Synthesis of myricetin derivatives and evaluation of their hypoglycemic activities

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Abstract

Myricetin is a common plant-derived flavonoid and exhibits a wide range of activities. However, myricetin also exhibits substantial limitations, such as its poor water-solubility and low stability in body when it was administrated by oral. To solve these problems, a series of myricetin derivatives with different disaccharide groups were designed, synthesized and evaluated their hypoglycemic activities. All synthesized compounds displayed significant α-glucosidase inhibitory activity in comparison with acarbose *in vitro*, which indicated that myricetin derivatives with different disaccharide groups had good hypoglycemic activity and could be further developed as hypoglycemic drugs.

Introduction

Myricetin (3,3',4',5,5',7-hexahydroxyflavone, Fig. 1), is a widespread naturally occurring flavonoid, which can be found in lots of berries, fruits, vegetables and herbal medicines [1]. Myricetin has multiple biological activities, such as antioxidant, anti-diabetic, anti-inflammatory, anti-carcinogenic and anti-proliferative effects [2–15]. In previous study, myricetin were also reported which could treat and prevent colitis and the risk of colitis-associated colorectal cancer (CAC) [16]. However, myricetin exhibits poor water-solubility and low stability in body when it was administrated by oral. It is reported that the chemical modification of lead compounds by saccharides and their derivatives can improve their biological activities, stability and water solubility, and decrease the toxicity and side effect efficiently [17]. Then M10, which was produced by adding a hydrophilic glycosylation group, was selected for further research and development because of its better water-solubility and metabolic stability, as well as higher efficacy and higher safety than myricetin (Fig. 1) [18]. This result indicated that the disaccharide group connected at C-3 of myricetin may play an important role in improve drug-like properties. Encouraged by the excellent result, a series of myricetin derivatives with different disaccharide groups were designed and synthesized, as well as their intracellular activities in hypoglycemic were determined for further structure activity relationship study (Fig. 1).

Results And Discussion

Chemistry

A series of myricetin derivatives with different glycosylation groups **4a–4i** were obtained via a sequence of linear steps according to our previous study (Scheme 1) [18]. Compound **3a-i** were produced from condensation of the tetrabenzyl myricetin **1** and various glycosyl donors **2a-i** in a mixture of 1, 2-dichloroethane and potassium carbonate solution at 45^{o}C in presence of a catalytic amount of tetrabutyl ammonium bromide. The tetrabenzyl groups of Compound **1** were introduced from benzyl bromide mediated by potassium carbonate, then by hydrolysis reaction in presence of 3M hydrochloric acid for 2 steps [18]. The glycosyl donors **2a-i** were synthesized via acetylation and bromination reaction successively from various disaccharide donors **2'a-i** (Scheme 1). These disaccharide donors **2'a-i** were

prepared by glycosylation of the corresponding saccharide acceptor with donor according to Magnusson's procedure [19].

Reagents and conditions: (a) Bu_4NBr (2 eq), K_2CO_3 (3.75 eq), H_2O, 1,2-dichloroethane, 45 ^{o} C, 3 h; (b) MeONa (1 eq), MeOH, rt, 5 h; (c) H_2, 10% Pd/C, MeOH, 12 h, rt.

Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, 12 h, rt.; (b) Ac_2O, AcONa, 5 h, rt; (c) HBr, Ac_2O, DCM, 0 ^{o} C, 5 h.

Next, the myricetin derivatives **4a-i** were obtained after complete hydrolysis of intermediate **3a-i** with 5.4 M sodium methoxide in methanol at room temperature for 5 h, then adjusting the pH to neutral by hydrogen ion resin, and catalytic hydrogenation of the resulting mixture with hydrogen gas in presence of 10% palladium over carbon at room temperature for 48 h. The yields of **3a-i** and **4a-i** were summarized in Table 1 and Table 2, respectively. The structures of compounds **4a-i** were characterized by MS and NMR.

Hypoglycemic activity

The hypoglycemic activities of the synthesized derivatives were evaluated by α-glucosidase inhibition assay, where acarbose at 200 μM was used as reference. As shown in Table 3, the inhibition rates of all of the compounds **4a-4i** were >80% comparing with the inhibitory rate of the positive control group at 24.03%. The result suggested that all compounds displayed significant α-glucosidase inhibitory activity at 50 μM concentration, and the rates were higher than myricetin at 59.86%.

Table 3 Hypoglycemic profile of **4a-i**

Compounds	Concentration (μM)	Inhibition rate (%)
Control group	—	0 ± 2.93
Acarbose	200	24.03 ± 10.21*
Myricetin	50	59.86 ± 0.58**
4a	50	86.41 ± 5.73**
4b	50	82.00 ± 2.28**
4c	50	83.11 ± 1.34**
4d	50	88.50 ± 1.99**
4e	50	82.93 ± 2.78**
4f	50	88.90 ± 1.99**
4g	50	80.29 ± 2.87**
4h	50	89.71 ± 1.90**
4i	50	87.38 ± 0.15**

*P < 0.05, **P < 0.01 versus the control group

Conclusion

In general, a library of myricetin derivatives with different disaccharide groups were designed, synthesized and evaluated in hypoglycemic activities. All synthesized compounds displayed significant α-glucosidase inhibitory activity in comparison with acarbose *in vitro*, which indicated that myricetin derivatives with different disaccharide groups had good hypoglycemic activity and could be for further research on hypoglycemic drug.

Experimental Section

Reagents and apparatus

Starting materials were purchased from commercial suppliers. Thin-layer chromatography (TLC) was performed using silica gel GF-254 plates (Qing-Dao Chemical Company, Qingdao, China) with detection by UV (254 nm or 365 nm). Column chromatography was performed on silica gel (200–300 mesh, Qingdao China). ^{1}H NMR and ^{13}C NMR spectra were obtained with tetramethylsilane (TMS) as an internal standard in DMSO-d_6 on a Bruker 400 spectrometer at 500 MHz and 125 MHz, respectively. The abbreviations used for NMR signals are as follows: s = singlet, d = doublet, and m = multiplet. ESI Mass spectra were recorded on a Waters Quattro Micro mass instrument.

Chemistry

General procedures for the synthesis of 2a-i

The synthesis procedures of myricetin derivatives **4a-i** are as follows. Firstly, Compound **2″a-i** (0.25 mmol) were dissolved in methanol (40 mL), 10% palladium-on-charcoal (100 mg) was added. The mixture was stirred at room temperature under hydrogen atmosphere for 12 h. After reaction, the palladium-on-charcoal was filtered, and the organic phase was evaporated to dryness. Then acetic anhydride (20 mL) and sodium acetate (0.3 mmol) were added successively, the mixture was stirred at room temperature for 5 h. After acetic anhydride was evaporated to dryness, the residue was diluted with dichloromethane (20 mL) and water (20 mL). The organic phase was separated, washed with brine, dried with anhydrous sodium sulfate, concentrated to afford Compound **2′a-i**. Then, the products were used directly in the next step without purification. Compound **2′a-i** were dissolved in dichloromethane (40 mL), then cooled to 0 °C. The hydrobromic acid in acetic acid (15 mL) was added under ice bath, and the reaction was performed at 0 °C for 30 min. The mixture was washed with water, saturated sodium bicarbonate solution until the pH value was neutral. The organic phase was dried over anhydrous sodium sulfate, concentrated, and purified with silica gel (petroleum ether/ethyl acetate, 2 : 1) to afford Compound **2a-i**.

*(2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-3,4,5-triacetoxy-6-bromotetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2a)

White solid (yield 91%); MS(ESI): m/z = 699 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-bromo-6-((((2R,3R,4S,5R,6R)-3,5-diacetoxy-4,6-bis(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2b)

White solid (yield 85%); MS(ESI): m/z = 699 $[M + H]^+$.

*(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2c)

White solid (yield 89%); MS(ESI): m/z = 699 $[M + H]^+$.

*(2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-(((2S,3R,4S,5R)-3,5-diacetoxy-2-bromotetrahydro-2H-pyran-4-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2d)

White solid (yield 81%); MS(ESI): m/z = 627 $[M + H]^+$.

*(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromotetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2e)

White solid (yield 88%); MS(ESI): m/z = 699 $[M + H]^+$.

*(2R,3R,4S,5S,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromotetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2f)

White solid (yield 88%); MS(ESI): *m/z* = 699 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-bromo-6-((((2R,3R,4R,5R)-3,4-diacetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2g)

White solid (yield 75%); MS(ESI): *m/z* = 627 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-bromo-6-((((2S,3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2h)

White solid (yield 85%); MS(ESI): *m/z* = 627 $[M + H]^+$.

*(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*2i)

White solid (yield 85%); MS(ESI): *m/z* = 699 $[M + H]^+$.

General procedures for the synthesis of 3a-i

To a suspension of **1** (2.95 mmol) in 1, 2-dichloroethane (20 mL), **2a-i** (5.90 mmol), tetra-butyl ammonium bromide (5.89 mmol) and 0.25 mol/L potassium carbonate solution (16 mL) were added. The mixture was stirred at 45°C for 3 h, then cooled to room temperature and diluted with dichloromethane (20 mL). The organic phase was separated, washed with brine, dried with anhydrous sodium sulfate, concentrated, and purified with silica gel (petroleum ether/ethyl acetate/dichloromethane, 2 : 1 : 1) to afford Compound **3a-i**.

*(2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-3,4,5-triacetoxy-6-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3a)

Yellow solid (yield 51%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.51 (s, 1H), 7.50 (d, *J* = 7.3 Hz, 4H), 7.48–7.31 (m, 15H), 7.29 (dd, *J* = 4.9, 1.7 Hz, 3H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 5.52 (d, *J* = 8 Hz, 1H), 5.33 (d, *J* = 2.8 Hz, 1H), 5.23 (m, 5H), 5.20 (d, *J* = 5.8 Hz, 4H), 5.12 (m, 2H), 4.91 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.40 (d, *J* = 7.9 Hz, 1H), 4.34 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.07 (d, *J* = 6.9 Hz, 2H), 3.91 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.82 (t, *J* = 6.9 Hz, 1H), 3.69 (t, *J* = 9.5 Hz, 1H), 3.60–3.50 (m, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.92 (s, 3H); MS(ESI): *m/z* = 1297 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)-6-((((2R,3R,4S,5R,6R)-3,5-diacetoxy-4,6-bis(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3b)

Yellow solid (yield 50%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.52 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 4H), 7.50–7.41 (m, 15H), 7.35 (dd, *J* = 4.9, 1.7 Hz, 3H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 5.61 (d, *J* = 8 Hz, 1H), 5.38 (d, *J* = 2.8 Hz, 1H), 5.25 (m, 5H), 5.18 (d, *J* = 5.8 Hz, 4H), 5.16–5.08 (m, 2H), 4.91 (dd, *J* = 10.4,

3.4 Hz, 1H), 4.51 (d, *J* = 7.9 Hz, 1H), 4.39 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.13 (d, *J* = 6.9 Hz, 2H), 3.95 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.88 (t, *J* = 6.9 Hz, 1H), 3.75 (t, *J* = 9.5 Hz, 1H), 3.60–3.48 (m, 1H), 2.18 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.81 (s, 3H); MS(ESI): *m/z* = 1297 $[M + H]^+$.

*(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3c)

Yellow solid (yield 53%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): *δ* 12.51 (s, 1H), 7.57 (d, *J* = 7.3 Hz, 4H), 7.50–7.39 (m, 15H), 7.31 (dd, *J* = 4.9, 1.7 Hz, 3H), 6.47 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 5.56 (d, *J* = 8 Hz, 1H), 5.33 (d, *J* = 2.8 Hz, 1H), 5.24 (m, 5H), 5.16 (d, *J* = 5.8 Hz, 4H), 5.12–5.05 (m, 2H), 4.92 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.41 (d, *J* = 7.9 Hz, 1H), 4.35 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.08 (d, *J* = 6.9 Hz, 2H), 3.90 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.85 (t, *J* = 6.9 Hz, 1H), 3.74 (t, *J* = 9.5 Hz, 1H), 3.60–3.48 (m, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.82 (s, 3H); MS(ESI): *m/z* = 1297 $[M + H]^+$.

*(2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-(((2S,3R,4S,5R)-3,5-diacetoxy-2-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-4-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3d)

Yellow solid (yield 74%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): *δ* 12.51 (s, 1H), 7.58 (d, *J* = 7.3 Hz, 4H), 7.42–7.35 (m, 15H), 7.31 (dd, *J* = 4.9, 1.7 Hz, 3H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 5.42 (d, *J* = 8 Hz, 1H), 5.30 (d, *J* = 2.8 Hz, 1H), 5.21 (m, 5H), 5.16 (d, *J* = 5.8 Hz, 4H), 5.10–5.01 (m, 2H), 4.90 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.41 (d, *J* = 7.9 Hz, 1H), 4.36 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.69 (t, *J* = 9.5 Hz, 1H), 3.56–3.50 (m, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.92 (s, 3H); MS(ESI): *m/z* = 1225 $[M + H]^+$.

*(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3e)

Yellow solid (yield 52%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): *δ* 12.45(s, 1H), 7.50 (d, *J* = 7.3 Hz, 4H), 7.47–7.34 (m, 15H), 7.32 (dd, *J* = 4.9, 1.7 Hz, 3H), 6.47 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 5.56 (d, *J* = 8 Hz, 1H), 5.37 (d, *J* = 2.8 Hz, 1H), 5.30 (m, 5H), 5.12 (d, *J* = 5.8 Hz, 4H), 5.10–5.01 (m, 2H), 4.92 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.41 (d, *J* = 7.9 Hz, 1H), 4.35 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.08 (d, *J* = 6.9 Hz, 2H), 3.92 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.83 (t, *J* = 6.9 Hz, 1H), 3.74 (t, *J* = 9.5 Hz, 1H), 3.59–3.48 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.91 (s, 3H), 1.80 (s, 3H); MS(ESI): *m/z* = 1297 $[M + H]^+$.

*(2R,3R,4S,5S,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-2-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3f)

Yellow solid (yield 54%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.51 (s, 1H), 7.50 (d, J = 7.3 Hz, 4H), 7.47–7.33 (m, 15H), 7.30 (dd, J = 4.9, 1.7 Hz, 3H), 6.48 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 5.56 (d, J = 8 Hz, 1H), 5.33 (d, J = 2.8 Hz, 1H), 5.24 (m, 5H), 5.18 (d, J = 5.8 Hz, 4H), 5.11–5.05 (m, 2H), 4.94 (dd, J = 10.4, 3.4 Hz, 1H), 4.41 (d, J = 7.9 Hz, 1H), 4.35 (dd, J = 12.0, 1.9 Hz, 1H), 4.08 (d, J = 6.9 Hz, 2H), 3.90 (dd, J = 12.0, 4.3 Hz, 1H), 3.83 (t, J = 6.9 Hz, 1H), 3.74 (t, J = 9.5 Hz, 1H), 3.60–3.48 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.82 (s, 3H); MS(ESI): m/z = 1297 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)-6-((((2R,3R,4R,5R)-3,4-diacetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3g)

Yellow solid (yield 51%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.50 (s, 1H), 7.52 (d, J = 7.3 Hz, 4H), 7.48–7.39 (m, 15H), 7.31 (dd, J = 4.9, 1.7 Hz, 3H), 6.49 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 5.52 (d, J = 8 Hz, 1H), 5.30 (d, J = 2.8 Hz, 1H), 5.22 (m, 5H), 5.16 (d, J = 5.8 Hz, 4H), 5.14–5.08 (m, 2H), 4.94 (dd, J = 10.4, 3.4 Hz, 1H), 4.39 (d, J = 7.9 Hz, 1H), 4.32 (dd, J = 12.0, 1.9 Hz, 1H), 4.14 (d, J = 6.9 Hz, 2H), 3.90 (d, J = 12.0 Hz, 1H), 3.74 (t, J = 9.5 Hz, 1H), 3.57–3.51 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H); MS(ESI): m/z = 1225 $[M + H]^+$.

*(2S,3R,4S,5S,6R)-2-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)-6-((((2R,3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3h)

Yellow solid (yield 55%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.42 (s, 1H), 7.51 (d, J = 7.3 Hz, 4H), 7.44–7.32 (m, 15H), 7.28 (dd, J = 4.9, 1.7 Hz, 3H), 6.48 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 2.2 Hz, 1H), 5.56 (d, J = 8 Hz, 1H), 5.42 (d, J = 2.8 Hz, 1H), 5.28 (m, 5H), 5.17 (d, J = 5.8 Hz, 4H), 5.13–5.06 (m, 2H), 4.94 (dd, J = 10.4, 3.4 Hz, 1H), 4.45 (d, J = 7.9 Hz, 1H), 4.38 (dd, J = 12.0, 1.9 Hz, 1H), 4.18 (d, J = 6.9 Hz, 2H), 3.95 (d, J = 12.0 Hz, 1H), 3.80 (t, J = 9.5 Hz, 1H), 3.62–3.50 (m, 1H), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.91 (s, 3H); MS(ESI): m/z = 1225 $[M + H]^+$.

*(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-((7-(benzyloxy)-5-hydroxy-4-oxo-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-3-yl)oxy)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (*3i)

Yellow solid (yield 52%); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm): δ 12.46 (s, 1H), 7.49 (d, J = 7.3 Hz, 4H), 7.44–7.34 (m, 15H), 7.32 (dd, J = 4.9, 1.7 Hz, 3H), 6.51 (d, J = 2.2 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 5.56 (d, J = 8 Hz, 1H), 5.30 (d, J = 2.8 Hz, 1H), 5.22 (m, 5H), 5.17 (d, J = 5.8 Hz, 4H), 5.13–5.07 (m, 2H), 4.94 (dd, J = 10.4, 3.4 Hz, 1H), 4.39 (d, J = 7.9 Hz, 1H), 4.35 (dd, J = 12.0, 1.9 Hz, 1H), 4.04 (d, J = 6.9 Hz, 2H), 3.90 (dd, J = 12.0, 4.3 Hz, 1H), 3.82 (t, J = 6.9 Hz, 1H), 3.74 (t, J = 9.5 Hz, 1H), 3.59–3.51 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.86 (s, 3H); MS(ESI): m/z = 1296 $[M + H]^+$.

General procedures for the synthesis of myricetin derivatives 4a-i

To a solution of **3a-i** (0.39 mmol) in methanol (5 mL), 5.4 M sodium methoxide (0.072 mL, 0.39 mmol) was added. The mixture was stirred at room temperature for 5 h and neutralized by ion-exchange resin (Amberlite® IR120). Then 10% palladium-on-charcoal (500 mg) was added to the filtrate. The mixture was stirred at room temperature under hydrogen atmosphere for 12 h. After reaction, the palladium-on-charcoal was filtered, and the organic phase was evaporated to afforded **4a-i**.

5,7-dihydroxy-3-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-((((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4a)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.64 (s, 1H), 10.82 (s, 1H), 9.16 (s, 2H), 8.89 (s, 1H), 7.15 (s, 2H), 6.35 (d, J = 2.0 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 5.45 (d, J = 7.7 Hz, 1H), 5.20 (d, J = 3.6 Hz, 1H), 5.13 (s, 1H), 5.00 (s, 1H), 4.56 (d, J = 3.6 Hz, 1H), 4.32 (s, 1H), 4.26 (s, 3H), 3.58 (m, 1H), 3.48 (m, 2H), 3.33 (m, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.34, 164.04, 161.25, 156.27, 156.25, 145.36(2C), 136.66, 133.24, 119.99, 108.54(2C), 103.86, 100.62, 98.70, 98.45, 93.35, 76.60, 75.63, 73.80, 70.28, 70.11, 69.64, 69.42, 68.42, 66.39, 61.28; MS(ESI): m/z = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.46; H, 4.72%.

5,7-dihydroxy-3-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-((((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4b)

Yellow solid (yield 98%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.62 (s, 1H), 10.77 (s, 1H), 9.07 (s, 3H), 7.16 (m, 2H), 6.36 (s, 1H), 6.19 (s, 1H), 5.46–5.24 (m, 1H), 5.04 (s, 1H), 4.86 (m, 1H), 4.60–4.52 (m, 2H), 4.42–4.33 (m, 4H), 4.02 (m, 1H), 3.66–3.56 (m, 4H), 3.54–3.48 (m, 5H), 3.42–3.37 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.36, 164.10, 161.24, 156.24, 156.17, 145.39(2C), 136.72, 133.63, 119.96, 108.55(2C), 103.86, 101.86, 99.44, 98.69, 93.38, 73.63, 73.08, 71.17, 70.94, 69.59, 69.55, 69.34, 68.37, 68.02, 61.05, 48.63; MS(ESI): m/z = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.48; H, 4.71%.

3-(((2S,3R,4R,5R,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4c)

Yellow solid (yield 98%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.62 (s, 1H), 10.84 (s, 1H), 9.08 (s, 3H), 7.19 (s, 2H), 6.36 (d, J = 1.5 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 5.28 (d, J = 7.5 Hz, 1H), 5.04 (s, 1H), 4.88 (s, 1H), 4.80–4.69 (m, 2H), 4.53–4.43 (m, 3H), 3.72–3.81 (m, 2H), 3.66–3.61 (m, 2H), 3.52–3.49 (m, 3H), 3.23–3.11 (m, 5H), 3.06–3.05 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.78, 164.54, 161.66, 156.73, 156.69, 145.80(2C), 137.14, 134.12, 120.39, 108.99(2C), 104.36, 102.52, 99.92, 99.08, 93.82,

73.71, 73.67, 73.49, 73.28, 72.34, 71.60, 70.45, 68.07, 66.42, 61.12; MS(ESI): *m/z* = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.45; H, 4.70%.

3-(((2S,3R,4S,5R)-3,5-dihydroxy-4-(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4d)

Yellow solid (yield 98%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.62 (s, 1H), 10.84 (s, 1H), 9.09 (s, 2H), 8.90 (s, 1H), 7.19 (s, 2H), 6.36 (s, 1H), 6.18 (s, 1H), 5.33 (d, *J* = 7.7 Hz, 1H), 5.03 (s, 1H), 4.85 (m, 2H), 4.70 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 5.0 Hz, 1H), 4.51 (d, *J* = 5.0 Hz, 1H), 4.39 (d, *J* = 5.0 Hz, 1H), 3.63–3.60 (m, 4H), 3.57–3.55 (m, 2H), 3.45–3.42 (m, 2H), 3.41–3.37 (m, 2H), 3.24 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.78, 164.54, 161.66, 156.73, 156.69, 145.80(2C), 137.14, 134.12, 120.39, 108.99(2C), 104.36, 102.52, 99.92, 99.08, 93.82, 73.71, 73.67, 73.49, 73.28, 72.34, 71.60, 70.45, 68.07, 66.42, 61.12; MS(ESI): *m/z* = 613 $[M + H]^+$. Anal.Calcd for $C_{26}H_{28}O_{17}$: C, 50.99; H, 4.61%. *Found*: C, 50.98; H, 4.62%.

5,7-dihydroxy-3-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-((((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4e)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.61 (s, 1H), 10.84 (s, 1H), 9.09 (s, 3H), 7.19 (s, 2H), 6.36 (s, 1H), 6.19 (s, 1H), 5.33 (d, *J* = 7.7 Hz, 1H), 5.04 (s, 1H), 4.88 (s, 1H), 4.69 (d, *J* = 18.0 Hz, 2H), 4.61 (d, *J* = 3.4 Hz, 1H), 4.51 (s, 1H), 4.42 (s, 1H), 4.33 (s, 1H), 3.75 (s, 1H), 3.63 (t, *J* = 7.9 Hz, 1H), 3.56 (s, 2H), 3.48 (d, *J* = 11.4 Hz, 1H), 3.40 (s, 3H), 3.26 (d, *J* = 10.6 Hz, 2H), 3.09 (s, 1H), 2.99 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.78, 164.54, 161.66, 156.73, 156.69, 145.80(2C), 137.14, 134.12, 120.39, 108.99(2C), 104.36, 102.52, 99.92, 99.08, 93.82, 73.71, 73.67, 73.49, 73.28, 72.34, 71.60, 70.45, 68.07, 66.42, 61.12, 40.47, 40.30, 40.13, 39.97, 39.80, 39.63, 39.47; MS(ESI): *m/z* = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.46; H, 4.70%..

5,7-dihydroxy-3-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-((((2S,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4f)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.60 (s, 1H), 10.90 (s, 1H), 9.10 (s, 3H), 7.23–7.19 (d, *J* = 4.5 Hz,, 2H), 6.37 (s, 1H), 6.18 (s, 1H), 5.34–5.32 (d, *J* = 7.5 Hz, 1H), 5.03 (s, 1H), 4.88 (s, 1H), 4.62–4.56 (m, 4H), 4.47–4.21 (m, 4H), 3.63–3.54 (m, 3H), 3.52–3.49 (m, 6H), 3.18–3.16 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.33, 164.12, 161.24, 156.25, 156.20, 145.39(2C), 136.72, 133.72, 119.97, 108.56(2C), 103.91, 102.01, 100.59, 98.67, 93.41, 74.10, 73.03, 72.90, 71.18, 70.92, 70.23, 67.74, 66.75, 61.05, 48.63; MS(ESI): *m/z* = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.49; H, 4.72%.

3-(((2S,3R,4S,5R,6R)-6-((((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)oxy)methyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4g)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.60 (s, 1H), 10.83 (s, 1H), 9.08 (s, 3H), 7.19 (s, 2H), 6.36 (s, 1H), 6.18 (s 1H), 5.31 (d, J = 7.5 Hz, 1H), 5.03 (s, 1H), 4.87–4.84 (m, 1H), 4.68–4.61 (m, 3H), 4.51–4.33 (m, 3H), 3.74 (s, 1H), 3.62–3.55 (m, 3H), 3.48–3.46 (m, 2H), 3.26–2.98 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.33, 164.11, 161.22, 156.31, 156.22, 145.39(2C), 136.71, 133.64, 124.92, 119.96, 108.54(2C), 103.85, 101.85, 101.03, 98.67, 93.36, 73.60, 73.12, 71.06, 70.77, 68.89, 68.10, 66.35, 63.59; MS(ESI): m/z = 613 $[M + H]^+$. Anal.Calcd for $C_{26}H_{28}O_{17}$: C, 50.99; H, 4.61%. *Found*: C, 50.97; H, 4.60%.

5,7-dihydroxy-3-(((2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-((((2S,3R,4S,5R)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4h)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.60 (s, 1H), 10.83 (s, 1H), 9.06 (s, 3H), 7.19 (s, 2H), 6.36 (d, J = 2.0 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 5.32 (d, J = 8.0 Hz, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 4.70 (s, 2H), 4.63–4.56 (m, 3H), 4.45 (s, 2H), 3.73 (s, 1H), 3.64–3.60 (m, 2H), 3.58–3.55 (m, 2H), 3.51–3.52 (m, 2H), 3.16 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.82, 164.50, 161.66, 156.80, 156.72, 145.79(2C), 137.12, 134.13, 120.43, 108.99(2C), 104.40, 102.50, 99.92, 99.04, 97.61, 93.81, 74.08, 73.77, 73.53, 72.30, 71.53, 70.24, 68.26, 66.64, 66.15, 62.35, 40.43, 40.26, 40.19, 40.10, 39.93, 39.76, 39.59, 39.43; MS(ESI): m/z = 613 $[M + H]^+$. Anal.Calcd for $C_{26}H_{28}O_{17}$: C, 50.99; H, 4.61%. *Found*: C, 50.98; H, 4.60%.

3-(((2S,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (4i)

Yellow solid (yield 97%); ^{1}H NMR (500 MHz, DMSO-d_6) (ppm): δ 12.64 (s, 1H), 10.86 (s, 1H), 9.18 (s, 2H), 8.91 (s, 1H), 7.19 (s, 2H), 6.38 (d, J = 1.9 Hz, 1H), 6.20 (d, J = 1.9 Hz, 1H), 5.51 (d, J = 6.8 Hz, 1H), 5.32 (s, 1H), 5.24 (s, 1H), 5.00 (s, 2H), 4.75 (s, 1H), 4.60 (s, 1H), 4.32 (s, 1H), 4.26 (d, J = 7.9 Hz, 1H), 4.09 (s, 1H), 3.69 (t, J = 13.3 Hz, 2H), 3.41 (s, 5H), 3.27 (s, 1H), 3.24–3.18 (m, 1H), 3.07 (d, J = 9.2 Hz, 1H), 3.00 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm): δ 177.76, 164.57, 161.68, 156.70, 145.84(2C), 137.11, 133.83, 120.42, 108.93(2C), 104.38, 103.71, 101.05, 99.08, 93.80, 81.03, 77.25, 76.91, 75.88, 75.34, 74.06, 73.73, 70.46, 61.46, 60.96, 49.05, 40.44, 40.27, 40.10, 39.93, 39.77, 39.60, 39.43; MS(ESI): m/z = 643 $[M + H]^+$. Anal.Calcd for $C_{27}H_{30}O_{18}$: C, 50.47; H, 4.71%. *Found*: C, 50.48; H, 4.70%.

Hypoglycemic activity

4-Nitrophenyl-α-D-glucopyranoside (PNPG) and α-glucosidase were purchased from Sigma-Aldrich company, USA. Acarbose were purchased from Solarbio Life Sciences, Beijing, China.

The PBS buffer (125 uL), test derivatives **4a-i** (10 uL) and PNPG (10 uL) were added to the 96-well plate in turn, shaken at 37°C for 8 min. Then, α-glucosidase (5 uL/well) was added and shaken at 37°C for 15 min, at end 0.2 M Na_2CO_3 (75 uL/well) was added to stop the reaction. The absorbance at 405 nm was measured with a Microplate Reader (Molecular Devices, Silicon Valley, USA). The data was analyzed by SPSS 13.0. The inhibition ratio of different concentration was calculated by the following equation:

$$\text{Inhibition Ratio}= \frac{A_{405control}-A_{405sample}}{A_{405control}} \times 100\%$$

Declarations

Acknowledgements

Not applicable.

Author contributions

FL, CY, and LZ synthesized compounds and contributed to the design and characterization of compounds. FL and WL performed to the preparation of the manuscript. FL and CY performed the biological assay. WL supervised all phases of the study. All authors read and approved the article.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Not applicable

References

1. Salvamani S, Gunasekaran B, Shaharuddin NA, Ahmad SA, Shukor MY (2014) Antiartherosclerotic effects of plant flavonoids. Biomed Res Int 2014: 1-11. https://doi.org/10.1155/2014/480258
2. Lee DH, Lee CS (2016) Flavonoid myricetin inhibits TNF-α-stimulated production of inflammatory mediators by suppressing the Akt, mTOR and NF-κB pathways in human keratinocytes. Eur J Pharmacol 784:164-172. https://doi.org/10.1016/j.ejphar.2016.05.025
3. Cho BO, Hong HY, Sang HP, Byun EB, Ha HY, Jang SI (2016) Anti-inflammatory activity of myricetin from Diospyros through suppression of NF-κB and STAT1 activation and Nrf2-mediated HO-1 induction in lipopolysaccharide-stimulated RAW264.7 macrophages. Biosci Biotech Bioch 80:1520-1530. https://doi.org/ 10.1080/09168451.2016.1171697
4. Tong Y, Zhou XM, Wang SJ, Yang Y, Cao YL (2009) Analgesic activity of myricetin isolated from Myrica rubra Sieb. et Zucc. leaves. Arch Pharm Res 32:527-533. https://doi.org/10.1007/s12272-009-1408-6
5. Kwon O, Eck P, Chen S, Corpe CP, Lee JH, Kruhlak M, Levine M (2007) Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. FASEB J 21:366-377. https://doi.org/10.1096/fj.06-6620com
6. Strobel P, Allard C, Perez-Acle T, Calderon R, Aldunate R, Leighton F (2005) Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. Biochem J 386:471478. https://doi.org/10.1042/BJ20040703
7. Ong KC, Khoo HE (1996) Insulinomimetic effects of myricetin on lipogenesis and glucose transport in rat adipocytes but not glucose transport translocation. Biochem Pharmacol 51:423-429. https://doi.org/10.1016/S0024-3205(00)00758-X
8. Manaharan T, Ming CH, Palanisamy UD (2013) Syzygium aqueum leaf extract and its bioactive compounds enhances preadipocyte differentiation and 2-NBDG uptake in 3T3-L1 cells. Food Chem 136:354-363. https://doi.org/10.1016/j.foodchem.2012.08.056
9. Kandasamy N, Ashokkumar N (2014) Protective effect of bioflavonoid myricetin enhances carbohydrate metabolic enzymes and insulin signaling molecules in streptozotocin-cadmium induced diabetic nephrotoxic rats. Toxicol Appl Pharmacol 279:173-185. https://doi.org/10.1016/j.taap.2014.05.014
10. Ong KC, Khoo HE (2000) Effects of myricetin on glycemia and glycogen metabolism in diabetic rats. Life Sci 67:1695-1705. https://doi.org/10.1016/S0024-3205(00)00758-X
11. Lin CY, Ni CC, Yin MC, Lii CK (2012) Flavonoids protect pancreatic beta-cells from cytokines mediated apoptosis through the activation of PI3-kinase pathway. Cytokine 59:65-71. https://doi.org/10.1016/j.cyto.2012.04.011
12. Ying L□Zheng X□Yi X□Liu C□Kong D□Zhang J□Min G (2017) Myricetin: a potent approach for the treatment of type 2 diabetes as a natural class B GPCR agonist. FASEB J 31:2603-2611. https://doi.org/10.1096/fj.201601339R

13. Castillo-Muñoz N, Gómez-Alonso S, García-Aomero E, Gómez MV Velders AH Hermosín-Gutiérrez I (2007) Flavonol 3-O-Glycosides Series of Vitis vinifera Cv. Petit Verdot Red Wine Grapes. J Agric Food Chem 55:992-1002. https://doi.org/ 10.1021/jf802863g
14. Arif H, Sohail A, Farhan M, Rehman AA Ahmad A Hadi, SM (2017) Flavonoids-Induced Redox Cycling of Copper Ions Leads to Generation of Reactive Oxygen Species: A Potential Role in Cancer Chemoprevention. Int J Biol Macromol 106:569-578. https://doi.org/ 10.1016/j.ijbiomac.2017.08.049
15. Silva LN, Da HG, Soares TA, Bojer MS Ingmer H Macedo AJ Trentin DS (2017) Myricetin protects Galleria mellonella against Staphylococcus aureus infection and inhibits multiple virulence factors. Sci Rep 7:2823-2838. https://doi.org/ 10.1038/s41598-017-02712-1
16. Li Y, Cui SX, Sun SY, Shi WN Qu XJ (2016) Chemoprevention of intestinal tumorigenesis by the natural dietary flavonoid myricetin in APC Min/+ mice. Oncotarget 7:60446-60460. https://doi.org/10.18632/oncotarget.11108
17. Yamauchi K, Mitsunaga T, Batubara I (2014) Synthesis of quercetin glycosides and their melanogenesis stimulatory activity in B16 melanoma cells. Bio Med Chem 22: 937-944. https://doi.org/10.1016/j.bmc.2013.12.062
18. Zhu SF, Yang C, Zhang L, Wang SX, Ma MX Zhao JC Song ZY Wang F, Qu XJ Li F, Li WB (2019) Development of M10, myricetin-3-O-β-D-lactose sodium salt, a derivative of myricetin as a potent agent of anti-chronic colonic inflammation. Eur J Med Chem 174:9-15. https://doi.org/ 10.1016/j.ejmech.2019.04.031
19. Magnusson JO (2000) Galabiosyl donors; efficient synthesis from 1,2,3,4, 6-penta-O-acetyl-beta-D-galactopyranose. Cheminform 329:49-55. https://doi.org/10.1016/S0008-6215(00)00154-3

Tables

Table 1 to 2 are available in the Supplementary Files section.

Schemes

Scheme 1 to 2 are available in Supplementary Files section.

Figures

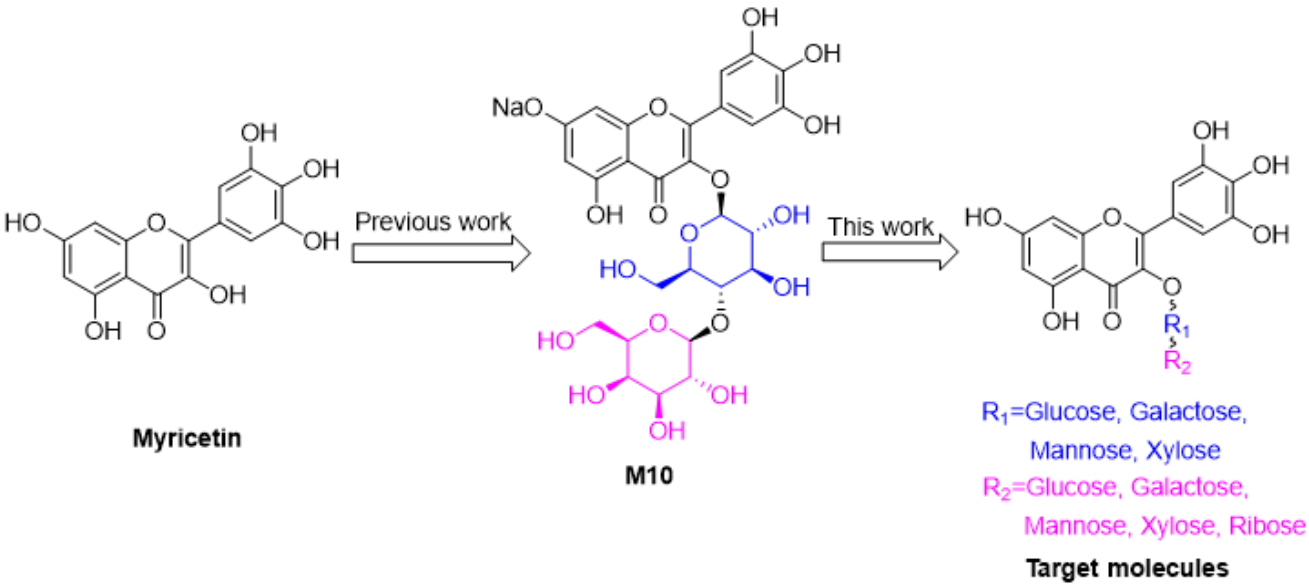

Figure 1

Structures of myricetin, M10 and target molecules.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1to2.docx
- Scheme1.png
- Scheme2.png
- supportinginformation.docx