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Bio-guided isolation of alpha-glucosidase inhibitory compounds from Vietnamese liverwort *Marchantia polymorpha*: in vitro and in silico studies†

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Bio-guided isolation was applied to Vietnamese *Marchantia polymorpha* L. to find alpha-glucosidase inhibition. Fifteen compounds were isolated and structurally determined, including two new compounds, marchatoside (7) and marchanol (8), along with thirteen known compounds: marchantin A (1), isoriccardin C (2), riccardin C (3), marchantin K (4), lunularin (5), 3*R*-(3,4-dimethoxybenzyl)-5,7-dimethoxyphthalide (6), vitexilactone (9), 12-oleanene-3-one (10), 3,11-dioxoursolic acid (11), ursolic acid (12), artemetin (13), kaempferol (14), and quercetin (15). The structures of these compounds were determined through extensive spectroscopic analyses (1D and 2D NMR, HRESIMS, and ECD) and by comparisons to the existing literature. There are five types of carbon skeleton, including bibenzyl (1–5), 3-benzylphthalide (6 and 7), diterpenoid (8 and 9), triterpenoid (10–12), and flavonoid (13–15). Compounds 6–12 were reported for the first time within the genus *Marchantia*. Compounds 1–12 were evaluated for their alpha-glucosidase inhibition. Among them, 1–5 and 10–12 displayed potent inhibition, with IC₅₀ values ranging from 28.9 to 130.6 μM, compared to the positive control acarbose 330.9 μM. A kinetic study and molecular docking were also performed to understand the mechanism.

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1. Introduction

Marchantia polymorpha L. is a liverwort belonging to the family Marchantiaceae, widely distributed in mountainous regions.¹ It is believed to be a valuable source of traditional medicines in India, China, Europe, and Vietnam.^{1,2} In folk medicine, it has been used to treat inflammation, liver disease, wounds, boils, insect bites, and snake bites.¹ Chemical data of this liverwort have been comprehensively investigated, indicating the presence of over 50 compounds (Fig. S1†).^{3–10} Among these compounds, 11 known components were found in the native

liverwort in Vietnam (Fig. S2†).^{11,12} The major carbon skeletons of these compounds were found to be bis-bibenzyls, sesquiterpenoids, flavonoids, phenolics, coumarins, and glycosides. The extracts of this liverwort showed antioxidant and antibacterial properties, inhibition of tyrosinase and alpha-glucosidase, as well as cytotoxicity against several cancer cell lines.^{13–18} However, little is known about the alpha-glucosidase inhibitors from this medicinal source, with only two reports.^{17,18} These authors conducted the biological evaluation of extracts derived from natural and cultured *M. polymorpha*, indicating the potent inhibition of all prepared extracts. Bio-guided isolation was applied to Vietnamese *M. polymorpha* to find alpha-glucosidase inhibition. Fifteen compounds were isolated (Fig. 1). The structures of these compounds were determined through extensive spectroscopic analyses (1D and 2D NMR, HRESIMS, and ECD). Two new compounds, marchatoside (7) and marchanol (8), together with thirteen known compounds, marchantin A (1), isoriccardin C (2), riccardin C (3), marchantin K (4), lunularin (5), 3*R*-(3,4-dimethoxybenzyl)-5,7-dimethoxyphthalide (6), vitexilactone (9), 12-oleanene-3-one (10), 3,11-dioxoursolic acid (11), ursolic acid (12), artemetin (13), kaempferol (14), and quercetin (15) were structurally determined. A brominated derivative 1a of marchantin A was prepared. All compounds

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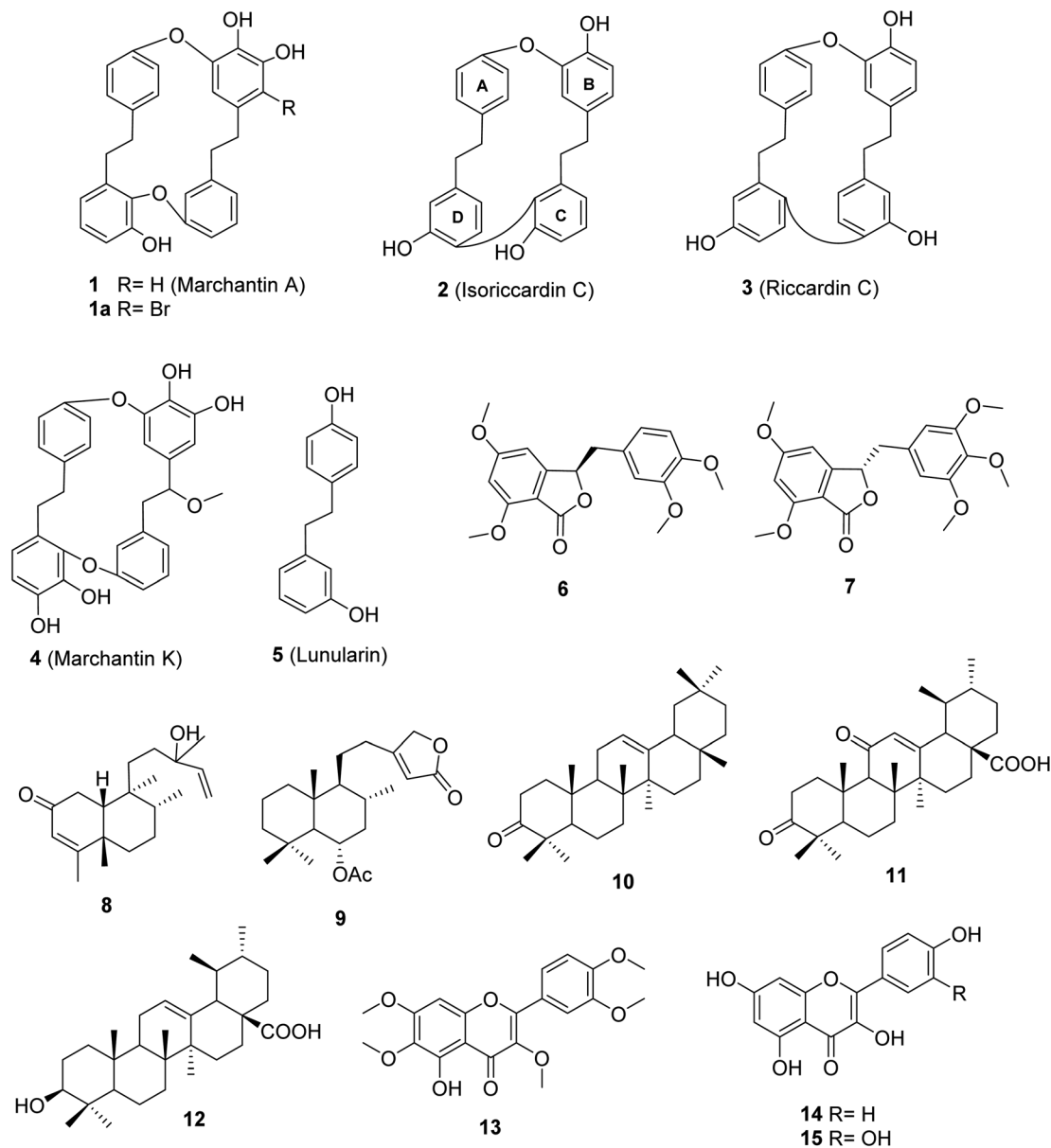


Fig. 1 Chemical structures of 1–15.

were evaluated for their alpha-glucosidase inhibition. A kinetic study and molecular docking were also performed to understand the mechanism.

2. Results and discussion

The crude extract of *M. polymorpha* was prepared using EtOAc. This crude extract was evaluated for alpha glucosidase inhibition, indicating moderate activity with an IC_{50} value of $27.7 \pm 1.2 \mu\text{g mL}^{-1}$. The solvent ethyl acetate was selected for maceration based on the results reported by Tran *et al.* (2018).¹⁶ These authors prepared four *n*-hexane, chloroform, ethyl acetate, and ethanol extracts from natural *M. polymorpha* and evaluated their alpha-glucosidase inhibition. The ethyl acetate extract showed the strongest activity, with an IC_{50} value of $10.3 \mu\text{g mL}^{-1}$.¹⁶ In 2020, this team also evaluated the inhibition of the cultured *M.*

polymorpha biomass,¹⁷ indicating that *n*-hexane extract showed potent inhibition with an IC_{50} value of $11.9 \mu\text{g mL}^{-1}$.

Two new compounds, marchatoside (7) and marchanol (8), along with thirteen known compounds, marchantin A (1),¹⁸ isoriccardin C (2),⁴ riccardin C (3),^{4,12} marchantin K (4),¹⁹ lunularin (5),¹² 3R-(3,4-dimethoxybenzyl)-5,7-dimethoxyphthalide (6),²⁰ vitexilactone (9),²¹ 12-oleanene-3-one (10),²² 3,11-dioxoursolic acid (11),²³ ursolic acid (12),²⁴ artemetin (13),²⁵ kaempferol (14),¹³ and quercetin (15)¹² were structurally determined. To the best of our knowledge, compounds 7–11 were reported for the first time in liverworts. Isolated compounds were classified as bis-bibenzyl (1–4), bibenzyl (5), 3-benzylphthalide (6 and 7), diterpene (8 and 9), triterpene (10–12), and flavanols (13–15). Many natural 3-benzylphthalide-type compounds have been reported, but little is known about their absolute configuration.^{26–29} 3-Benzylphthalide-type compounds have not



been reported in the genus *Marchantia*, but they were found previously in *Frullania* sp. and *Porella perrottetiana* liverworts.²⁹ A few clerodane-type and *ent*-labdane-type diterpenoids were previously isolated in liverworts: *Gottschieia schizopleura*³⁰ and *Jamesoniella autumnalis*.³¹ However, these types of compound were rarely found in liverworts. Compound **6** was previously isolated from the liverwort *Frullania muscicola*,²⁰ but the absolute configuration of C-3 was unknown. ECD data of **6** was recorded, showing a strong negative Cotton effect around 240–250 nm. This CE was consistent with that of julacelide reported in our previous paper,³² proposing the absolute C-3 configuration as 3*R*. Comparison of NMR data of known compounds **1–6**, **8–11** with those reported in the literature gave consistency (see Tables S1–S12†). Compound **1** was selected for bromination in order to find a better alpha-glucosidase inhibitor. Electrophilic aromatic bromination was applied to **1**, yielding product **1a** (see Scheme S1†). The chemical structure of **1a** was defined using the spectroscopic method (see Table S13†). Unfortunately, compound **1a** showed weaker activity than the parent compound **1**, thus no further halogenated modifications were conducted on **1**.

Compound **7** was obtained as a colorless oil. The molecular formula of **7** was deduced as C₂₀H₂₂O₇ from the protonated molecular ion peak at *m/z* 375.1397 (calcd for [C₂₀H₂₂O₇ + H]⁺, 375.14438) in the HRESI mass spectrum (Fig. S9A†). The ¹H NMR spectrum showed two aromatic protons of a symmetric 1,3,4,5-tetrasubstituted benzene ring (δ_{H} 6.58, s, H-2' and H-6'), two meta-coupled aromatic protons [δ_{H} 6.59 (1H, d, *J* = 1.5, H-4) and 6.54 (1H, d, *J* = 1.5, H-6)], five methoxy groups [δ_{H} 3.88 (3H, s, 5-OCH₃), 3.87 (3H, s, 7-OCH₃), 3.75 (6H, s, 3'-OCH₃ and 5'-OCH₃), and 3.67 (3H, s, 4'-OCH₃)], and one oxygenated methine [δ_{H} 5.62 (1H, dd, *J* = 6.5, 5.5, H-3)] coupled with two protons of one methylene group [δ_{H} 3.25 (1H, dd, *J* = 14.5, 5.5, H-10a) and 3.10 (1H, dd, *J* = 14.0, 6.5, H-10b)]. The JMOD and HSQC spectra exhibited 20 carbon resonances attributable to a carboxyl ester group (δ_{C} 167.5), four aromatic methine carbons (δ_{C} 108.2 $\times$ 2, 99.7, and 99.4), one oxygenated methine carbon (δ_{C} 80.2), one methylene carbon (δ_{C} 41.4), five methoxy carbons (δ_{C} 60.5, 56.4, 56.4, 56.4, and 56.2), and eight quaternary carbons [δ_{C} 167.4, 160.4, 155.3, 154.1 ($\times$ 2), 137.2, 132.6, and 107.8]. The above spectroscopic data indicated that **1** was a 3-benzylphthalide derivative.³² In the so-called A-ring, the protons at δ_{H} 6.59 (H-4) and δ_{H} 6.54 (H-6) gave HMBC correlations to the same carbons at δ_{C} 167.4 (C-5), 155.3 (C-9), and 107.8 (C-8)

indicated the connection through C-4 to C-9 (Fig. 2). The methoxy groups at δ_{H} 3.88 and 3.87 were determined to be located at C-5 and C-7 in this A-ring due to their HMBC correlations to these carbons. The methine group at δ_{H} 5.62 was coupled with the methylene CH₂-10 (δ_{H} 3.25 and 3.10) in an ABX system characteristic of 3-benzylphthalide derivatives.^{25–28} Next, the methylene group H₂-10 gave HMBC correlations to carbons at δ_{C} 132.6 (C-1') and 108.2 (C-2' and C-6'), and 122.9 (C-6') indicated the connectivity between A and B-rings through C-3 and C-10 (Fig. 2). The lactonization between C-1 and C-3 was defined by the HMBC correlation of H-3 to C-1 and the down-field chemical shift of H-3.³² NMR data of **7** were similar to those of **6** (Table 1). The only difference is the occurrence of the methoxy group at C-3'. The absolute configuration of **7** was defined using ECD data. Particularly, a positive Cotton effect at 260 nm indicated the 3*S* configuration of **7** (Fig. 3). This CE was opposite that of julacelide isolated from the moss *Erythrodontium julaceum*. Combined, the chemical structure of **7** was elucidated as shown in Fig. 1, namely marchatoside.

Compound **8** was obtained as a colorless oil. The molecular formula of **8** was deduced as C₂₀H₃₂O₂ from the sodiated molecular ion peak at *m/z* 327.2295 (calcd for [C₂₀H₃₂O₂ + Na]⁺, 327.2300) in the HRESI mass spectrum (Fig. S10A†). The ¹H NMR spectrum showed an olefinic proton (δ_{H} 5.56, d, *J* = 1.0, H-3), a vinyl group [δ_{H} 5.93 (1H, dd, *J* = 17.0, 1.5, H-14), 5.21 (1H, dd, *J* = 17.5, 2.0, H-15a), and 4.98 (1H, dd, *J* = 11.0, 2.0, H-15b)], five methyl groups [δ_{H} 1.96 (d, *J* = 1.0), 1.25, 1.24, 0.78 (d, *J* = 7.0), 0.56], and an ABX system of a methylene [δ_{H} 2.66 (1H, dd, *J* = 18.5, 7.0, H-1a) and 2.43 (1H, d, *J* = 18.0, H-1b)] coupled with a methine [δ_{H} 1.90 (1H, m, H-10)]. The JMOD and HSQC spectra exhibited a ketone carbonyl group (δ_{C} 198.8), two olefinic methine carbons (δ_{C} 129.1 and 147.1), one olefinic methylene carbon (δ_{C} 111.5), one oxygenated quaternary carbon (δ_{C} 72.8), five methyl carbons (δ_{C} 32.3, 28.5, 20.5, 19.6, and 16.3), five methylene carbons (δ_{C} 37.5, 37.4, 35.8, 35.7, and 31.3), two sp³ methine (δ_{C} 47.9 and 37.4), and three quaternary carbons (δ_{C} 169.4, 40.3, and 40.1). The above spectroscopic data indicated that **1** was a clerodane diterpene.^{33–36} HMBC correlations supported the chemical structure of **8** (Fig. 4). At first, the HMBC correlations of H₃-18 (δ_{H} 1.96) and H₃-19 (δ_{H} 1.25) to C-4 (δ_{C} 169.4) and C-5 (δ_{C} 40.1), of H-3 (δ_{H} 5.56) to C-4 and C-1 (δ_{C} 35.7), and of H₂-1 (δ_{H} 2.66 and 2.43) and H-10 (δ_{H} 1.99) to C-2 (δ_{C} 198.8) defined the structure of the A-ring (Fig. 4). Both methyl H₃-19 and H₃-20 (δ_{H} 0.56) gave a HMBC correlation to C-10 (δ_{C}

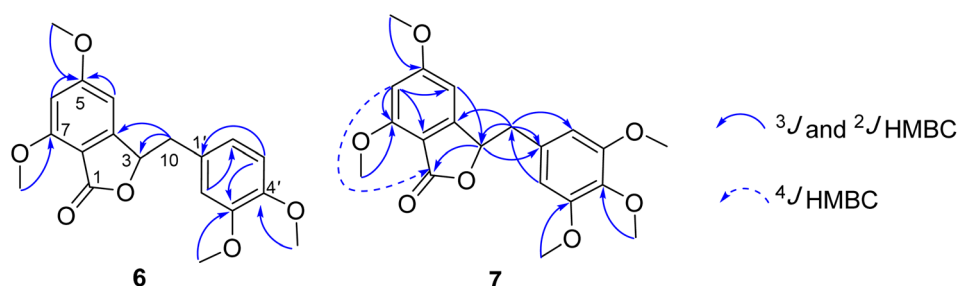


Fig. 2 Selected HMBC correlations of **6** and **7**.



Table 1 ^1H NMR (500 MHz, δ_{H} , multi, (J in Hz)) and ^{13}C NMR (125 MHz) spectral data of 6–7 and julacelide in acetone- d_6

No.	Julacelide		6		7	
	δ_{H} (multi, J in Hz)	δ_{C}	δ_{H} (multi, J in Hz)	δ_{C}	δ_{H} (multi, J in Hz)	δ_{C}
1		166.5		167.1		167.5
2	5.69 (dd, 6.0, 5.5)	80.5	5.85 (t, 6.0)	80.3	5.62 (dd, 6.5, 5.0)	80.2
3	7.05 (dd, 8.0, 2.0)	115.1	6.61 (s)	99.5	6.59 (d, 1.5)	99.7
4	7.65 (dd, 8.5, 8.0)	136.7		166.8		167.4
5	7.05 (dd, 8.0, 2.0)	111.8	6.54 (d, 2.0)	99.6	6.54 (d, 1.5)	99.4
6		159.3		160.3		160.4
7		123.5		105.1		107.8
8		153.2		154.8		155.3
9	3.25 (dd, 14.5, 5.0), 3.12 (dd, 14.0, 6.0)	40.6	3.25 (dd, 14.0, 5.0), 3.10 (dd, 14.0, 6.0)	40.6	3.25 (dd, 14.5, 5.0), 3.10 (dd, 14.5, 6.5)	41.4
1'		129.1		129.3		132.6
2'	6.82 (d, 2.0)	114.6	6.87 (d, 1.5)	114.6	6.58 (s)	108.2
3'		150.0		150.0		154.1
4'		149.3		148.3		137.2
5'	6.80 (d, 8.0)	112.5	6.82 (d, 8.0)	112.6		154.1
6'	6.73 (dd, 8.0, 2.0)	122.9	6.77 (dd, 8.5, 2.0)	122.9	6.57 (s)	108.2
5-OCH ₃			3.87 (s)	56.4	3.88 (s)	56.4
7-OCH ₃	3.89 (s)	56.0	3.89 (s)	56.0	3.87 (s)	56.2
3'-OCH ₃	3.74 (s)	56.0	3.75 (s)	56.3	3.75 (s)	56.4
4'-OCH ₃	3.71 (s)	56.1	3.73 (s)	56.4	3.67 (s)	60.5
5'-OCH ₃					3.75 (s)	56.4

47.9), while H-10 gave HMBC correlations to C-19 and C-20, supporting the position of H-20. Moreover, H₃-20 and H₃-17 (δ_{H} 0.78) gave HMBC correlations to the same carbons, C-8 (δ_{C} 37.4) and C-9 (δ_{C} 40.3), indicating their locations. A vinyl group was defined to attach at C-13 due to HMBC correlations of H₃-16 (δ_{H} 1.24), H₂-15 (δ_{H} 5.21 and 4.98), and H-14 (δ_{H} 5.93) to C-13 (δ_{C} 72.8) (Fig. 4). The NMR data of **8** were highly similar to those of (–)-roseostachenone³⁵ and 13-*epi*-(–)-roseostachenone,³⁶ indicating that they shared the same planar structure. The difference between them was easily observed in the change of the chemical shifts of H₃-19 (δ_{H} 1.25 in **8** vs. 1.06 in (–)-roseostachenone and 13-*epi*-(–)-roseostachenone) and CH₃-20 (δ_{H} 0.58 in **8** vs. 0.76 in (–)-roseostachenone and 13-*epi*-(–)-roseostachenone) recorded in the same deuterated solvent (CDCl₃). This finding proposes that **8** should have a *cis*-clerodane skeleton rather than a *trans*-clerodane of (–)-roseostachenone and 13-*epi*-(–)-roseostachenone. NOESY correlations (in CDCl₃) of H₃-17 (δ_{H} 0.77)/H₃-20 (δ_{H} 0.58)/H-1a (δ_{H} 2.50) indicated their same orientation. In contrast, NOESY correlations of H₃-19 (δ_{H} 1.25)/H-10 (δ_{H} 1.83)/H-1b (δ_{H} 2.69) indicated their same β -face. The downfield ^{13}C chemical shift of C-19 at δ_{C} 32.3 also supported the *cis* conjunction of H-10 and H₃-19.^{33,34} Combined, the chemical structure of **8** was elucidated as shown in Fig. 1, namely marchanol.

2.1 Alpha-glucosidase inhibition and kinetic study

Compounds **1**–**5** and **10**–**12** displayed strong inhibition, with IC₅₀ values ranging from 28.9 to 130.6 μM , while compounds **6**–**9** showed weak activity (Table 3). Alpha-glucosidase inhibition of compounds **13**–**15** was previously evaluated in many published reports.³⁷ Among the tested compounds, bis-bibenzyl-

type compounds **1**–**4** showed better inhibition. The main difference between **1**–**4** is in the linkage between C- and D-rings (Fig. 1). The ether connection in **1** and **4** might significantly decrease the activity, compared to the direct connection in **2**–**3**. The activity of **2** was stronger than **3**, indicating the important role of connectivity between C- and D-rings. The bis-bibenzyl series showed strong cytotoxicity against many cancer cell lines.³⁸ Nevertheless, fewer studies about the alpha-glucosidase inhibition of this series were conducted. Only marchantin C and riccardin C have been investigated so far.³⁸ In 2008, Dodo and co-workers reported the alpha-glucosidase inhibition of riccardin C and their oxygenated analogues.³⁹ All tested compounds showed potent activity, with IC₅₀ values ranging from 4.9 to 49 μM .³⁹ While ursolic acid (**12**) were thought to be a potent alpha-glucosidase inhibitor, the activities of 12-oleanene-3-one (**10**) and 3,11-dioxoursolic acid (**11**) have not been reported.

The most active compound **2** was selected for the enzyme inhibitory kinetic analysis. To examine the inhibition mechanism, activity at concentrations of 0, 3.61, 7.22, 14.44, and 28.88 μM of **2** was recorded. Lineweaver–Burk plots of **2** gave a group of lines with the same Michaelis constant (K_{m}), intersecting the y-axis in the second quadrant (Fig. 5A and B). Increasing inhibitor concentrations cause a decrease in the V_{max} of α -glucosidase. The kinetics of enzyme inhibition showed that **2** acted as a non-competitive inhibitor. The K_{i} value of **2** was determined as $67.1 \pm 1.28 \mu\text{M}$, respectively.

2.2 In silico docking study

The estimated binding energies of synthesized compounds to 4J5T protein obtained from 250 runs each per complex have





Table 2 ¹H and ¹³C NMR spectral data of **8**, (–)-roseostachenone and 13-*epi*-(–)-roseostachenone

No.	8			(–)-Roseostachenone		13- <i>epi</i> -(–)-Roseostachenone	
	δ_{H} (multi, <i>J</i> in Hz) (acetone- <i>d</i> ₆ , 500 MHz)	δ_{C} (acetone- <i>d</i> ₆ , 125 MHz)	δ_{H} (multi, <i>J</i> in Hz) (CDCl ₃ , 500 MHz)	δ_{H} (multi, <i>J</i> in Hz) (CDCl ₃ , 200 MHz)	δ_{C} (CDCl ₃ , 50 MHz)	δ_{H} (multi, <i>J</i> in Hz) (CDCl ₃ , 200 MHz)	δ_{C} (CDCl ₃ , 50 MHz)
1	2.66 (dd, 18.5, 7.0), 2.43 (d, 18.0)	35.7	2.69 (dd, 18.5, 6.5), 2.50 (d, 18.5)	2.28 (m)	34.8	2.28 (m)	34.3
2		198.8			200.4		200.5
3	5.56 (d, 1.0)	129.1	5.84 (brs)	5.67 (m)	125.4	5.66 (d, 1.2)	127.4
4		169.4			172.5		172.6
5		40.1			39.7		39.7
6		37.5			34.8		35.5
7		29.1			26.8		26.8
8		37.4			35.8		35.8
9		40.3			38.3		38.3
10	1.90 (m)	47.9	1.83 (d, 6.5)	1.87 (m)	45.5		45.5
11		31.3			31.1		31.1
12		35.8			35.5		34.7
13		72.8			73.0		73.0
14	5.93 (dd, 17.0, 10.5)	147.1	5.87 (dd, 10.5, 17.5)	5.83 (dd, 10.70, 17.33)	144.9	5.82 (dd, 17.4, 10.7)	144.8
15	5.21 (dd, 17.5, 2.0), 4.98 (dd, 11.0, 2.0)	111.5	5.09 (d, 11.0), 5.20 (d, 16.5)	5.03 (dd, 10.7, 1.0), 5.16 (dd, 17.3, 1.0)	112.0	5.14 (dd, 17.4, 1.3), 5.03 (dd, 10.7, 1.3)	111.9
16	1.24 (s)	28.5	1.22 (s)	1.23 (s)	27.6	1.22 (s)	27.7
17	0.78 (d, 7.0)	16.3	0.77 (d, 7.0)	0.77 (d, 6.5)	15.8	0.79 (d, 6.8)	15.6
18	1.96 (d, 1.0)	20.5	1.94 (d, 1.5)	1.84 (d, 1.0)	18.9	1.83 (d, 1.1)	18.9
19	1.25 (s)	32.3	1.25 (s)	1.06 (s)	18.3	1.06 (s)	18.2
20	0.56 (s)	19.6	0.58 (s)	0.76 (s)	18.0	0.76 (s)	17.9



The other structure of **3** showed a slight difference in the order of the aromatic nuclei as well as the deletion of a hydroxy group, which reduced the number of hydrogen bonds but ensured hydrophobic interactions. Only one H-bond with Asp 568 and one pi-pi stacking with Tyr 709 were the major interactions of **3**. Regarding **2**, the aromatic scaffolds of this structure were arranged in accordance with the pi-pi stacking regions of Phe 385, Phe 389, or Tyr 709. Therefore, unlike **1** or **1a**, compound **2** performed four H-bonds with Arg 387, Glu 429,

The NMR spectra were recorded on a Bruker Avance III spectrometer (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR). The HRESIMS was recorded using an HRESIMS MicroTOF-Q mass spectrometer on an LC-Agilent 1100 LC-MSD Trap spectrometer. Thin layer chromatography (TLC) was carried out on pre-coated silica gel 60 F₂₅₄ or silica gel 60 RP-18 F_{254S} (Merck). Spots were visualized by spraying with a 10% H_2SO_4 solution, followed by heating. Gravity-column chromatography was performed on silica gel 60 (0.040–0.063 mm, Himedia).

3.3.1. Marchantin A (1). Yellow powder. $C_{28}H_{24}O_5$. 1H NMR (500 MHz, $CDCl_3$, δ , ppm, J /Hz): 7.13 (1H, dd, $J = 8.0, 7.5$ Hz, H-11), 7.00 (1H, dd, $J = 8.0, 1.5$ Hz, H-10), 6.97 (1H, t, $J = 7.8, H-13'$), 6.91 (1H, d, $J = 8.5$ Hz, H-3), 6.91 (1H, d, $J = 8.5$ Hz, H-5), 6.85 (1H, dd, $J = 8.0, 1.5$ Hz, H-12), 6.57 (1H, d, $J = 8.0$ Hz, H-2), 6.57 (1H, d, $J = 8.0$ Hz, H-6), 6.57 (1H, dd, $J = 2.5, 2.0$ Hz, H-10'), 6.53 (1H, dd, $J = 8.5, 2.0$ Hz, H-12'), 6.46 (1H, d, $J = 1.5$ Hz, H-5'), 6.39 (1H, brd, $J = 7.5$ Hz, H-14'), 5.13 (1H, d, $J = 1.5$ Hz, H-3'),





Fig. 5 (A) Lineweaver–Burk plot for alpha-glucosidase inhibition by **2**. (B) Plots of slope versus concentration of **2** for the determination of the inhibition constant K_i .

2.97–3.01 (2H, m, H-7, H-8), 2.78–2.80 (2H, m, H-7'), 2.72–2.74 (2H, m, H-8'). ^{13}C NMR (125 MHz, CDCl_3 , δ , ppm): 156.8 (C-11'), 153.2 (C-1), 148.7 (C-13), 146.5 (C-2'), 144.3 (C-6'), 143.1 (C-9'), 139.7 (C-14), 139.1 (C-4), 136.2 (C-9), 132.5 (C-4'), 130.8 (C-1'), 129.6 (C-3), 129.6 (C-5), 128.9 (C-13'), 126.0 (C-11), 123.2 (C-14'),

121.9 (C-10), 121.2 (C-2), 121.2 (C-6), 115.5 (C-10'), 114.4 (C-12), 112.0 (C-12'), 109.3 (C-5'), 107.9 (C-3'), 35.5 (C-8'), 35.3 (C-7), 34.1 (C-7'), 30.3 (C-8).

3.3.2. Isoriccardin C (2). Yellow powder. $\text{C}_{28}\text{H}_{26}\text{O}_4$. ^1H NMR (500 MHz, acetone- d_6 , δ , ppm, J/Hz): 7.13 (1H, dd, $J = 7.5$, 2.5 Hz, H-5), 7.10 (1H, dd, $J = 7.5$, 2.5 Hz, H-3), 7.305 (1H, t, $J = 8.0$ Hz, H-13'), 6.86 (1H, d, $J = 7.5$ Hz, H-12'), 6.82 (1H, d, $J = 8.5$ Hz, H-2), 6.81 (1H, d, $J = 8.5$ Hz, H-6), 6.81 (1H, m, H-13), 6.74 (1H, d, $J = 8.0$ Hz, H-6'), 6.70 (1H, dd, $J = 8.0$, 2.0 Hz, H-14'), 6.69 (1H, dd, $J = 8.0$, 2.0 Hz, H-5'), 6.65 (1H, brs, H-10), 6.54 (1H, d, $J = 7.5$ Hz, H-14), 5.73 (1H, d, $J = 1.0$ Hz, H-3'), 3.02–3.16 (4H, m, H-7, H-8), 2.50–2.64 (2H, m, H-8'), 2.30–2.33 (2H, m, H-7'). ^{13}C NMR (125 MHz, acetone- d_6 , δ , ppm): 206.1 (C-11'), 177.1 (C-12), 155.5 (C-1), 154.9 (C-11), 145.5 (C-2'), 143.4 (C-1'), 142.1 (C-9), 138.1 (C-4), 138.1 (C-9'), 134.6 (C-4'), 131.9 (C-3), 131.6 (C-13), 131.4 (C-5), 129.1 (C-13'), 122.4 (C-14), 122.1 (C-2), 122.1 (C-6), 121.6 (C-5'), 121.6 (C-14'), 120.5 (C-10'), 117.5 (C-10), 116.4 (C-3'), 116.3 (C-6'), 113.7 (C-12'), 38.5 (C-7'), 37.6 (C-8'), 36.8 (C-8), 35.4 (C-7).

3.3.3. Riccardin C (3). Yellow powder. $\text{C}_{28}\text{H}_{26}\text{O}_4$. ^1H NMR (500 MHz, acetone- d_6 , δ , ppm, J/Hz): 7.03 (1H, t, $J = 8.0$ Hz, H-13), 6.95 (1H, t, $J = 8.0$ Hz, H-3), 6.95 (1H, t, $J = 8.0$ Hz, H-5),

Table 3 Alpha-glucosidase inhibition (IC_{50}) of the test compounds

Bio-source		IC_{50} (μM)
Compound	1	57.3 ± 1.9
	1a	150.6 ± 2.9
	2	28.9 ± 0.2
	3	42.2 ± 1.4
	4	130.6 ± 3.0
	5	129.5 ± 2.0
	6	>200
	7	>200
	8	>200
	9	>200
	10	75.1 ± 1.8
	11	101.0 ± 3.0
	12	86.0 ± 6.9
Positive control	Acarbose	330.9 ± 4.2



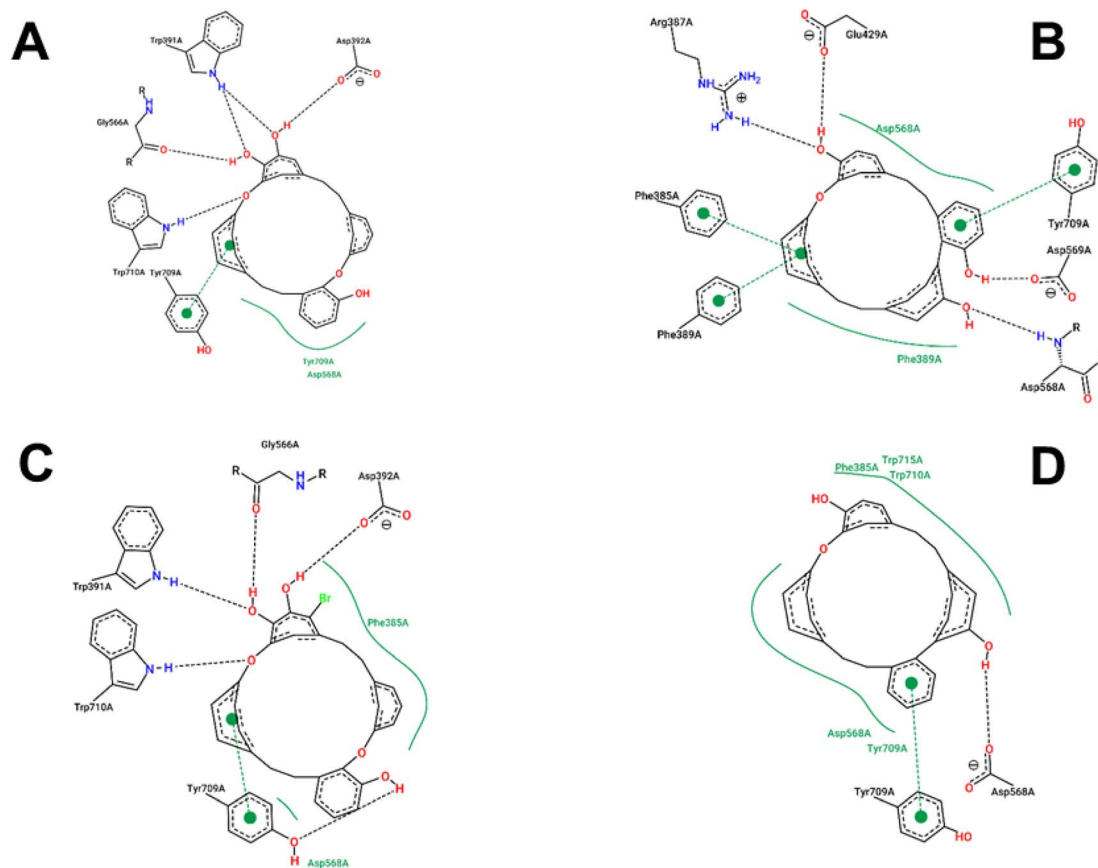


Fig. 6 1–4J5T (A), 2–4J5T (B), 1a–4J5T (C) and 3–4J5T (D) interactions.

6.93 (1H, m, H-10), 6.77 (1H, d, $J = 8.0$ Hz, H-11'), 6.73 (1H, m, H-2), 6.73 (1H, m, H-6), 6.73 (1H, m, H-12), 6.72 (1H, d, $J = 8.0$ Hz, H-6'), 6.50 (1H, m, H-5'), 5.36 (1H, d, H-3'), 2.63–3.03 (m, H-7, H-8, H-7', H-8'). ^{13}C NMR (100 MHz, acetone- d_6 , δ , ppm): 157.8 (C-11), 154.4 (C-1), 154.1 (C-13'), 148.0 (C-2'), 145.4 (C-1'), 144.3 (C-9), 141.8 (C-9'), 140.8 (C-4), 133.5 (C-4'), 133.4 (C-13), 133.1 (C-11'), 130.3 (C-3), 130.3 (C-5), 128.9 (C-14), 126.8 (C-12'), 122.9 (C-2), 122.9 (C-6), 122.7 (C-10'), 121.5 (C-5'), 117.7 (C-10), 117.4 (C-14'), 116.6 (C-6'), 114.0 (C-12), 38.7 (C-7), 38.5 (C-8'), 37.9 (C-7'), 36.0 (C-8).

3.3.4. Marchantin K (4). White amorphous powder. $\text{C}_{29}\text{H}_{28}\text{O}_7$. ^1H NMR (500 MHz, acetone- d_6 , δ , ppm, J/Hz): 6.95 (1H, brd, $J = 8.0$ Hz, H-3), 6.95 (1H, brd, $J = 8.0$ Hz, H-5), 6.88 (1H, t, $J = 7.5$ Hz, H-13'), 6.82 (1H, dd, $J = 8.0, 1.5$ Hz, H-10), 6.93 (1H, m, H-10), 6.76 (1H, d, $J = 8.5$ Hz, H-11), 6.68 (1H, d, $J =$

2.0 Hz, H-10'), 6.59 (1H, d, $J = 2.0$ Hz, H-5'), 6.51 (1H, brd, $J = 8.0$ Hz, H-2), 6.51 (1H, brd, $J = 8.0$ Hz, H-6), 6.45 (1H, dd, $J = 8.5, 3.0$ Hz, H-12'), 6.05 (1H, brd, $J = 7.0$ Hz, H-14'), 4.97 (1H, d, $J = 2.0$ Hz, H-3'), 4.08 (1H, dd, $J = 9.5, 4.0$ Hz, H-7'), 3.20 (s, -OMe), 3.09–3.14 (1H, m, H-7a), 2.95–3.06 (1H, m, H-7b), 2.95–3.06 (2H, m, H-8) 3.00 (1H, m, H-8'a), 2.59 (1H, dd, $J = 13.0, 10.0$ Hz, H-8'b). ^{13}C NMR (125 MHz, acetone- d_6 , δ , ppm): 157.6 (C-11'), 153.9 (C-1), 149.9 (C-2'), 147.3 (C-6'), 147.1 (C-12), 146.3 (C-14), 140.0 (C-4), 139.1 (C-9'), 138.8 (C-13), 136.8 (C-1'), 133.3 (C-4'), 131.4 (C-9), 129.4 (C-3), 129.4 (C-5), 127.8 (C-13'), 125.5 (C-14'), 123.4 (C-2), 121.4 (C-6), 120.9 (C-10), 116.9 (C-10'), 114.4 (C-12'), 112.3 (C-11), 107.6 (C-3'), 106.0 (C-5'), 84.1 (C-7'), 43.8 (C-8'), 35.5 (C-7), 30.1 (C-8).

3.3.5. Lunularin (5). White amorphous solid. $\text{C}_{14}\text{H}_{14}\text{O}_2$. ^1H NMR (500 MHz, acetone- d_6 , δ , ppm, J/Hz): 7.07 (1H, t, $J = 7.8$ Hz, H-5'), 7.03 (1H, d, $J = 8.0$ Hz, H-3), 7.03 (1H, d, $J = 8.0$ Hz, H-5), 6.73 (1H, d, $J = 8.5$ Hz, H-2), 6.73 (1H, d, $J = 8.5$ Hz, H-6), 6.69 (1H, d, $J = 2.0$ Hz, H-4'), 6.67 (1H, s, H-2'), 6.63 (1H, d, $J = 8.0$ Hz, H-6'), 2.78 (2H, s, H-7), 2.78 (2H, s, H-8). ^{13}C NMR (125 MHz, acetone- d_6 , δ , ppm): 157.4 (C-3'), 155.5 (C-1), 143.6 (C-1'), 132.6 (C-4), 129.3 (C-5'), 129.1 (C-3), 129.1 (C-5), 119.5 (C-6'), 115.4 (C-3'), 115.0 (C-2), 115.0 (C-6), 112.7 (C-4'), 38.1 (C-8), 36.8 (C-7).

3.3.6. 3R-(3,4-Dimethoxybenzyl)-5,7-dimethoxyphthalide (6). Colorless oil. $\text{C}_{19}\text{H}_{20}\text{O}_6$. ^1H NMR (500 MHz, acetone- d_6 , δ , ppm, J/Hz): 6.87 (1H, d, $J = 1.5$ Hz, H-2'), 6.82 (1H, d, $J = 8.0$ Hz, H-5'), 6.77 (1H, dd, $J = 8.5, 2.0$ Hz, H-6'), 6.61 (1H, s, H-4),

Table 4 The best binding energy between ligands and the 4J5T protein

Ligand	Best binding energy from docking (kcal mol $^{-1}$)
1	−8.26
1a	−9.74
2	−9.84
3	−9.31



6.54 (1H, d, $J = 2.0$ Hz, H-6), 5.85 (1H, t, $J = 6.0$ Hz, H-3), 3.89 (3H, s, 7-OCH₃), 3.87 (3H, s, 5-OCH₃), 3.75 (3H, s, 3'-OCH₃), 3.73 (3H, s, 4'-OCH₃), 3.25 (1H, dd, $J = 14.0, 5.0$ Hz, H-10a), 3.10 (1H, dd, $J = 14.0, 5.0$ Hz, H-10b). ¹³C NMR (125 MHz, acetone-*d*₆, δ , ppm): 167.1 (C-1), 167.1 (C-5), 160.3 (C-7), 154.8 (C-9), 150.0 (C-3'), 148.3 (C-4'), 129.3 (C-1'), 122.9 (C-6'), 114.6 (C-2'), 112.6 (C-5'), 105.1 (C-8), 99.6 (C-6), 99.5 (C-4), 99.5 (C-3), 56.4 (5-OCH₃), 56.4 (4'-OCH₃), 56.3 (3'-OCH₃), 56.0 (7-OCH₃).

3.3.7. Marchatoside (7). Colorless oil. C₂₀H₂₂O₇. HRESIMS m/z : 375.1397 [M + H]⁺ (calcd for C₂₀H₂₃O₇⁺, 375.1443). ¹H NMR (500 MHz, acetone-*d*₆, δ , ppm, J /Hz) and ¹³C NMR (125 MHz, acetone-*d*₆, δ , ppm) data: see Table 1.

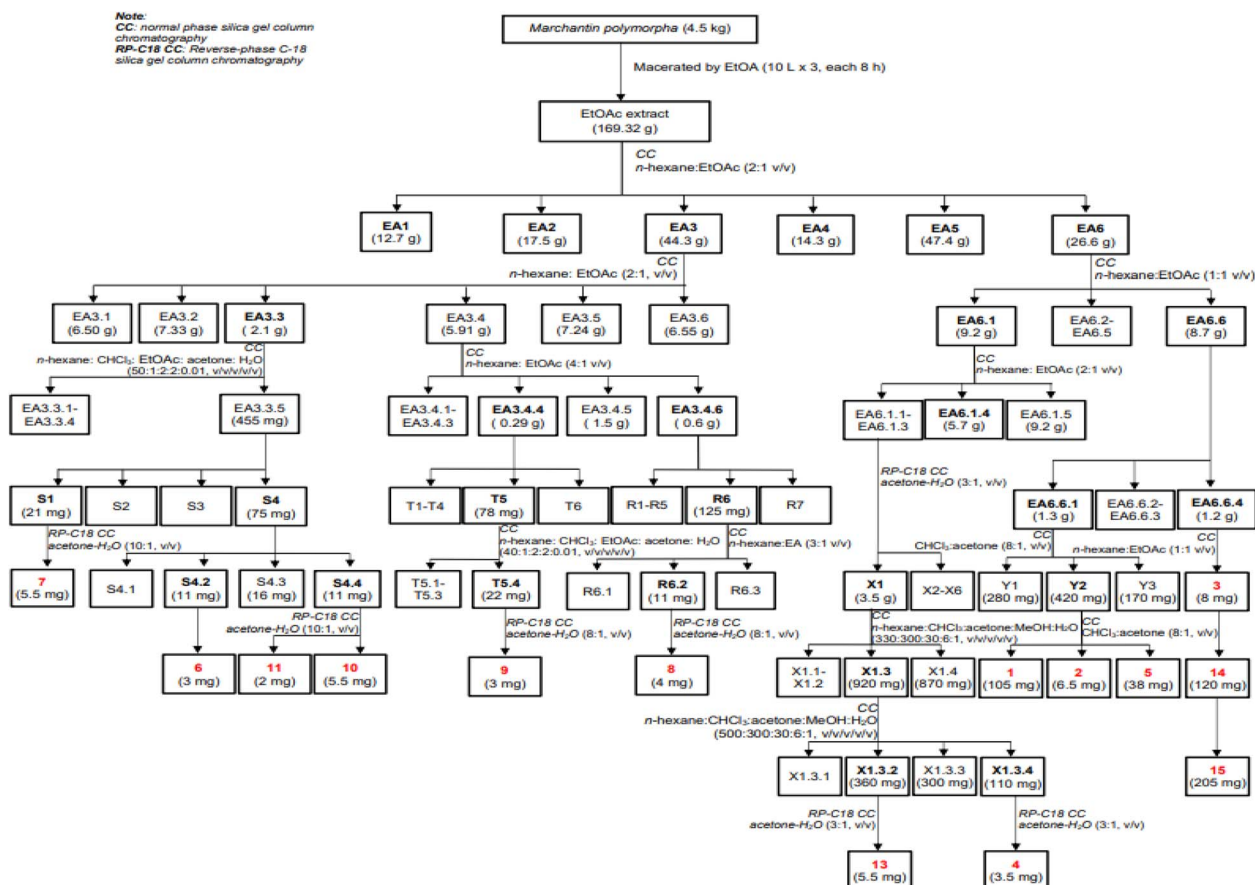
3.3.8. Marchanol (8). Colorless oil. C₂₀H₃₂O₂. HRESIMS m/z : 327.2295 [M + Na]⁺ (calcd for C₂₀H₃₂O₂Na⁺, 327.2300). ¹H NMR (500 MHz, acetone-*d*₆, δ , ppm, J /Hz) and ¹³C NMR (125 MHz, acetone-*d*₆, δ , ppm) data: see Table 2.

3.3.9. Vitexilactone (9). Colorless oil. C₂₂H₃₄O₄. ¹H NMR (500 MHz, acetone-*d*₆, δ , ppm, J /Hz): 5.86 (1H, p, $J = 1.5, 1.5, 2.0, 2.0$ Hz, H-14), 5.34 (1H, q, $J = 3.0, 3.0, 2.5$ Hz, H-6), 4.85 (1H, d, $J = 2.0$ Hz, H-16), 2.61 (2H, m, H-12), 2.17 (1H, m, H-8), 2.02 (1H, m, H-9), 2.00 (1H, s, H-2'), 1.85 (1H, q, $J = 6.5, 4.5, 3.0$ Hz, H-11a), 1.82 (1H, q, $J = 4.0, 4.0, 6.5$ Hz, H-11b), 1.76 (1H, d, 2.5 Hz, H-5), 1.71–1.50 (2H, m, H-2), 1.47–1.44 (2H, m, H-7), 1.43–1.32 (2H, m, H-1), 1.37–1.24 (2H, m, H-3), 1.30 (3H, s, 20-CH₃), 1.02 (3H, s, 19-CH₃), 0.93 (3H, s, 18-CH₃), 0.92 (3H, s, 17-CH₃). ¹³C NMR (125 MHz, acetone-*d*₆, δ , ppm): 174.0 (C-15), 173.4 (C-13), 170.5

(C-1'), 114.8 (C-14), 73.8 (C-16), 70.4 (C-6), 44.7 (C-10), 45.6 (C-5), 43.0 (C-3), 37.4 (C-7), 36.9 (C-9), 34.7 (C-4), 34.0 (C-18), 32.8 (C-8), 32.6 (C-11), 32.5 (C-1), 26.0 (C-12), 24.1 (C-19), 21.8 (C-2'), 19.6 (C-2), 19.5 (C-20), 16.4 (C-17).

3.3.10. 12-Oleanene-3-one (10). Yellow amorphous powder. C₂₀H₂₀O₈. ¹H NMR (500 MHz, acetone-*d*₆, δ , ppm, J /Hz): 5.24 (1H, t, $J = 4.0$ Hz, H-12), 2.31 (1H, m, H-9), 1.19 (3H, s, H-27), 1.10 (3H, s, H-25), 1.06 (3H, s, H-26), 1.05 (3H, s, H-24), 1.03 (3H, s, H-23), 0.89 (3H, s, H-29), 0.86 (3H, s, H-30), 0.84 (3H, s, H-28). ¹H NMR (500 MHz, CDCl₃, δ , ppm, J /Hz): 5.21 (1H, t, $J = 3.5, 4.0$ Hz, H-12), 2.37 (1H, m, H-9), 1.25 (3H, s, H-27), 1.07 (3H, s, H-24), 1.06 (3H, s, H-23), 1.02 (3H, s, H-25), 1.00 (3H, s, H-26), 0.92 (3H, s, H-29), 0.87 (3H, s, H-30), 0.84 (3H, s, H-28). ¹³C NMR (125 MHz, acetone-*d*₆, δ , ppm): 216.2 (C-3), 146.0 (C-13), 122.8 (C-12), 56.0 (C-5), 47.8 (C-9), 47.7 (C-4), 47.3 (C-19), 47.0 (C-18), 41.9 (C-14), 40.0 (C-7), 39.8 (C-1), 37.1 (C-22), 35.5 (C-10), 34.7 (C-2), 34.7 (C-21), 33.1 (C-7), 32.3 (C-17), 32.3 (C-30), 31.3 (C-20), 28.9 (C-28), 26.9 (C-16), 26.4 (C-15), 26.4 (C-23), 24.6 (C-27), 23.7 (C-29), 23.7 (C-11), 21.9 (C-24), 20.4 (C-6), 17.3 (C-26), 15.6 (C-25).

3.3.11. 3,11-Dioxoursolic acid (11). White amorphous powder. C₃₀H₄₄O₄. ¹H NMR (400 MHz, CDCl₃, δ , ppm, J /Hz): 5.63 (1H, s, H-12), 2.39 (1H, s, H-9), 1.31 (3H, s, H-27), 1.24 (3H, s, H-26), 1.02 (3H, s, H-25), 0.97 (3H, d, $J = 8.0$ Hz, H-30), 0.95 (3H, s, H-24), 0.90 (3H, s, H-23), 0.87 (3H, d, $J = 8.0$ Hz, H-29). ¹³C NMR (100 MHz, acetone-*d*₆, δ , ppm): 217.4 (C-3),



Scheme 1 Isolation procedure of compounds 1–15.



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