seven polyphenols from plants have shown promising α-glucosidase inhibitory activity. Gallic acid (251), an important constituent of many plants species [50,59], showed strong inhibitory activity against glucosidase both *in vitro* and *in vivo*; its IC_{50} value (24.3 μmol/L) was lower than that of acarbose (59.5 μmol/L) [50]. Moreover, methyl gallate (252) obtained from the dried stem and bark extracts of *Terminalia superb* (IC_{50} = 11.5 μmol/L) [59] and propyl gallate (253) isolated from green tea extracts (IC_{50} = 11.5 μmol/L, K_i = 43.12 μmol/L) [48] showed strong α-glucosidase inhibitory activity.

Rosmarinic acid (254) isolated from the methanol extract of *P. madagascariensis* exhibited inhibitory activity against α-glucosidase (IC_{50} = 33.0 ± 4.6 μmol/L) [9].

Three compounds trans-*N*-*p*-coumaroyltyramine (255) (IC_{50} = 0.40 μmol/L), 1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (256) (IC_{50} = 0.38 mmol/L), and 6-hydroxy-2,4,7-trimethoxyphe-nanth-rene (257) (IC_{50} = 0.77 mmol/L) isolated from the air-dried slices of fresh tuberous rhizomes of *Dioscorea opposita* showed yeast α-glucosidase inhibitory activity [60].

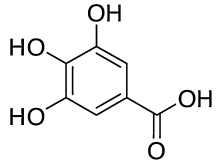
Epicatechin (EC, 258), epicatechin-(4β,8)-epicatechingallate (B 2-3′-*O*-gallate, 259), epicatechin gallate (ECG, 260), and 2-(4-hydroxyphenyl)ethyl 3,4,5-trihydroxybenzoate (HETB, 261) isolated from the roots of *Rhodiola crenulata* demonstrated significant α-glucosidase inhibitory activity (IC_{50} = 29.85 ± 2.20, 0.31 ± 0.01, 0.71 ± 0.01, and 4.77 ± 0.22 μmol/L, respectively). Compared with the known α-glucosidase inhibitor quercetin (IC_{50} = 5.30 ± 0.11 μmol/L), compounds 259–261 showed strong α-glucosidase inhibitory effect. The inhibition kinetics study indicated that 259 and 260 were mixed competitive inhibitors (K_i = 0.30 ± 0.03 and 0.21 ± 0.04 μmol/L), while 261 was a competitive inhibitor (K_i = 3.10 ± 0.09 μmol/L) [61].

Ten compounds (262–271) were isolated from the ethyl acetate extract of the edible mushroom *Sarcodon leucopus*. Of all the compounds tested, sarcoviolin β (262) showed the strongest inhibition (IC_{50} = 0.58 ± 0.01 μmol/L). Compounds 263 and 266–271 exhibited moderate inhibitory activity (IC_{50} = 1.07 ± 0.04, 3.35 ± 0.09, 3.53 ± 0.03, 6.22 ± 0.03, 3.62 ± 0.06, 4.20 ± 0.02, and 1.23 ± 0.06 μmol/L, respectively). Compounds 264–265 showed relatively weak inhibitory activity (IC_{50} = 35 ± 0.1 and 19 ± 0.1 μmol/L). The configuration at N-1β and C-2β greatly influenced the α-glucosidase inhibitory activity of sarcodonins and sarcoviolins. Compounds 262 and 271 with cis configuration at N-1β and C-2β showed stronger activity than compounds 263 and 269 with trans configuration. For the *p*-terphenyl derivatives (264–268), the number of phenolic hydroxyl groups in the structure greatly contributed to their α-glucosidase inhibitory activity [62].

Stilbene dimmers—cassigarol E (272), scirpusin A (273), and scirpusin B (274) isolated from *Cyperus rotundus* L. (Cyperaceae) rhizomes showed higher α-glucosidase inhibitory activity (IC_{50} = 210.5 ± 17.3, 168.1 ± 12.5, and 94.3 ± 6.8 μmol/L, respectively) compared with acarbose (IC_{50} = 2060 ± 97.5 μmol/L) [63].

2,3-Di-*O*-galloyl-1,5-anhydro-*D*-glucitol (275), 2,4-di-*O*-galloyl-1,5-anhydro-*D*-glucitol (276), ginnalin A (277), 3,6-di-*O*-galloyl-1,5-anhydro-*D*-glucitol (278), 2,4,6-tri-*O*-galloyl-1,5-anhydro-*D*-glucitol (279), methyl gallate (280), and 3,4-dihydroxy-5-methoxybenzoic acid methyl ester (281) were isolated from red maple (*Acer rubrum*) stems. Compounds 275, 276, 280, and 281 had weaker α-glucosidase inhibitory activity (IC_{50} = 1745.78 ± 168.05, 1221.84 ± 16.30, 317 ± 3.70, and 6541.11 ± 19.90 μmol/L, respectively) than acarbose (IC_{50} = 161.38 ± 5.5 μmol/L). Compounds 277–279 had stronger α-glucosidase inhibitory activity (IC_{50} = 95.38 ± 11.65, 88.42 ± 6.94, and 8.26 ± 0.37 μmol/L, respectively) than acarbose [64].

Six phenolic compounds—unicatannin C (282), hippomanin A (283), gemin D (284), 3,4,6-tri-*O*-galloyl-β-*D*-glucose (285), gallic acid 3-*O*-β-*D*-(6′-*O*-galloyl)-glucopyranoside (286), and phloridzin (287) were isolated from the flowers of pomegranate (*Punica granatum*). Compounds 282–285 and 287 (IC_{50} = 80.34 ± 0.17, 118.19 ± 0.57, 64.19 ± 1.63, 56.43 ± 2.09, and 79.78 ± 0.21 μmol/L, respectively) showed more potent yeast α-glucosidase inhibitory activity than acarbose (IC_{50} = 301.72 ± 18.93 μmol/L), while compound 286 showed weak inhibitory activity than acrbose (IC_{50} = 737.18 ± 70.18 μmol/L). Compound 282 (IC_{50} = 366.95 ± 54.75 μmol/L) and 285 (IC_{50} = 255.90 ± 15.57 μmol/L) showed weak inhibitory activity toward rat α-glucosidase, while acarbose exhibited potent inhibitory activity (IC_{50} = 21.92 ± 1.55 μmol/L) [65].



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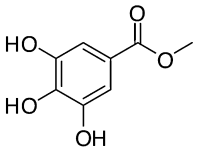

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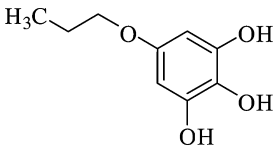

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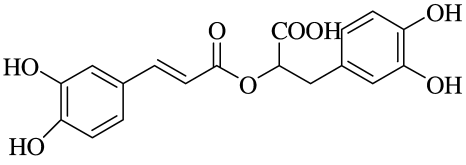

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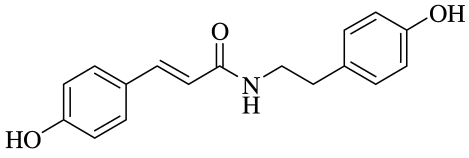

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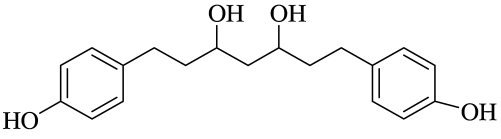

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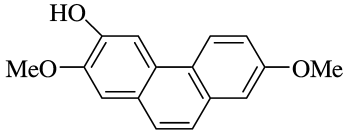

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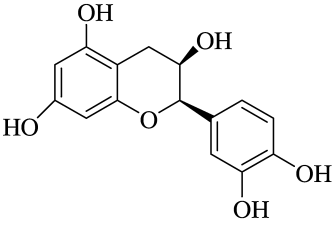

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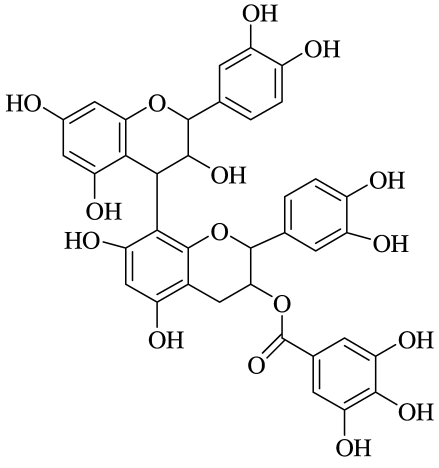

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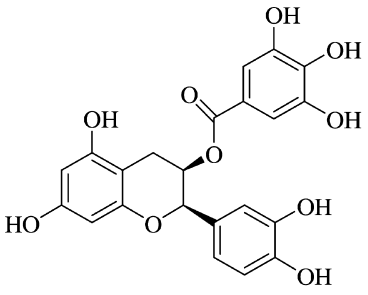

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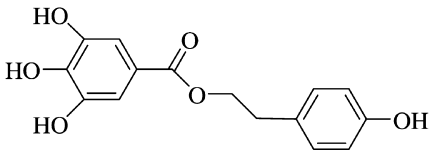

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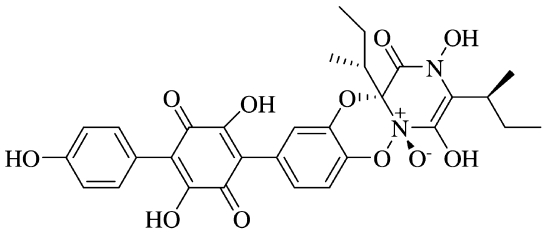

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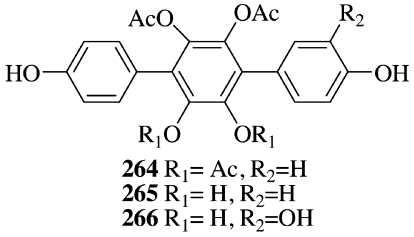
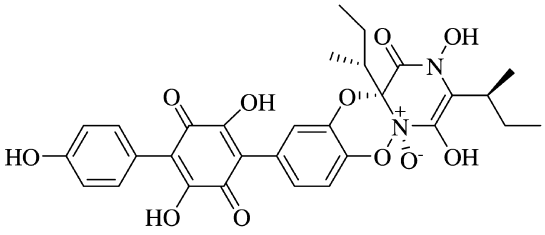


264 R_1= Ac, R_2=H
265 R_1= H, R_2=H
266 R_1= H, R_2=OH



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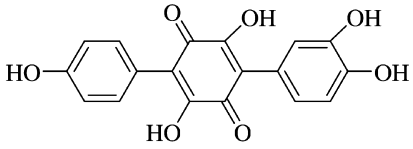

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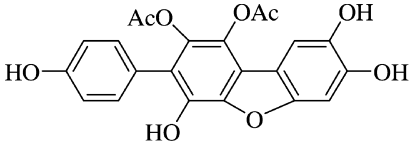

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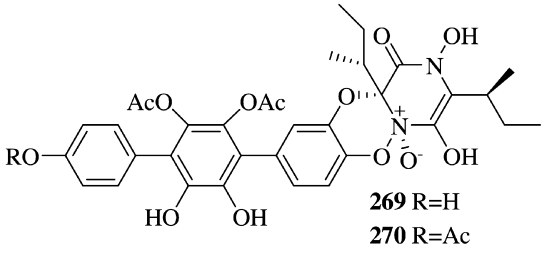
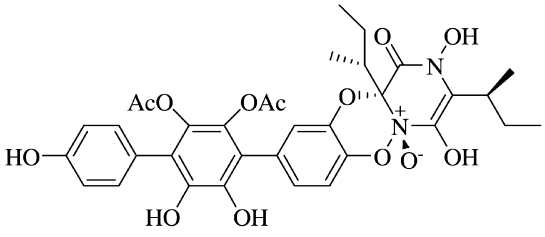


269 R=H
270 R=Ac

269, 270



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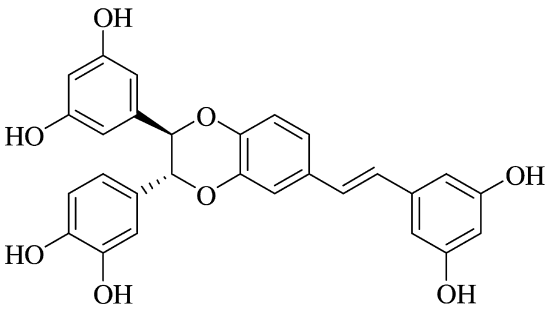

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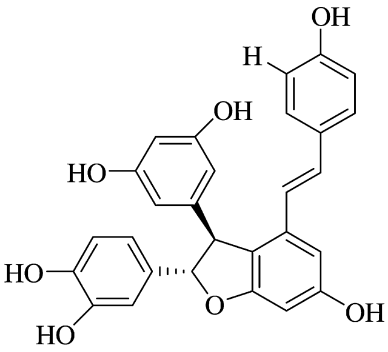

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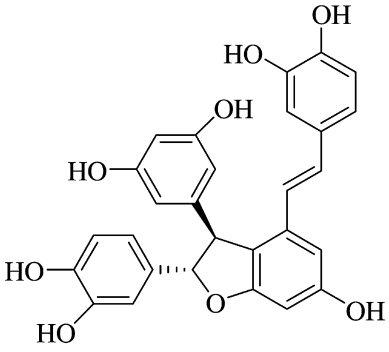

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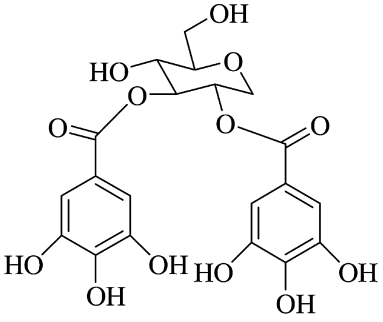

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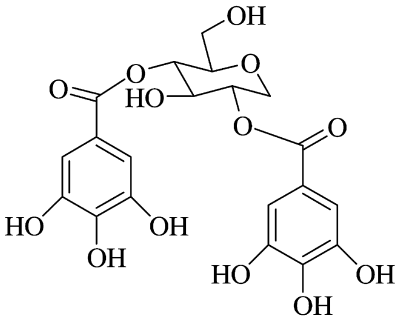

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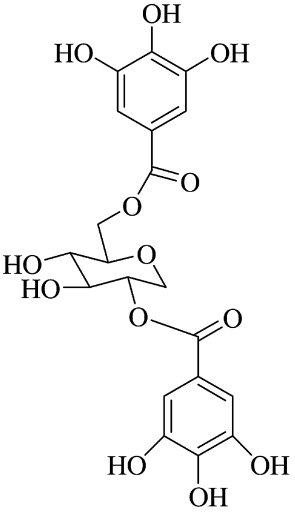

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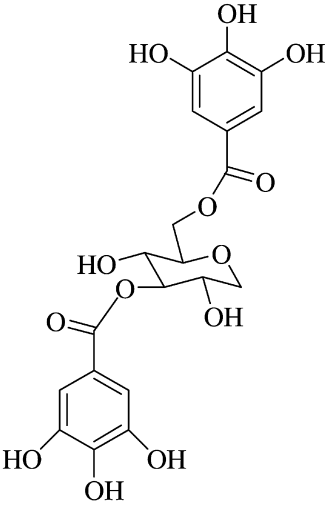

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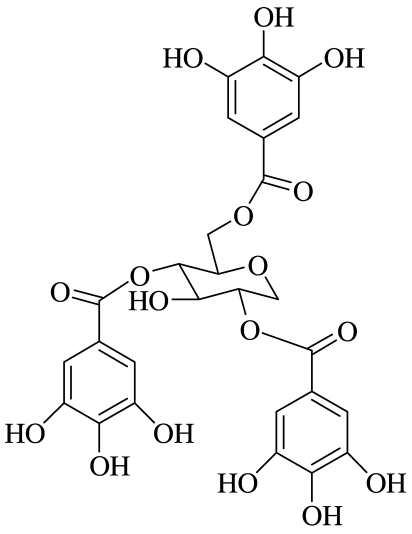

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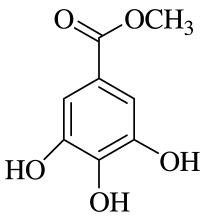

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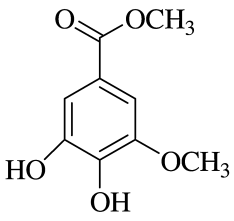

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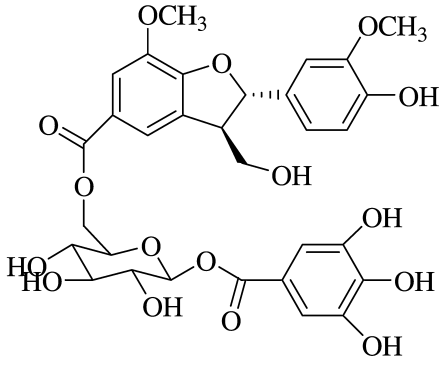

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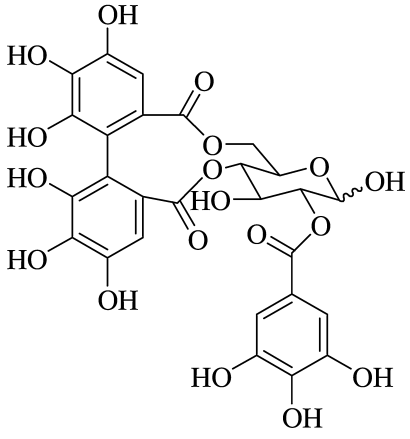

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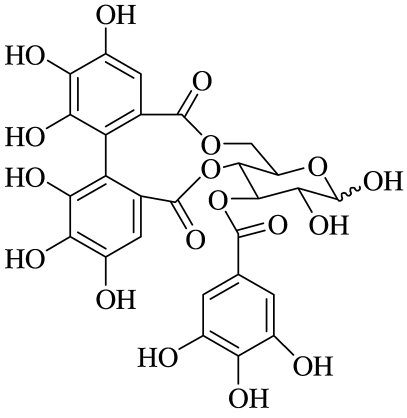

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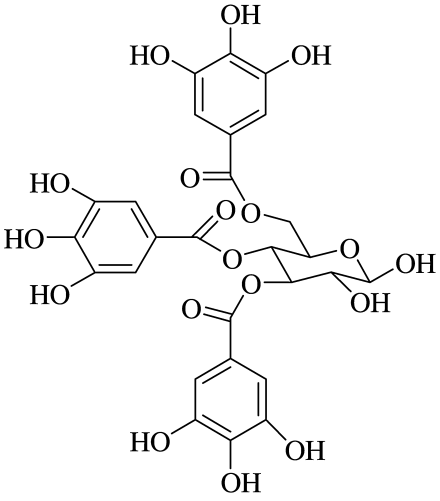

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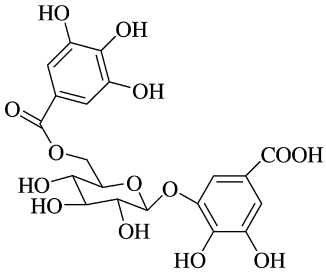

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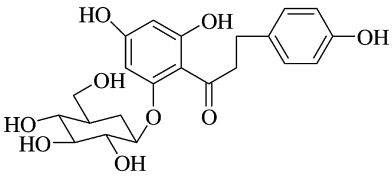

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2.7. Phenylpropanoids

Seventy-three active compounds were reported including phenyl acids, stilbenes, coumarins, and lignins. Three compounds 288–290 (IC_{50} = 496.74, 800.75, and 462.62 μg/mL, respectively), isolated from *F. suspensa* (Thunb) Vahl., showed lower yeast α-glucosidase inhibitory activity than that of acarbose (IC_{50} = 1081.27 μg/mL). Compound 288 showed a non-competitive inhibitory profile (K_i = 30.52 μg/mL) [44].

Three phenyl acids (291–293) (IC_{50} = 0.91, 0.90, 0.89 mmol/L, respectively) isolated from the flower buds of *Tussilago farfara* L. had rat intestinal α-glucosidase inhibitory activity. The IC_{50} values of all were less than 1 mmol/L [66]. Compounds 294 and 295 isolated from aqueous methanol extracts of dried hyssop (*Hyssopus officinalis*) leaves exhibited inhibitory rates of 53% and 54%, respectively, for rat intestinal glucosidase at a concentration of 3 mmol/L, but the inhibitory activity was considerably less significant than all the other analogs [67].

Compounds 296–298 were isolated from the methanol extracts of rhizome of the Himalayan rhubarb *R. emodi*. The first two 296 and 297 showed higher inhibitory activity on yeast α-glucosidase with inhibitory rates higher than 70%, while compound 298 showed strong inhibitory activity on the mammalian intestinal α-glucosidase [33].

Three curcuminoids 299–301 isolated from *Curcuma longa* showed strong inhibitory activity on α-glucosidase (IC_{50} = 37.2, 42.7, and 23.0 μmol/L, respectively). Compound 301 has been proved to be a non-competitive α-glucosidase inhibitor. In addition, synthesized analogs of such compounds have been made and were regarded as good α-glucosidase inhibitors [68].

Two structurally similar phenylpropanoids 302 and 303 were isolated from the Devil tree (*A. scholaris*), and in spite of structural similarity, their activity profiles were significantly different. The IC_{50} values of 302 toward small intestinal sucrase and maltase were 1.95 and 1.43 mmol/L, respectively, whereas the IC_{50} values of 303 for both of these enzymes were more than 10 mmol/L. Therefore, the configuration of a compound could significantly influence its inhibitory activity [47].

Seven stilbenoids (304–310) were isolated from the ethanol extracts of *Syagrus romanzoffiana* seeds and possessed potent inhibitory activity against α-glucosidase type IV from *B. stearothermophilus* (IC_{50} = 6.5, 11.2, 8.3, 4.9, 19.2, 23.2, and 23.9 μmol/L, respectively). From SAR studies, it was determined that by keeping the basic pharmacophore constant, the glucosidase inhibitory activity could be increased by increasing the number of OH substitutions in the aromatic ring, as seen in compounds 304 vs. 305, 307 vs. 306, and 307 vs. 308. Furthermore, *in vivo* assay on normal Wistar rats using oral sucrose challenge demonstrated that compounds 305 and 307 could significantly reduce postprandial blood glucose level. Thus, the therapeutic potential of stilbenoids could be further explored to develop them as hypoglycemic agents [69].

Phenylpropanoid glycosides darendoside B (311), acteoside (312), and 2-(3-hydroxy-4-methoxyphenyl)ethyl-*O*-α-*L*-arabinopyranosyl-(6)-*O*-[6-deoxy-α-*L*-mannopyranosyl-(1→3)]-β-*D*-Glucopyranoside (313) obtained from the roots of *S. ningpoensis* Hemsl exhibited moderate α-glucosidase inhibitory activity (IC_{50} = 5.51 ± 1.12, 1.62 ± 0.29, and 12.01 ± 0.63 mmol/L, respectively) compared with acarbose (IC_{50} = 0.37 ± 0.01 mmol/L) [12].

Phenylpropanoids (314–318) were isolated from the entire plant body of *P. stewartii*. Compounds 314–315 and 317–318 showed better α-glucosidase inhibitory potential (IC_{50} = 26.1 ± 0.3, 26.6 ± 0.2, 14.5 ± 0.1, and 27.4 ± 0.2 μmol/L, respectively) than acarbose (IC_{50} = 38.3 ± 0.1 μmol/L). Tiliroside (317) was the most active (IC_{50} = 14.5 ± 0.1 μmol/L), whereas its methoxy derivative phlomispentanol (316) showed the least activity (IC_{50} > 500 μmol/L). This indicated that the presence of hydroxyl group in ring C of 317 had an important role in enzyme inhibition. The activity of stewartiiside (314) (IC_{50} = 26.1 ± 0.3 μmol/L) was comparable with that of lunariifolioside (315) (IC_{50} = 26.6 ± 0.2 μmol/L). This means that the glycone part did not played an important role in enzyme inhibition [14].

Verbascoside (319), leucosceptoside A (320), and isoacteoside (321) isolated from the dried roots of *Clerodendrum bungei* exhibited stronger α-glucosidase inhibitory effects (IC_{50} = 0.5 ± 0.03, 0.7 ± 0.04, and 0.1 ± 0.01 mmol/L, respectively) than acarbose (IC_{50} = 14.4 ± 0.3 mmol/L) [70]. 3-*O*-Caffeoylquinic acid (chlorogenic acid) (322) and its structural isomer, i.e., 5-*O*-caffeoylquinic acid (323) isolated from the leaves of *Nerium indicum*, inhibited α-glucosidase in a non-competitive manner [71].

Methyl *p*-coumarate (324) isolated from *C. plicata* showed yeast α-glucosidase inhibitory activity (IC_{50} = 54.15 ± 0.005 μmol/L), which was slightly weaker than that of acarbose (IC_{50} = 38.25 ± 0.12 μmol/L) [30].

p-Coumarica (325) ($IC_{50} > 30$ mmol/L), ferulic acid (326) ($IC_{50} = 4.9 \pm 0.3$ mmol/L), and sinapic acid (327) ($IC_{50} = 6.1 \pm 0.8$ mmol/L) isolated from the sprouts of *Triticum aestivum* L. had lower α-glucosidase inhibitory activity than acarbose ($IC_{50} = 1.7 \pm 0.1$ mmol/L) [72].

Epi-mukulin (328) and diasesartemin (329) were isolated from guggul, the oleogum resin of *Commiphora wightii*. Compound 329 ($IC_{50} = 60.6 \pm 0.01$ μmol/L) was found to be more potent than acarbose ($IC_{50} = 92.94 \pm 0.01$ μmol/L). The IC_{50} value of 328 was found to be 159.33 ± 0.04 μmol/L [73].

Ten honokiol oligomers (330–339), including four trimers (330–333) and four dimers (334–337), were obtained from *Momordica charantia*. All the honokioltrimers and dimers had good inhibitory effects on α-glucosidase with IC_{50} values ranging from 1.38 to 95.31 μmol/L. The potency of honokiol trimers (331–332) were found to be higher than those of dimers (334–339), and among the six dimers, the potency of the carbon oxygen linkage dimers (334–336) appeared to be much stronger than those of the carbon acarbon linkage ones (337–339). Among all the tested compounds, the compound 331 ($IC_{50} = 1.38$ μmol/L), i.e., the honokioltrimer, exhibited the most significant inhibitory activity toward α-glucosidase in a concentration-dependent manner and was 128-fold more potent than that of honokiol ($IC_{50} = 177.03$ μmol/L). Compared with genistein ($IC_{50} = 15.31$ μmol/L) and 1-DNJ ($IC_{50} = 239.17$ μmol/L) as positive controls, compound 331 was 11 and 173 times more active [74].

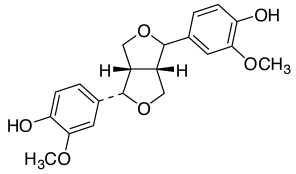
Extracts isolated from plants containing coumarin compounds also showed good α-glucosidase inhibitory activity. Two coumarin derivatives 340 and 341 ($IC_{50} = 35.03$ and 69.26 μg/mL, respectively), isolated from the branch extract of *L. pinceana* Hook, showed strong α-glucosidase inhibitory activity. Kinetic analysis revealed that both the compounds were non-competitive inhibitors of α-glucosidase ($K_i = 2.44$ and 167.83 μg/mL, respectively) [6].

Four coumarins (342–345), isolated from the aqueous extract of *M. recutita* L., showed inhibitory activity against rat intestinal maltase and sucrose at the concentration of 400 μmol/L; compound 344 recorded the highest activity ($IC_{50} = 534$ and 72 μmol/L, respectively) [42]. Scandenin A (346), isolated from *D. scandens* Benth, showed rat intestinal α-glucosidase inhibitory activity with $IC_{50} = 25.17$ μg/mL [46].

Three compounds 347–349 with a coumarin nucleus isolated from the fruit extract of *Terminalia chebula* Retz. (Combretaceae) showed strong inhibitory activity ($IC_{50} = 960$, 97 and 36 μmol/L, respectively) on α-glucosidase. Chebulagic acid (348) and chebulinic acid (349) belong to the class of non-competitive α-glucosidase inhibitors ($K_i = 208$ and 24 μmol/L, respectively) [75]. The stem and bark extract of another plant named *T. superba* contained three coumarins (350–352), with IC_{50} values of 194.1, 184.6, and 118.7 μmol/L, respectively, on yeast α-glucosidase [59].

Psoralidin (353) isolated from *P. corylifolia* had α-glucosidase inhibitory activity ($IC_{50} = 40.74$ mmol/L), which was stronger than that of acarbose ($IC_{50} = 38.25 \pm 0.12$ mg/L) [58].

Coumarins compounds (354–360) isolated from the root extract of *R. rugosa* showed potent sucrase inhibitory activity ($61.88 \pm 3.19\%$ to $84.70 \pm 3.07\%$) at a concentration of 1.0 mmol/L ($IC_{50} = 0.25 \pm 0.04$, 0.48 ± 0.12, 0.43 ± 0.11, 0.40 ± 0.18, 0.52 ± 0.01, and 0.31 ± 0.02 mmol/L, respectively), and the activity was comparable with that of acarbose ($50.96 \pm 2.97\%$ inhibition, $IC_{50} < 0.5$ mmol/L) [13].



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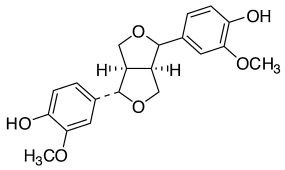

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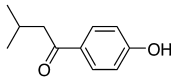

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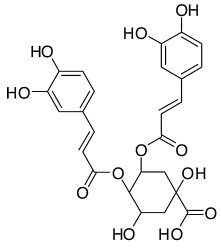

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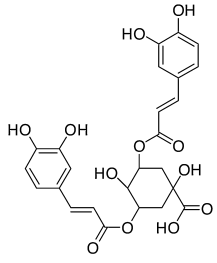

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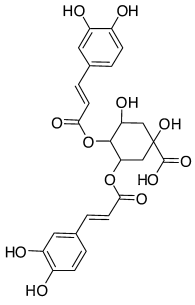

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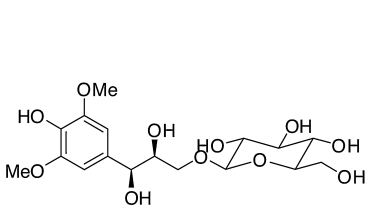

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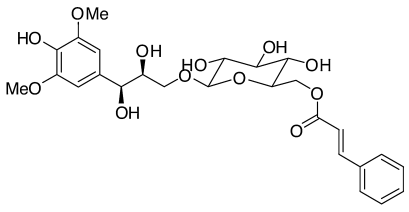

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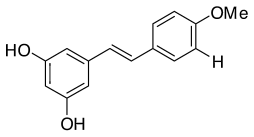

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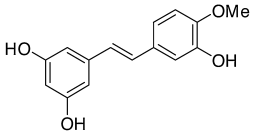

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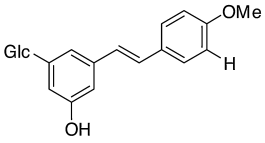

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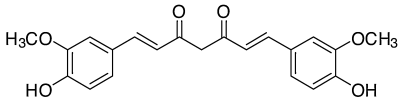

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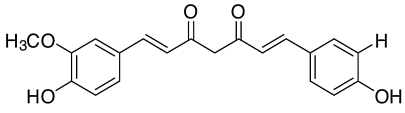

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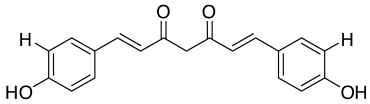

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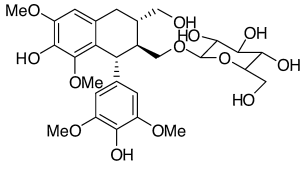

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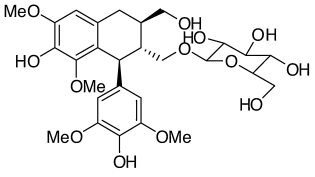

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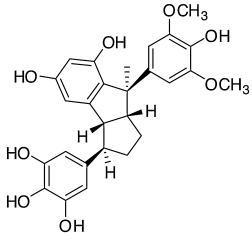

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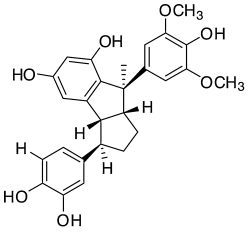

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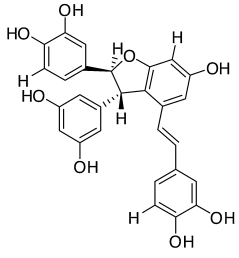

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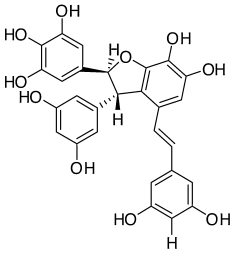

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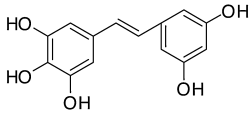

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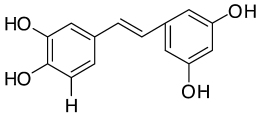

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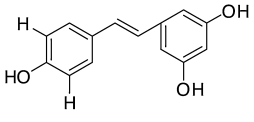

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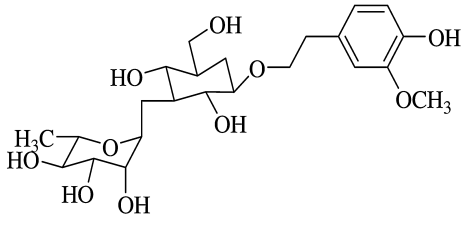

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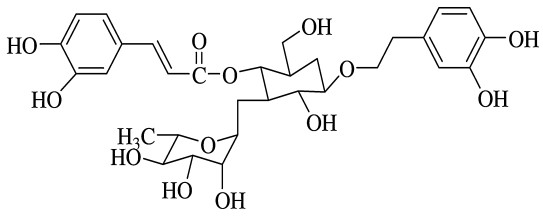

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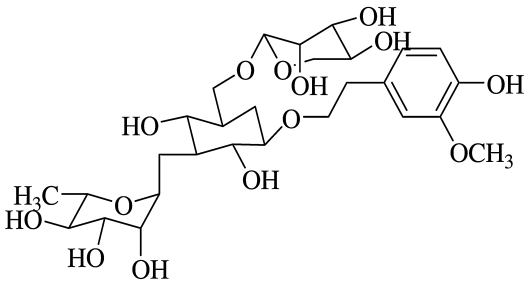

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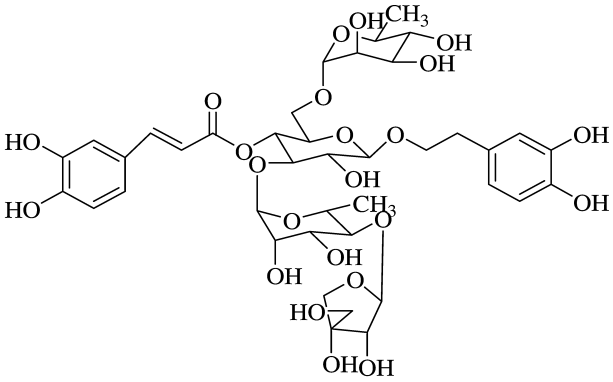

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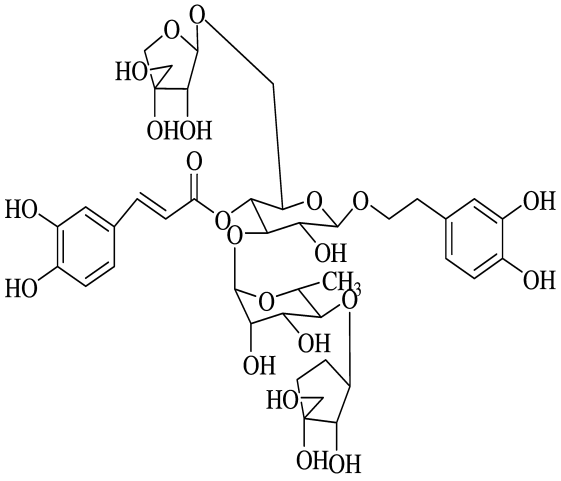

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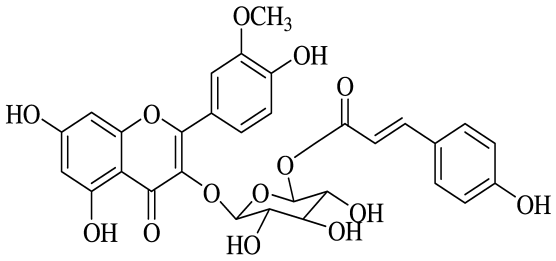

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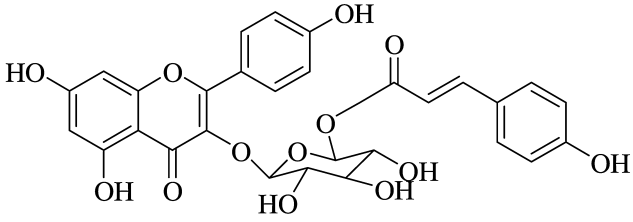

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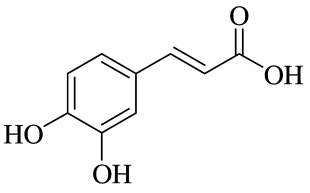

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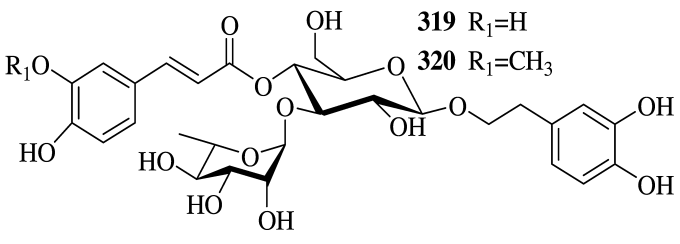

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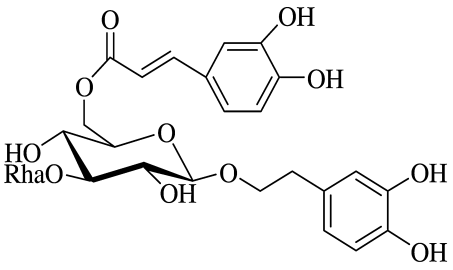

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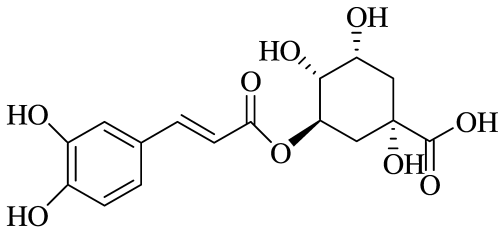

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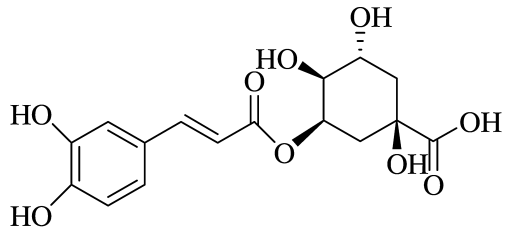

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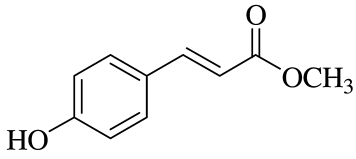

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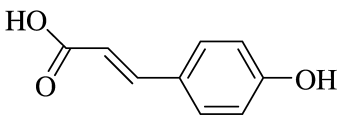

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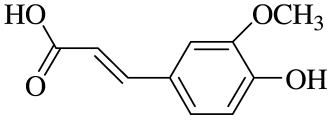

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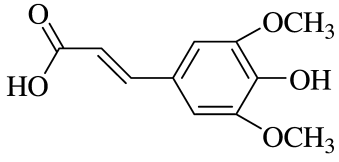

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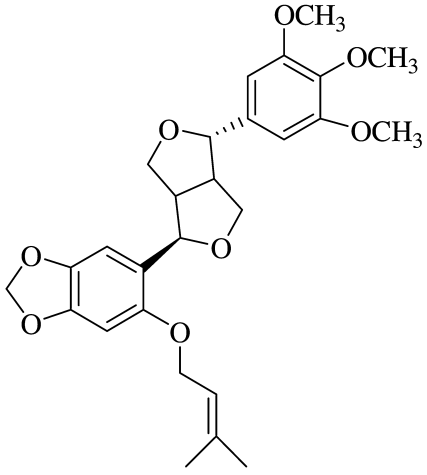

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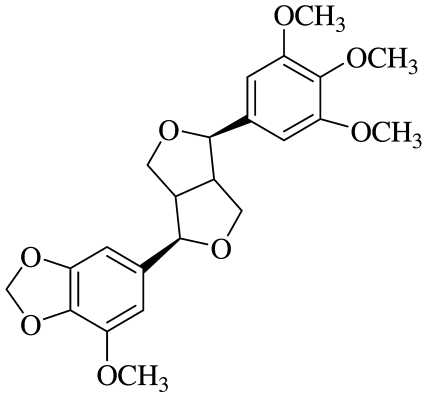

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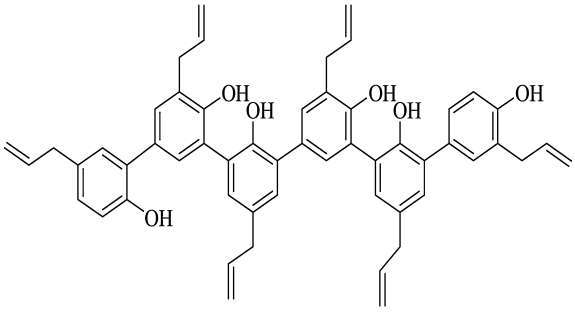

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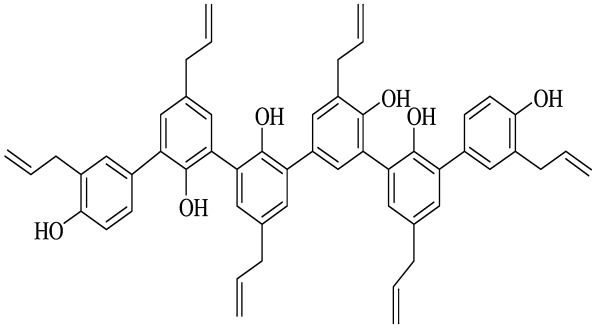

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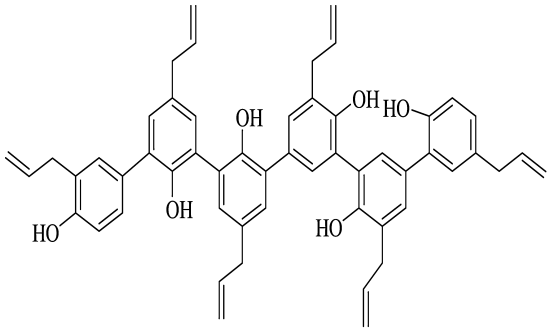

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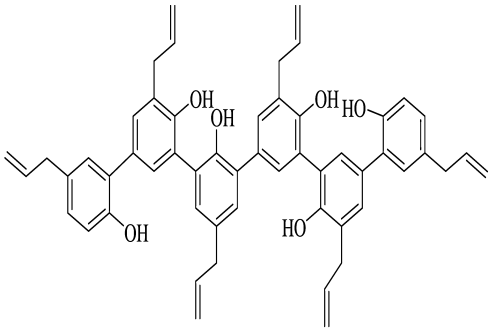

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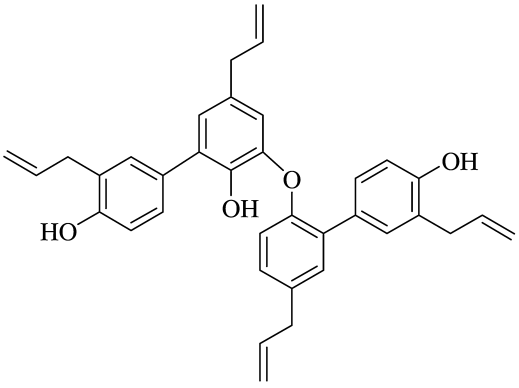

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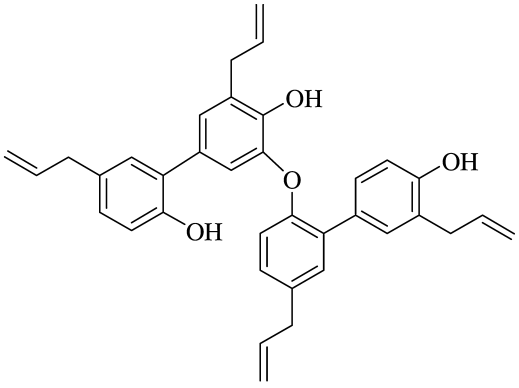

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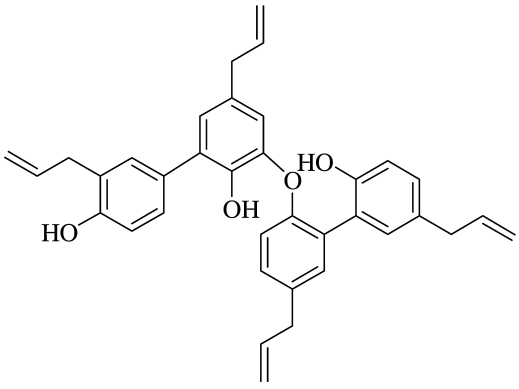

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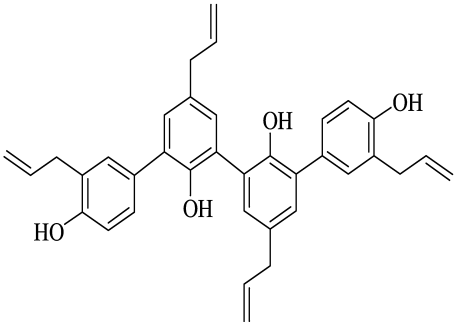

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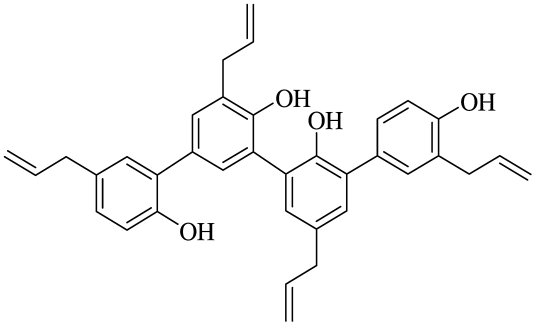

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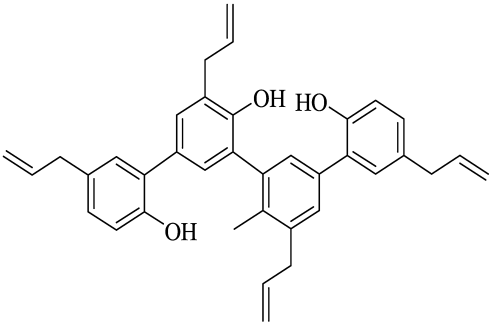

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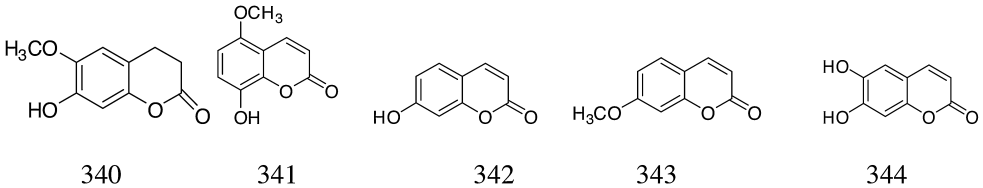

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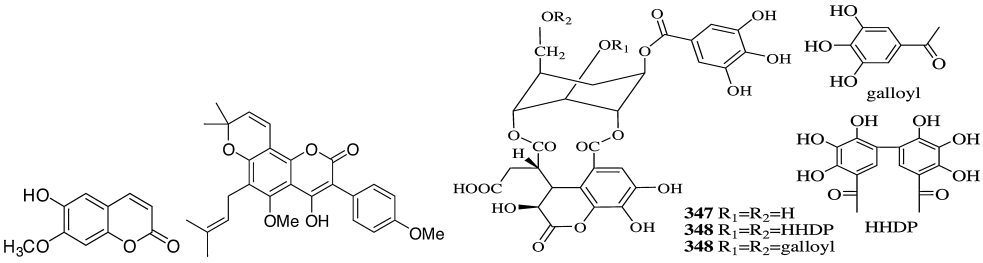

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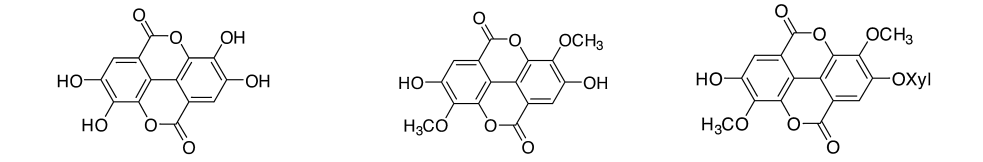

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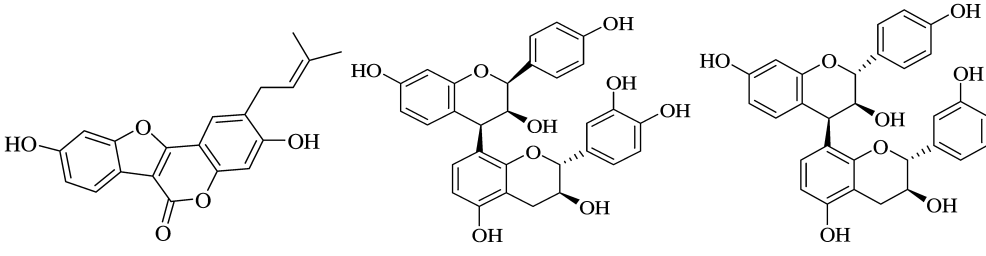

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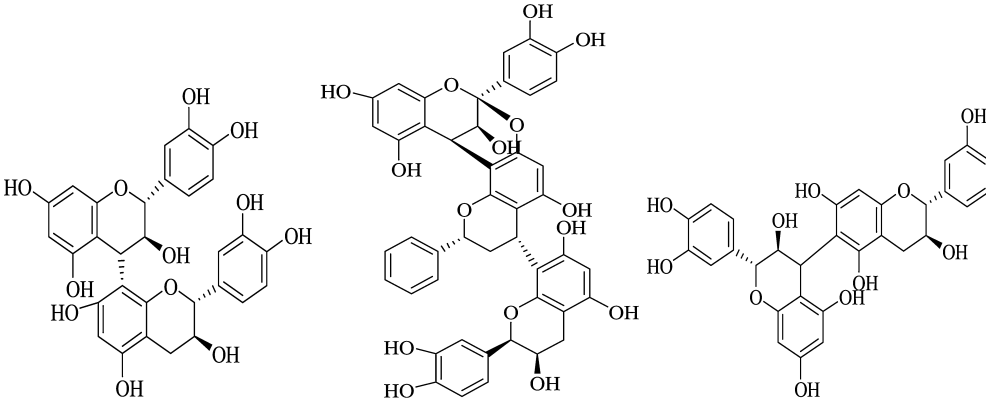

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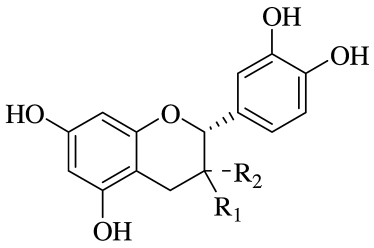


359 R_1 = β-OH, R_2 = α-OH

360 R_1 = α-OH, R_2 = β-OH

2.8. Sterides

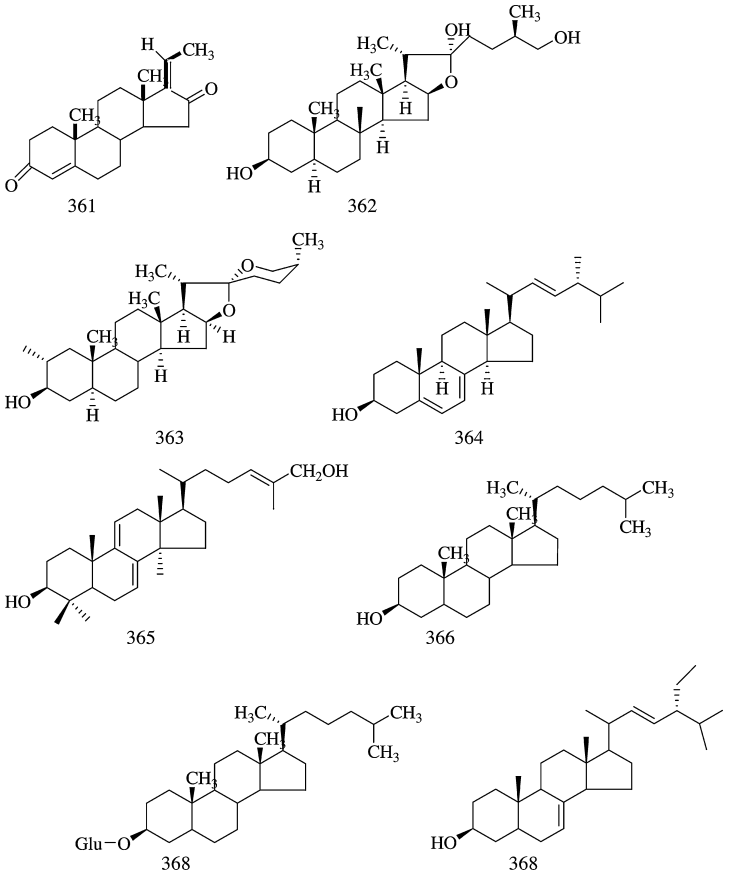
Eight active compounds were reported for this class. (*Z*)-Guggulsterone (361), with an IC_{50} value of 132.14 ± 0.08 μmol/L, was isolated from the guggul, the oleogum resin of *C. wightii*. It was less potent than acarbose (IC_{50} = 92.94 ± 0.01 μmol/L) [73].

(25*S*)-5*a*-Furastan-3*β*,22,26-triol (362) and gitogenin (363), isolated from the entire plant body of *T. longipetalus*, were found to be good inhibitors of α-glucosidase (IC_{50} = 33.5 ± 0.22 and 37.2 ± 0.18 μmol/L, respectively) compared with acarbose (IC_{50} = 38.3 ± 0.12 μmol/L) [76].

Ergosterol (364) and ganodero B (365) were isolated from the fruiting body of *Ganoderma lucidum*. Compound 365 had stronger α-glucosidase inhibitory activity (IC_{50} = 119.8 μmol/L) than acarbose (IC_{50} = 3521.5 μmol/L), while compound 364 had weaker inhibitory activity than acarbose (IC_{50} > 839.5 μmol/L) [77].

β-Sitosterol (366) and *β*-sitosterol-3-*O*-*β*-*D*-glucopyranoside (367) isolated from *C. plicata* showed yeast α-glucosidase inhibitory activity (IC_{50} = 277.7 ± 0.003 and 258.71 ± 0.07 μmol/L), but the inhibitory activity was lower than that of acarbose (IC_{50} = 38.25 ± 0.12 μmol/L) [30].

Compound 368 (chondrillasterol) isolated from *A. fragrantissima* expressed lower α-glucosidase inhibitory activity (IC_{50} = 138 ± 2.01 mg/mL) than acarbose (IC_{50} = 224 ± 2.31 mg/mL) [54].



2.9. Other compound types

Forty-three active compounds reported are presented here. Numerous organic compounds of plant origin containing functional groups such as organic acid, ester, alcohol, allyl, and others have shown strong α-glucosidase inhibitory activity. For example, vanillic acid (369) (IC_{50} = 69.4 μmol/L) was isolated from the bark of Rutaceae *F. tessmannii* [5], 4-hydroxybenzoic acid (370) (IC_{50} = 56.4 μmol/L) from the seeds of *S. romanzoffiana* (Cham.) [69], and 4-hydroxyphenylacetic acid (371) isolated from *C. plicata* showed inhibitory activity against yeast α-glucosidase (IC_{50} = 27.42 ± 0.15 μmol/L). All these compounds were stronger inhibitors than acarbose (IC_{50} = 38.25 ± 0.12 μmol/L) [30]. The γ-aminobutyric acid (372), isolated from the sprouts of *T. aestivum* L., showed high α-glucosidase inhibitory activity (IC_{50} = 1.4 ± 0.4 mmol/L) and was more effective than acarbose (1.7 ± 0.1 mmol/L) [72].

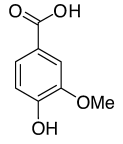
Butyrolactone I (373) and II (374) were isolated from *Aspergillus terreus*. Compound 377 (IC_{50} = 52.17 ± 5.68 μmol/L) had the most potent inhibitory activity against glucosidase of *S. cerevisiae* and exhibited kinetic profile of a mixed inhibitor (K_i = 70.51 μmol/L). Compound 374 was less active against α-glucosidase (IC_{50} = 96.01 ± 3.70 μmol/L), and displayed non-competitive inhibition kinetics (K_i = 152.64 μmol/L), as compared with quercetin (IC_{50} = 14.6 ± 3.72 μmol/L and exhibited mixed inhibition kinetics; K_i = 27.13 μmol/L) [78]. 3-(*Z*)-Butylidenephthalide (375), isolated from the roots of *Ligusticum porteri*, inhibited yeast α-glucosidase (IC_{50} = 2.35 mmol/L) in a non-competitive manner (K_i = 11.48 mmol/L) [79].

Eight new geranylated 2-arylbenzofuran derivatives, including two monoterpenoid 2-arylbenzofurans (376 and 377), two geranylated 2-arylbenzofuran enantiomers (378 and 379), and four geranylated 2-arylbenzofurans (380–383) along with three known 2-arylbenzofurans (384–386), were isolated from the root and bark of *Morus alba* var. *tatarica*. Compounds 376–386 showed α-glucosidase inhibitory activity with IC_{50} values between 11.9 and 131.9 μmol/L. SAR analysis revealed that by increasing the number of hydroxyl groups in the straight side chain of geranylated 2-arylbenzofurans, we would expect improved inhibitory effects against α-glucosidase [80].

1,2,3,4,6-Penta-*O*-galloyl-β-*D*-glucose (387) (IC_{50} = 140 μmol/L), separated from *T. superba*, showed very strong α-glycosidase inhibitory activity [68]. 6-Hydroxyacetyl-5-hydroxy-2,2-dimethyl-2H-chromene (388) isolated from *B. cavanillesii* inhibited the activity of yeast α-glucosidase (IC_{50} = 0.42 mmol/L vs. 1.7 mmol/L for acarbose), and the inhibition was non-competitive in nature (K_i = 0.13 mmol/L) [18]. Eucommiol (389), isolated from Toch-cha (*E. ulmoides*) and α-bisabolol (390) along with α-farnesene (391) separated from *Matricaria chamomilla* L., showed significant α-glycosidase inhibitory activity [42].

Four sulfonium pseudo-sugars, i.e., salacinol (392), kotalanol (393), neosalacinol (394), and neokotalanol (395), were isolated from Ayurvedic traditional medicine species, i.e., *Salacia*. IC_{50} values of 392–395 for rat intestinal α-glucosidase were 6.0, 2.0, 22.2, and 1.6 μmol/L, respectively, for maltase (acarbose 1.7 μmol/L); 1.3, 0.43, 2.5, and 1.5 μmol/L, respectively, for sucrase (acarbose 1.5 μmol/L); 1.3, 1.8, 0.68, and 0.46 μmol/L, respectively, for isomaltase (acarbose 645 μmol/L) [81].

Sixteen iminosugars (396–411) (IC_{50} = 0.92, 0.09, 0.08, 24.34, 19.25, 24.95, 22.13, 0.72, 4.22, 22.95, 24.34, 38.55, 22.17, 20.00, and 5.53 μmol/L, respectively), isolated from the leaves of *Suregada glomerulata*, showed moderate rat small intestinal α-glucosidase inhibitory activity compared with acarbose (IC_{50} = 0.54 μmol/L). *In vivo* results showed that four major iminosugars (396–398) and 405 (10 mg/kg) could lower the postprandial blood glucose level after the intake of sucrose and starch load in healthy male ICR mice [82].



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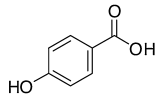

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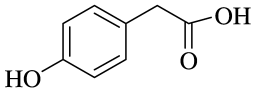

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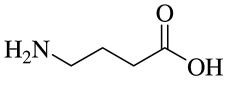

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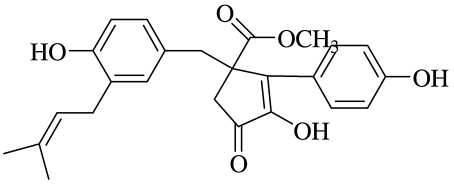

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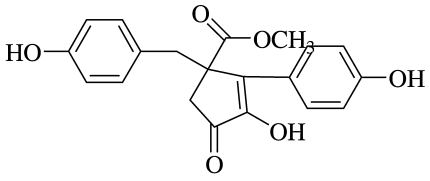

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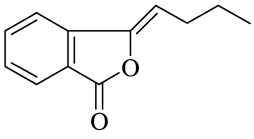

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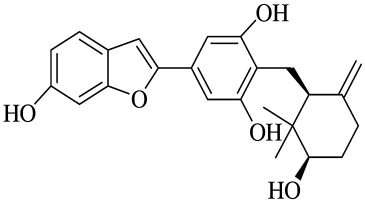

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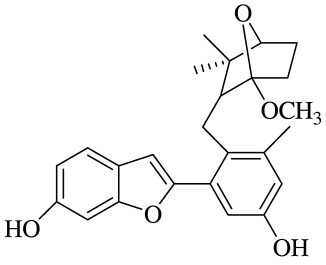

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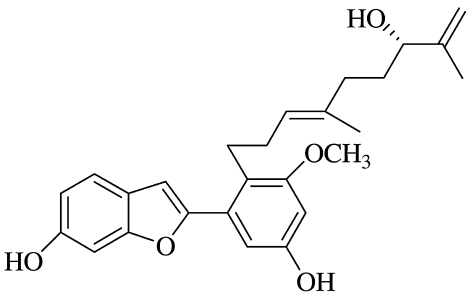

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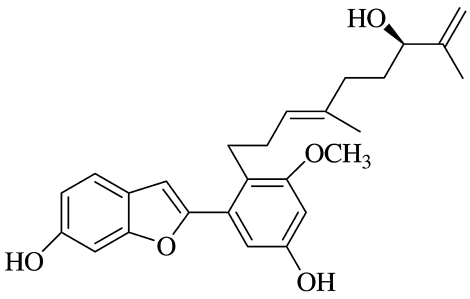

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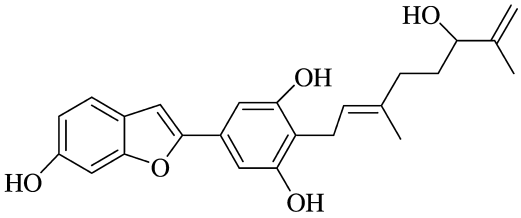

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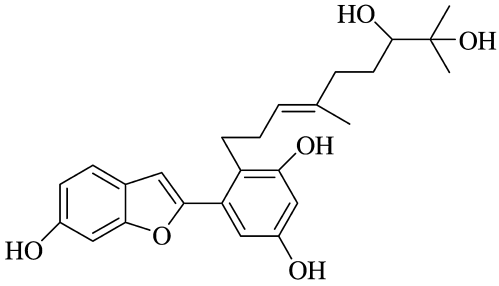

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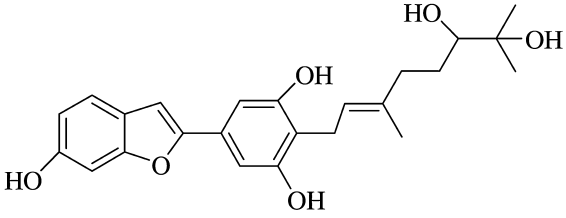

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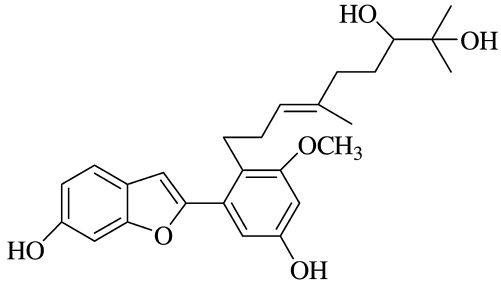

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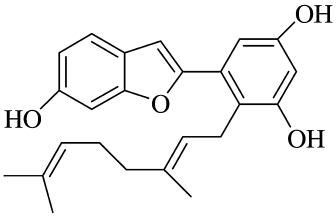

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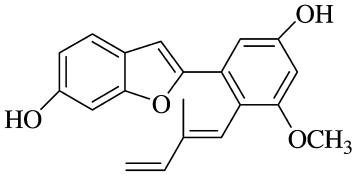
Albafuran B (385)



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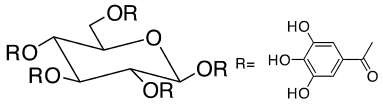

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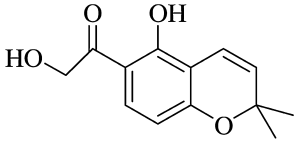

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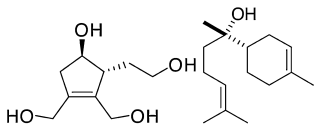

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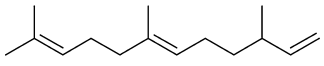

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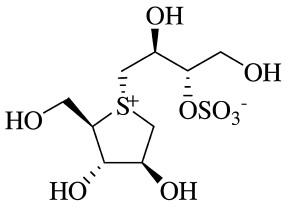

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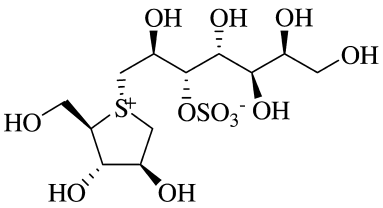

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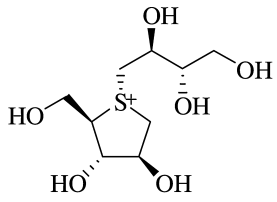

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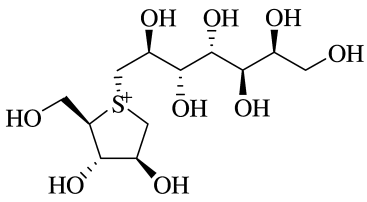

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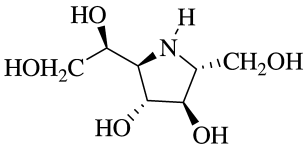

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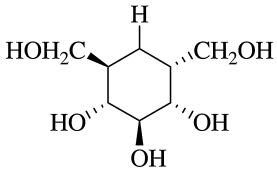

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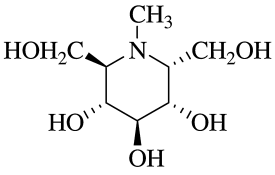

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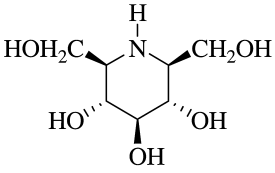

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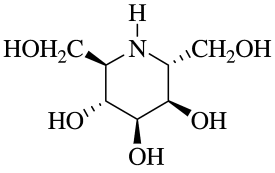

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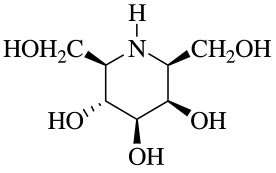

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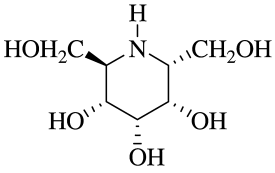

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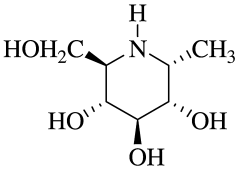

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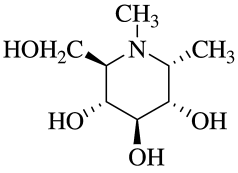

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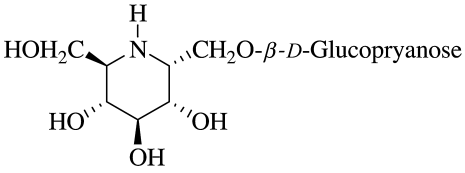

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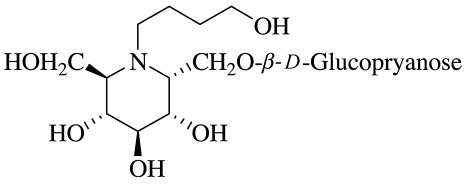

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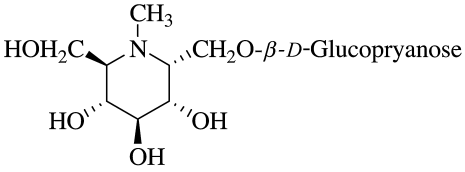

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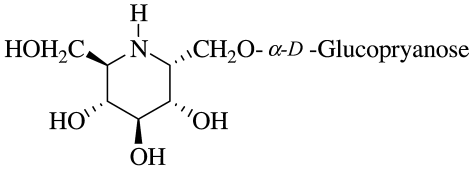

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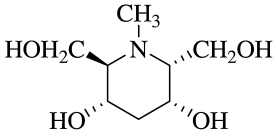

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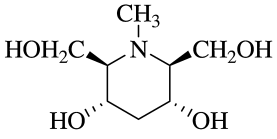

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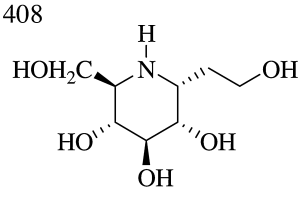

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3. Conclusion

Natural products are still considered as potential resources for drug discovery and play an important role in drug development programs. Moreover, many medicinal herbs are a rich source of bioactive chemicals that are remarkably free from undesirable side-effects and display powerful pharmacological actions. Compounds having α-glucosidase inhibitory activity are ubiquitous in medicinal plants. A systematic review of literature revealed that 411 compounds belonging to different structural frameworks, i.e., terpenes, alkaloids, quinines, flavonoids, phenols, phenylpropanoids, sterides, and compounds with other structural and functional motifs isolated from medicinal plants, showed potent inhibitory activity toward α-glucosidase.

With the future rise in diabetic population worldwide, the search foractive compounds with α-glucosidase inhibitory activity from medicinal plants has become a very meaningful task. Furthermore, these compounds can be evaluated for potential pharmacological activity against other metabolic diseases.

In short, efforts should be made to optimize the procedure of screening natural products isolated from different plants for the discovery of new natural herbal antidiabetic drugs. These natural products can be used as alternatives to synthetic oral hypoglycemic drugs with less or even no prominent side effects.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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