

HETEROCYCLES, Vol. 92, No. 7, 2016, pp. 1245 - 1260. © 2016 The Japan Institute of Heterocyclic Chemistry  
Received, 7th March, 2016, Accepted, 18th May, 2016, Published online, 24th May, 2016  
DOI: 10.3987/COM-16-13455

## SYNTHESIS OF QUERCETIN GLYCOSIDES AND THEIR $\alpha$ -GLUCOSIDASE INHIBITORY ACTIVITIES

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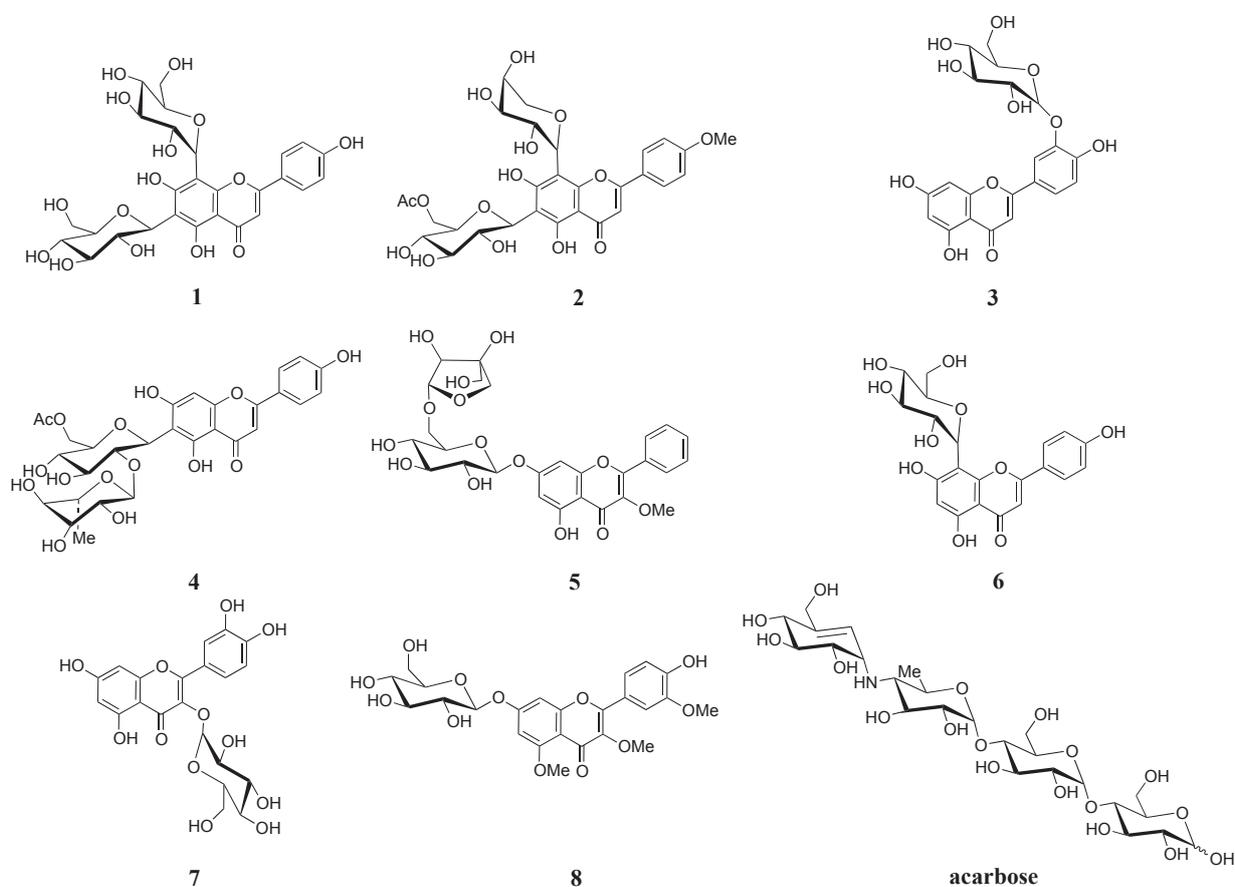
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**Abstract** – A series of quercetin glycosides as the analogues of 3,5,5'-trimethyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (**8**) were synthesized, their structures were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS. The inhibitory activities of those compounds against  $\alpha$ -glucosidase were evaluated *in vitro*, in particular, the compounds **V-c** and **V-d-2** showed promising bioactivities with IC<sub>50</sub> of 19.4  $\mu\text{mol}\cdot\text{L}^{-1}$  and 19.7  $\mu\text{mol}\cdot\text{L}^{-1}$ , are much higher than **8** (IC<sub>50</sub> > 100  $\mu\text{mol}\cdot\text{L}^{-1}$ ). This research will provide a reference in the study of the synthetic methods and hypoglycemic activity for the quercetin glycosides.

Diabetes mellitus is metabolic disorder characterized by insufficient secretion or inefficient processing of hormonal insulin and it is becoming the third leading cause of death, after cancer and cardiovascular diseases.<sup>1</sup> The number of people with diabetes has increased from 153 million in 1980 to 382 million in 2013. The International Diabetes Federation (IDF) predicted that the number of people with diabetes will increase to 435 million in 2030.<sup>2</sup> One of therapeutics for diabetes is inhibition of  $\alpha$ -glucosidase which is the key enzyme of carbohydrate digestion by specifically hydrolyzing the  $\alpha$ -glucopyranoside bond to release  $\alpha$ -D-glucose from the non-reducing end of the sugar. Therefore, the inhibition of  $\alpha$ -glucosidase is an effective approach in preventing and treating diabetes through reduction of postprandial hyperglycaemia.<sup>3,4</sup>

At present, though some inhibitors have potent effect on  $\alpha$ -glucosidase, the corresponding side effects cannot be ignored. For example, acarbose probably causes abdominal distension, flatulence and meteorism.<sup>5</sup> In recent years, large amount of synthetic chemicals or natural products have been screened to get more effective and safe  $\alpha$ -glucosidase inhibitors.<sup>6</sup> Searching lead compounds from natural products

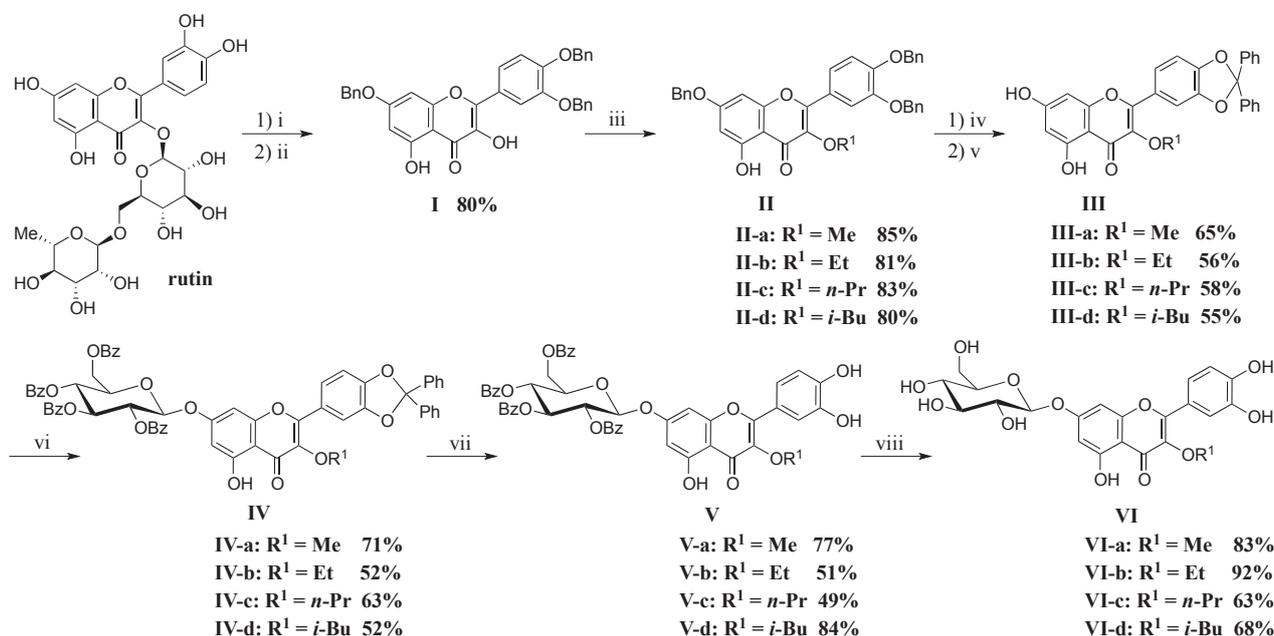
remains an attractive strategy for pharmaceutical researchers. Many natural products have hypoglycemic effect, such as, polysaccharide,<sup>7</sup> quercetin<sup>8</sup> and 6,8-di-*C*-glucosylapigenin (**1**),<sup>9</sup> the 6,8-di-*C*-glucosylapigenin belongs to the flavonoid glycosides, some studies have proved that a part of flavonoid glycosides can inhibit  $\alpha$ -glucosidase, as shown in Figure 1. For instance, acacetin-6-*C*-(6''-acetyl- $\beta$ -D-glucopyranoside)-8-*C*- $\alpha$ -L-arabinopyranoside (**2**),<sup>10</sup> luteolin-3'-*O*- $\beta$ -D-glucoside (**3**),<sup>11</sup> apigenin-6-*C*- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-(6''-*O*-acetyl)- $\beta$ -D-glucopyranoside (**4**),<sup>12</sup> 5-hydroxy-3-methoxyflavone-7-*O*-[ $\beta$ -D-aposyl-(1 $\rightarrow$ 6)]- $\beta$ -D-glucoside (**5**)<sup>13</sup> and apigenin-8-*C*-glucoside (**6**)<sup>14</sup> exhibited significant inhibitory activities against  $\alpha$ -glucosidase. Interestingly, some references indicated that quercetin<sup>8</sup> and quercetin-3-*O*- $\beta$ -D-glucoside (**7**)<sup>11</sup> both have strong inhibitory activities against  $\alpha$ -glucosidase than acarbose. In addition, our preliminary research indicated that 3,5,5'-trimethyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (**8**) is an active ingredient of *Agrimonia pilosa* Ledeb, a Chinese traditional medicine used for the treatment of diabetes, tumor, gynecology, etc.,<sup>15</sup> and Abdallah's study<sup>16</sup> proved that compound **8** exerted its hypoglycemic effect could be by inhibition of aldose reductase, which is a key enzyme in the polyol pathway, catalyzes the reduction of excess glucose, in various tissues (nerves, retina, lens and kidney), into sorbitol. But our research showed the  $\alpha$ -glucosidase



**Figure 1.** Structures of acarbose and eight flavonoid glycosides (1-8)

inhibitory activity of compound **8** is low, and its  $IC_{50}$  value is more than  $100 \mu\text{mol}\cdot\text{L}^{-1}$ . In order to improve its inhibition against  $\alpha$ -glucosidase, we have designed and synthesized a novel series of analogues of compound **8** which position-3 were substituted by several kind of alkyls and position-7 were replaced by 2,3,4,6-tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyls or  $\beta$ -D-glucopyranosyls and their inhibitory activity against  $\alpha$ -glucosidase were assayed *in vitro*. This result has been published on a patent, WO2016041195 (A1).<sup>17</sup>

The reactivity of the five hydroxyls of quercetin is in the order of the hydroxyl at position-7 > 3  $\approx$  4' > 3' >> 5, and the lowest reactivity of hydroxyl at position-5 is due to the intramolecular hydrogen bond formed with carbonyl at position-4.<sup>18,19</sup> In our study, it is not easy to modify the hydroxyl of quercetin one by one without protecting other hydroxyls, so we chose the rutin rather than quercetin as starting material. As shown in Scheme 1, the quercetin glycosides **V-a** ~ **V-d** and **VI-a** ~ **VI-d** were synthesized starting from rutin in seven or eight steps. Selective benzylation of rutin with benzyl bromide in the presence of potassium carbonate at room temperature, followed by hydrolysis with concentrated hydrochloric acid in EtOH provided compound **I** in 80% yield over two steps. The selective alkylation of compound **I** with methyl iodide afforded compound **II-a**. After hydrogenolysis of the benzyl groups of compound **II-a** using palladium on charcoal, the resulting product's hydroxyls at positions 3' and 4' were

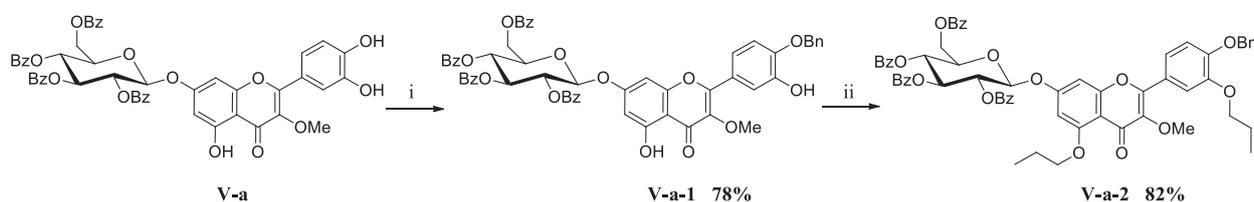


**Scheme 1.** Synthetic route of quercetin glycosides **V** and **VI**

Reagents and conditions: (i) BnBr, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 2.5 days; (ii) EtOH, concentrated hydrochloric acid, 70 °C, 3 h; (iii) R<sup>1</sup>I, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 8 h; (iv) H<sub>2</sub>, 10% Pd/C, EtOH/THF, 25 °C, 15 h; (v) dichlorodiphenylmethane, diphenyl ether, 175 °C, 1 h; (vi)  $\alpha$ -D-glucopyranosyl bromide tetrabenzoate, K<sub>2</sub>CO<sub>3</sub>, TBAB, CHCl<sub>3</sub>/DMF/H<sub>2</sub>O, 25 °C, 48 h; (vii) 10% Pd/C, H<sub>2</sub>, MeOH/THF/H<sub>2</sub>O, 45 °C, 48 h; (viii) MeONa, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 30 min.

protected by dichlorodiphenylmethane at 175 °C for 1 h to afford **III-a** in a better yield than Rolando's method.<sup>18</sup> The selective glycosylation of compound **III-a** was carried out by reaction with  $\alpha$ -D-glucopyranosyl bromide tetrabenzoate using tetrabutylammonium bromide (TBAB)<sup>20,21</sup> as phase transfer catalyst (PTC) in the presence of potassium carbonate to give compound **IV-a** in a satisfactory 71% yield, and the tetrabutylammonium iodide (TBAI)<sup>22</sup> and methyltrioctylammonium chloride (Aliquat 336)<sup>23,24</sup> also were used as PTC for synthesis **IV-a** with  $\beta$  selectivity in 59% and 81% yields in our study, respectively. The deprotection of the catechol ring by H<sub>2</sub> catalyzed by Pd/C provided compound **V-a**. Debenzoylation of compound **V-a** with MeONa/MeOH to afford compound **VI-a**. The same procedure described above was used for synthesis of compounds **V-b**, **V-c**, **V-d** and **VI-b**, **VI-c**, **VI-d** from compound **I** by replacement of methyl iodide with ethyl iodide, *n*-propyl iodide or *i*-butyl iodide, respectively. The desired compounds were obtained via this synthetic route efficiently, and all the reaction conditions are mildly apart from using dichlorodiphenyl methane to protect the hydroxyls at positions 3' and 4' needed high temperature.

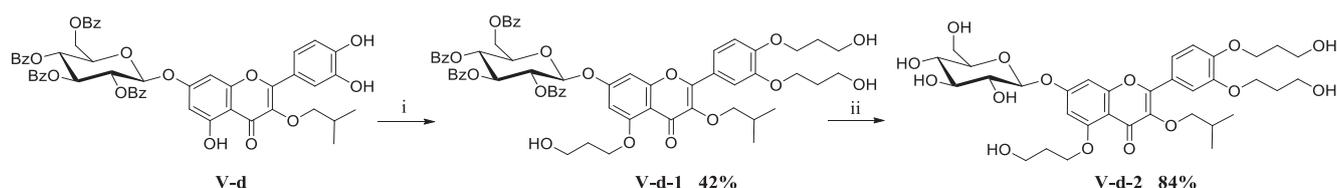
As described in Scheme 2, selective benzylation of hydroxyl at the position-4' of **V-a** with benzyl bromide and followed by alkylation of the other two hydroxyls of **V-a-1** with *n*-propyl iodide gave compound **V-a-2**.



**Scheme 2.** Synthetic route of quercetin glycosides **V-a-1** and **V-a-2**

Reagents and conditions: (i) BnBr, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 10 h; (ii) *n*-propyl iodide, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 10 h.

As displayed in Scheme 3, the other three hydroxyls of **V-d** were substituted by 3-hydroxypropyls using Br(CH<sub>2</sub>)<sub>3</sub>OH in the presence of potassium carbonate at room temperature and debenzoylation of **V-d-1** with MeONa/MeOH to get the compound **V-d-2**.

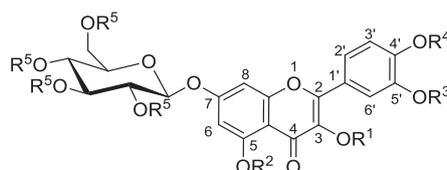


**Scheme 3.** Synthetic route of quercetin glycosides **V-d-1** and **V-d-2**

Reagents and conditions: (i) Br(CH<sub>2</sub>)<sub>3</sub>OH, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 12 h; (ii) MeONa, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 30 min.

The inhibitory activities of target compounds against  $\alpha$ -glucosidase *in vitro* are summarized in Table 1. Compounds **V-c**, **V-d** and **V-d-2** showed potential bioactivities with  $IC_{50}$  values less than  $25 \mu\text{mol}\cdot\text{L}^{-1}$ , compounds **V-b**, **V-a-2** and **V-d-1** showed  $IC_{50}$  values no more than  $70 \mu\text{mol}\cdot\text{L}^{-1}$ , and the rest four compounds have no significant inhibitory activities. This result indicated that the inhibitory activities of benzoylated compounds **V-b**, **V-c** and **V-d** are much better than the inhibitory activities of debenzoylated compounds **VI-b**, **VI-c** and **VI-d**, respectively, and **V-c** exhibited the best inhibitory activity with  $IC_{50}$  of  $19.4 \mu\text{mol}\cdot\text{L}^{-1}$ , which is also closely related to the *n*-propyl substituted on the position-3. Besides, the modification of hydroxyls at position-3', 4' and 5 is a promising strategy to obtain potential drugs against  $\alpha$ -glucosidase, such as **V-d-2**, which also showed good inhibitory activity with  $IC_{50}$  of  $19.7 \mu\text{mol}\cdot\text{L}^{-1}$ . Generally, the bioactivity of **V-c**, **V-d** and **V-d-2** as analogues of compound **8** was significantly improved.

**Table 1.** The structures of target compounds and their inhibitory activities against  $\alpha$ -glucosidase *in vitro*



Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	$IC_{50}/(\mu\text{mol}\cdot\text{L}^{-1})$
<b>V-a</b>	Me	-H	-H	-H	-Bz	ND <sup>a</sup>
<b>V-b</b>	Et	-H	-H	-H	-Bz	56.5
<b>V-c</b>	<i>n</i> -Pr	-H	-H	-H	-Bz	19.4
<b>V-d</b>	<i>i</i> -Bu	-H	-H	-H	-Bz	21.5
<b>VI-a</b>	Me	-H	-H	-H	-H	>100
<b>VI-b</b>	Et	-H	-H	-H	-H	>100
<b>VI-c</b>	<i>n</i> -Pr	-H	-H	-H	-H	>100
<b>VI-d</b>	<i>i</i> -Bu	-H	-H	-H	-H	>100
<b>V-a-1</b>	Me	-H	-H	-Bn	-Bz	ND <sup>a</sup>
<b>V-a-2</b>	Me	<i>n</i> -Pr	<i>n</i> -Pr	-Bn	-Bz	45.8
<b>V-d-1</b>	<i>i</i> -Bu	-(CH <sub>2</sub> ) <sub>3</sub> OH	-(CH <sub>2</sub> ) <sub>3</sub> OH	-(CH <sub>2</sub> ) <sub>3</sub> OH	-Bz	68.1
<b>V-d-2</b>	<i>i</i> -Bu	-(CH <sub>2</sub> ) <sub>3</sub> OH	-(CH <sub>2</sub> ) <sub>3</sub> OH	-(CH <sub>2</sub> ) <sub>3</sub> OH	-H	19.7
<b>8</b>	Me	Me	Me	-H	-H	>100
acarbose <sup>b</sup>						$2.5 \times 10^{-3}$

<sup>a</sup> Not determined; <sup>b</sup> Used as a positive control.

## EXPERIMENTAL

Mass spectra (MS) were obtained on an electrospray ionization (ESI) mode on HP-5793 mass spectrometer (Hewlett-Packard, USA). Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 ( $^1\text{H}$  NMR, 400 MHz;  $^{13}\text{C}$  NMR, 100 MHz, Varian Unit, USA) or WNMN-I ( $^1\text{H}$  NMR, 500 MHz;  $^{13}\text{C}$  NMR, 125 MHz, WIPM, China) with TMS as an internal standard. Column chromatography was performed on silica gel (300-400 mesh) and thin-layer chromatography (TLC) analysis was carried out on silica gel plates GF254 purchased from Qingdao Ocean Chemical Reagent Co. (Qingdao, China). Model 550 microplate reader was provided from Bio-Rad Laboratories (USA), 96-well microplate was purchased from Greiner Co. (Germany), single-channel and multi-channel pipettes were obtained from Eppendorf Co. (Germany),  $\alpha$ -glucosidase, bovine serum albumin (BSA) and *p*-nitrophenyl- $\alpha$ -D-glucopyranoside (PNPG) were purchased from Sigma Chemical Co. (St. Louis, Mo, USA), acarbose was obtained from Bayer Healthcare Company Ltd. (Germany). Other reagents were analytical grade or guaranteed reagent commercial product and used without further purification, unless otherwise noted.

**Synthesis of 3',4',7-tri-*O*-benzylquercetin (I).**<sup>25,26</sup> To a mixture of anhydrous rutin (50 g, 0.08 mol) and anhydrous  $\text{K}_2\text{CO}_3$  (56 g, 0.41 mol, 5 eq.) in 600 mL of anhydrous *N,N*-dimethylformamide (DMF), benzyl bromide (BnBr, 36.9 mL, 0.3 mol, 3.8 eq.) was added under argon. After stirring at room temperature for 2.5 days, the reaction mixture was poured into ice water and its pH was adjusted to 6 with concentrated hydrochloric acid, the resulting precipitate was filtered to afford a crude product which was used for the next step without further purification. To a solution of the previous step's product in 600 mL EtOH was added 200 mL concentrated hydrochloric acid. The mixture was stirred 70 °C for 3 h, after cooling to room temperature, the reaction mixture was poured into cold water and the resulting precipitate was filtered and washed with cold water, the obtained residue was purified by column chromatography on silica gel (1:2 EtOAc–petroleum ether) to give compound I (46.8 g, 80% yield over two steps) as a yellowish brown solid. ESI-MS  $m/z$  595.2  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.48 (s, 1H), 7.81 (d,  $J = 1.9$  Hz, 1H), 7.84 (dd,  $J = 8.8, 1.9$  Hz, 1H), 7.30–7.55 (m, 15H), 7.25 (d,  $J = 8.8$  Hz, 1H), 6.86 (d,  $J = 1.9$  Hz, 1H), 6.47 (d,  $J = 1.9$  Hz, 1H), 5.24 (s, 4H), 5.21 (s, 2H).

**General Procedure<sup>25</sup> for the Synthesis of Compounds II-a ~ II-d.** To a mixture of compound I (10g, 17.5 mmol) and  $\text{K}_2\text{CO}_3$  (4.35 g, 31.5 mmol, 1.8 eq.) in 600 mL dry DMF, MeI (EtI, *n*-PrI or *i*-BuI) (21 mmol, 1.2 eq.) was added under argon. The reaction mixture was stirred at room temperature for 8 h, the resulting mixture was poured into water and extracted with EtOAc, and the organic phase was washed with brine, dried over  $\text{MgSO}_4$ . After removal of solvent, the obtained residue was purified by column chromatography on silica gel to afford II-a (II-b, II-c or II-d).

**3',4',7-Tri-*O*-benzyl-3-*O*-methylquercetin (II-a):**<sup>27</sup> Yellow powder, yield 85%;  $R_f$  0.45 (1:3 EtOAc–

petroleum ether); ESI-MS  $m/z$  609.0  $[M + Na]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.58 (s, 1H), 7.73 (d,  $J = 2.1$  Hz, 1H), 7.68 (dd,  $J = 8.6, 2.1$  Hz, 1H), 7.51–7.29 (m, 16H), 6.83 (d,  $J = 2.2$  Hz, 1H), 6.45 (d,  $J = 2.2$  Hz, 1H), 5.25 (s, 2H), 5.23 (s, 2H), 5.22 (s, 2H), 3.70 (s, 3H).

**3',4',7-Tri-*O*-benzyl-3-*O*-ethylquercetin (II-b):** Yellow powder, yield 81%;  $R_f$  0.20 (1:2 CHCl<sub>3</sub>–petroleum ether); ESI-MS  $m/z$  623.2  $[M + Na]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.51 (s, 1H), 7.75 (d,  $J = 2.3$  Hz, 1H), 7.60 (dd,  $J = 8.7, 2.3$  Hz, 1H), 7.49–7.26 (m, 15H), 7.13 (d,  $J = 8.6$  Hz, 1H), 6.73 (d,  $J = 2.1$  Hz, 1H), 6.16 (d,  $J = 2.2$  Hz, 1H), 5.16 (s, 2H), 5.15 (s, 2H), 5.13 (s, 2H), 3.80 (q,  $J = 6.8$  Hz, 2H), 1.24 (t,  $J = 6.8$  Hz, 3H).

**3',4',7-Tri-*O*-benzyl-3-*O*-*n*-propylquercetin (II-c):** Yellow powder, yield 83%;  $R_f$  0.20 (1:2 CHCl<sub>3</sub>–petroleum ether); ESI-MS  $m/z$  637.2  $[M + Na]^+$ ;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  12.68 (s, 1H), 7.77 (d,  $J = 1.9$  Hz, 1H), 7.67 (dd,  $J = 8.6, 2.0$  Hz, 1H), 7.51–7.44 (m, 5H), 7.44–7.29 (m, 10H), 7.02 (d,  $J = 8.6$  Hz, 1H), 6.46 (d,  $J = 2.1$  Hz, 1H), 6.42 (d,  $J = 2.1$  Hz, 1H), 5.26 (s, 2H), 5.23 (s, 2H), 5.13 (s, 2H), 3.90 (t,  $J = 6.9$  Hz, 2H), 1.72–1.61 (m, 2H), 0.91 (t,  $J = 7.4$  Hz, 3H).

**3',4',7-Tri-*O*-benzyl-3-*O*-*i*-butylquercetin (II-d):** Yellow powder, yield 80%;  $R_f$  0.15 (1:2 CHCl<sub>3</sub>–petroleum ether); ESI-MS  $m/z$  651.2  $[M + Na]^+$ ;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  12.68 (s, 1H), 7.72 (d,  $J = 2.0$  Hz, 1H), 7.67 (dd,  $J = 8.6, 2.0$  Hz, 1H), 7.52–7.29 (m, 15H), 7.02 (d,  $J = 8.6$  Hz, 1H), 6.46 (d,  $J = 2.1$  Hz, 1H), 6.42 (d,  $J = 2.1$  Hz, 1H), 5.25 (s, 2H), 5.22 (s, 2H), 5.13 (s, 2H), 3.72 (d,  $J = 6.7$  Hz, 2H), 2.08–1.93 (m, 1H), 0.95 (d,  $J = 6.7$  Hz, 6H).

**General Procedure for the Synthesis of Compounds III-a ~ III-d.** To a solution of II-a (II-b, II-c or II-d) (9 mmol) in 100 mL EtOH and 100 mL THF was added 10% Pd/C (20% wt. of II-a (II-b, II-c or II-d)). Three purges of vacuum/argon were performed, followed by 3 purges of vacuum/H<sub>2</sub>. After stirring for 15 h at room temperature under hydrogen, the reaction mixture was filtered through diatomite and the filtrate concentrated, the obtained product was used in the next reaction without further purification. The previous crude product was dissolved in 80 mL dry diphenyl ether and dichlorodiphenylmethane (2.6 mL, 13.5 mmol, 1.5 eq.) was added under argon. The reaction mixture was stirred at 175 °C for 1 h as Rolando's method.<sup>18</sup> After cooling to room temperature, the resulting mixture was dissolved in CHCl<sub>3</sub> and washed sequentially with saturated aqueous NaHCO<sub>3</sub> solution, water and brine. The organic layer was dried with MgSO<sub>4</sub>. Removal of the solvent gave a residue which was purified by column chromatography on silica gel to afford compound III-a (III-b, III-c or III-d).

**3',4'-*O*-(Phenylbenzylidene)-3-*O*-methylquercetin (III-a):** Yellowish brown powder, yield 65%, over two steps;  $R_f$  0.25 (1:28 EtOAc–CHCl<sub>3</sub>); ESI-MS  $m/z$  503.1  $[M + Na]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.56 (s, 1H), 7.67 (d,  $J = 0.9$  Hz, 1H), 7.57–7.53 (m, 4H), 7.48–7.42 (m, 6H), 7.23 (dd,  $J = 7.8, 1.0$  Hz, 1H), 6.45 (d,  $J = 2.1$  Hz, 1H), 6.19 (d,  $J = 2.1$  Hz, 1H), 3.77 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  177.92, 164.27, 161.18, 156.37, 154.61, 148.48, 146.74, 139.25, 138.19, 129.57, 128.65, 125.77, 124.12,

123.90, 117.32, 108.99, 108.36, 104.28, 98.65, 93.86, 59.84.

**3',4'-O-(Phenylbenzylidene)-3-O-ethylquercetin (III-b):** Yellowish brown powder, yield 56%, over two steps;  $R_f$  0.20 (1:28 EtOAc–CHCl<sub>3</sub>); ESI-MS  $m/z$  517.1 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.60 (s, 1H), 7.72 (dd,  $J = 10.4, 1.9$  Hz, 1H), 7.71 (d,  $J = 2.2$  Hz, 1H), 7.58–7.52 (m,  $J = 7.7, 1.5$  Hz, 3H), 7.49–7.43 (m, 6H), 7.23 (d,  $J = 8.2$  Hz, 1H), 6.46 (d,  $J = 1.9$  Hz, 1H), 6.20 (d,  $J = 1.9$  Hz, 1H), 4.02 (q,  $J = 7.0$  Hz, 2H), 1.21 (t,  $J = 7.0$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  178.29, 164.41, 161.36, 156.58, 155.12, 148.59, 146.86, 139.41, 137.30, 129.77, 128.85, 125.93, 124.44, 124.18, 117.46, 109.12, 108.59, 104.42, 98.81, 94.03, 68.19, 15.46.

**3',4'-O-(Phenylbenzylidene)-3-O-*n*-propylquercetin (III-c):** Yellowish brown powder, yield 58%, over two steps;  $R_f$  0.20 (1:28 EtOAc–CHCl<sub>3</sub>); ESI-MS  $m/z$  531.1 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.59 (s, 1H), 7.69–7.65 (m, 2H), 7.57–7.53 (m, 4H), 7.48–7.42 (m, 7H), 7.22 (d,  $J = 8.8$  Hz, 1H), 6.44 (d,  $J = 2.1$  Hz, 1H), 6.19 (d,  $J = 2.1$  Hz, 1H), 3.88 (t,  $J = 6.5$  Hz, 2H), 1.66–1.52 (m, 2H), 0.83 (t,  $J = 7.4$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  178.21, 164.37, 161.36, 156.57, 155.19, 148.57, 146.78, 139.38, 137.44, 129.76, 128.82, 125.91, 124.34, 124.17, 117.42, 109.06, 108.78, 104.45, 98.79, 94.00, 74.00, 22.89, 10.51.

**3',4'-O-(Phenylbenzylidene)-3-O-*i*-butylquercetin (III-d):** Yellowish brown powder, yield 55%, over two steps;  $R_f$  0.20 (1:28 EtOAc–CHCl<sub>3</sub>); ESI-MS  $m/z$  545.1 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.59 (s, 1H), 7.65–7.60 (m, 2H), 7.57–7.51 (m, 4H), 7.48–7.41 (m, 6H), 7.20 (d,  $J = 8.3$  Hz, 1H), 6.43 (d,  $J = 2.1$  Hz, 1H), 6.18 (d,  $J = 2.1$  Hz, 1H), 3.68 (d,  $J = 6.4$  Hz, 2H), 1.92–1.80 (m, 1H), 0.84 (d,  $J = 6.7$  Hz, 6H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  178.15, 164.37, 161.39, 156.59, 155.28, 148.59, 146.74, 139.38, 137.58, 129.76, 128.82, 125.92, 124.27, 124.18, 117.41, 109.02, 108.99, 104.51, 98.81, 94.00, 78.64, 28.56, 19.13.

**General Procedure<sup>24</sup> for the Synthesis of Compounds IV-a ~ IV-d.** To a mixture of III-a (III-b, III-c or III-d) (0.416 mmol), TBAB (14 mg, 0.042 mmol, 0.1 eq.) and K<sub>2</sub>CO<sub>3</sub> (0.403 g, 2.91 mmol, 7.0 eq.) in 5 mL DMF and 5 mL water was added dropwise a solution of  $\alpha$ -D-glucopyranosyl bromide tetrabenzoate in CHCl<sub>3</sub> under argon. The resulting reaction mixture was stirred at room temperature for 48 h. After cooling to room temperature the mixture was dilute with EtOAc and water, the organic phase was separated and washed with brine, dried over MgSO<sub>4</sub> and evaporated in *vacuo* to provide a residue which was purified by column chromatography on silica gel to afford IV-a (IV-b, IV-c or IV-d).

**3',4'-O-(Phenylbenzylidene)-3-O-methyl-7-O-(2,3,4,6-tetra-O-benzoyl- $\beta$ -D-glucopyranosyl)quercetin (IV-a):** Yellow oil, yield 71%;  $R_f$  0.20 (1:3.5 CHCl<sub>3</sub>–petroleum ether); ESI-MS  $m/z$  1081.2 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  12.60 (s, 1H), 7.99–7.93 (m, 6H), 7.90–7.86 (m, 2H), 7.68–7.56 (m, 6H), 7.55–7.50 (m, 2H), 7.47 (t,  $J = 7.4$  Hz, 1H), 7.43–7.30 (m, 13H), 7.28–7.20 (m, 3H), 6.96 (d,  $J = 8.4$  Hz, 1H), 6.53 (d,  $J = 2.2$  Hz, 1H), 6.50 (d,  $J = 2.2$  Hz, 1H), 6.01 (t,  $J = 9.2$  Hz, 1H), 5.81 (dd,  $J = 9.1, 7.3$  Hz,

1H), 5.76 (d,  $J = 9.3$  Hz, 1H), 5.58 (d,  $J = 7.3$  Hz, 1H), 4.86–4.66 (m, 1H), 4.57–4.32 (m, 2H), 3.85 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.92, 166.25, 165.83, 165.32, 165.11, 162.31, 161.98, 156.31, 156.10, 149.66, 147.69, 139.87, 139.83, 139.17, 133.79, 133.66, 133.58, 133.24, 130.05, 129.99, 129.96, 129.74, 129.52, 129.32, 128.95, 128.75, 128.68, 128.65, 128.61, 128.52, 128.45, 126.35, 124.06, 123.95, 118.14, 108.76, 107.42, 99.60, 98.28, 95.19, 77.36, 73.09, 72.68, 71.53, 69.33, 63.15, 60.36.

**3',4'-O-(Phenylbenzylidene)-3-O-ethyl-7-O-(2,3,4,6-tetra-O-benzoyl- $\beta$ -D-glucopyranosyl)quercetin (IV-b):** Yellow oil, yield 52%;  $R_f$  0.20 (1:3.5  $\text{CHCl}_3$ –petroleum ether); ESI-MS  $m/z$  1095.3  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.65 (s, 1H), 8.00–7.93 (m, 6H), 7.90–7.85 (m, 2H), 7.66 (dd,  $J = 8.4, 1.8$  Hz, 1H), 7.62–7.57 (m, 5H), 7.55–7.50 (m, 2H), 7.47 (t,  $J = 7.5$  Hz, 1H), 7.42–7.37 (m, 9H), 7.36–7.29 (m, 4H), 7.26–7.20 (m, 3H), 7.19–7.13 (m, 2H), 6.95 (d,  $J = 8.4$  Hz, 1H), 6.53 (d,  $J = 2.2$  Hz, 1H), 6.49 (d,  $J = 2.2$  Hz, 1H), 6.00 (t,  $J = 9.2$  Hz, 1H), 5.81 (dd,  $J = 9.1, 7.4$  Hz, 1H), 5.74 (t,  $J = 9.3$  Hz, 1H), 5.57 (d,  $J = 7.3$  Hz, 1H), 4.74 (d,  $J = 9.7$  Hz, 1H), 4.50–4.40 (m, 2H), 4.11–4.01 (m, 2H), 1.33 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  179.46, 166.58, 166.15, 165.65, 165.43, 162.68, 162.28, 156.66, 149.88, 147.94, 140.23, 140.19, 138.52, 134.11, 133.97, 133.89, 133.56, 130.37, 130.31, 130.28, 130.07, 129.83, 129.66, 129.49, 129.29, 129.09, 129.02, 128.97, 128.93, 128.84, 128.78, 128.68, 126.67, 125.75, 124.63, 124.36, 109.15, 108.97, 107.73, 99.88, 98.65, 95.49, 77.68, 73.43, 73.02, 71.86, 69.69, 69.14, 63.49.

**3',4'-O-(Phenylbenzylidene)-3-O-*n*-propyl-7-O-(2,3,4,6-tetra-O-benzoyl- $\beta$ -D-glucopyranosyl)-quercetin (IV-c):** Yellow oil, yield 63%;  $R_f$  0.20 (1:3.5  $\text{CHCl}_3$ –petroleum ether); ESI-MS  $m/z$  1109.3  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.66 (s, 1H), 7.99–7.93 (m, 6H), 7.90–7.86 (m, 2H), 7.65–7.57 (m, 6H), 7.55–7.44 (m, 3H), 7.42–7.37 (m, 9H), 7.37–7.30 (m, 4H), 7.25–7.21 (m, 2H), 6.95 (d,  $J = 8.3$  Hz, 1H), 6.53 (d,  $J = 2.2$  Hz, 1H), 6.50 (d,  $J = 2.2$  Hz, 1H), 6.01 (t,  $J = 9.2$  Hz, 1H), 5.82 (dd,  $J = 9.2, 7.4$  Hz, 1H), 5.74 (t,  $J = 9.4$  Hz, 1H), 5.57 (d,  $J = 7.4$  Hz, 1H), 4.74 (d,  $J = 9.5$  Hz, 1H), 4.50–4.40 (m, 2H), 3.98–3.87 (m, 2H), 1.79–1.68 (m, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.93, 166.08, 165.66, 165.16, 164.94, 162.20, 161.78, 156.18, 149.37, 147.41, 139.73, 139.70, 138.22, 133.62, 133.47, 133.40, 133.07, 129.88, 129.82, 129.79, 129.59, 129.33, 129.18, 128.80, 128.60, 128.53, 128.48, 128.44, 128.37, 128.34, 128.29, 126.19, 124.08, 123.90, 108.79, 108.46, 107.29, 99.37, 98.17, 95.00, 74.55, 72.94, 72.53, 71.37, 69.20, 63.01, 23.30, 10.38.

**3',4'-O-(Phenylbenzylidene)-3-O-*i*-butyl-7-O-(2,3,4,6-tetra-O-benzoyl- $\beta$ -D-glucopyranosyl)quercetin (IV-d):** Yellow oil, yield 52%;  $R_f$  0.20 (1:3.5  $\text{CHCl}_3$ –petroleum ether); ESI-MS  $m/z$  1123.3  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00–7.92 (m, 7H), 7.90–7.84 (m, 2H), 7.61–7.44 (m, 10H), 7.41–7.30 (m, 15H), 7.24 (s, 2H), 6.94 (d,  $J = 10.0$  Hz, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 6.00 (t,  $J = 8.8$  Hz, 1H), 5.81 (t,  $J = 7.6$  Hz, 1H), 5.74 (t,  $J = 9.2$  Hz, 1H), 5.56 (d,  $J = 6.2$  Hz, 1H), 4.73 (d,  $J = 11.5$  Hz, 1H), 4.52–4.38 (m, 2H), 3.80–3.63 (m, 2H), 2.09–1.97 (m, 1H), 0.96 (d,  $J = 5.7$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  178.91, 166.11, 165.69, 165.18, 164.97, 162.25, 161.80, 156.22, 149.40, 147.40, 139.75, 139.72, 138.40,

133.63, 133.49, 133.42, 133.09, 129.90, 129.85, 129.81, 129.62, 129.35, 129.21, 128.84, 128.63, 128.57, 128.50, 128.46, 128.39, 128.35, 128.32, 126.22, 124.04, 123.95, 117.89, 108.94, 108.43, 107.37, 99.38, 98.23, 95.03, 79.24, 72.97, 72.56, 71.40, 69.23, 63.04, 28.99, 19.18.

**General Procedure<sup>19</sup> for the Synthesis of Compounds V-a ~ V-d.** 10% Pd/C (20% wt. of IV-a (IV-b, IV-c or IV-d)) was added to a solution of IV-a (IV-b, IV-c or IV-d) (0.523 mmol) in 80 mL EtOH, 20 mL THF and 1 mL water. Three purges of vacuum/argon were performed, followed by 3 purges of vacuum/H<sub>2</sub>. After stirring for 48 h at 45 °C under hydrogen, the reaction mixture was filtered through diatomite and evaporated in *vacuo* to give a residue which was purified by column chromatography on silica gel to afford V-a (V-b, V-c or V-d).

**3-O-Methyl-7-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)quercetin (V-a):** Yellow oil, yield 77%; *R<sub>f</sub>* 0.20 (1:70 MeOH–CHCl<sub>3</sub>); ESI-MS *m/z* 917.2 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.49 (s, 1H), 8.01–7.84 (m, 8H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.54–7.27 (m, 14H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 3.1 Hz, 2H), 6.02 (t, *J* = 9.2 Hz, 1H), 5.83–5.73 (m, 2H), 5.53 (d, *J* = 7.3 Hz, 1H), 4.77–4.71 (m, 1H), 4.53–4.40 (m, 2H), 3.79 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 193.77, 193.63, 183.23, 170.20, 166.47, 165.34, 163.87, 162.21, 156.13, 154.13, 147.42, 144.33, 133.81, 133.63, 133.35, 129.97, 129.77, 128.93, 128.65, 128.51, 126.35, 122.40, 117.63, 115.46, 107.37, 104.69, 99.61, 98.28, 91.38, 78.82, 69.41, 67.05, 63.16, 60.24, 55.90, 39.34, 32.08, 29.85, 29.47, 24.91, 22.85, 11.52, 7.91.

**3-O-Ethyl-7-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)quercetin (V-b):** Yellow oil, yield 51%; *R<sub>f</sub>* 0.20 (1:70 MeOH–CHCl<sub>3</sub>); ESI-MS *m/z* 931.3 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.54 (s, 1H), 7.99–7.86 (m, 8H), 7.75 (s, 1H), 7.55–7.41 (m, 5H), 7.40–7.23 (m, 10H), 7.02–6.94 (m, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 6.03 (t, *J* = 9.2 Hz, 1H), 5.81 (dd, *J* = 8.9, 7.3 Hz, 1H), 5.77 (t, *J* = 8.8 Hz, 1H), 5.54 (d, *J* = 7.3 Hz, 1H), 4.74 (dd, *J* = 12.0, 2.5 Hz, 1H), 4.55–4.39 (m, 2H), 4.46–4.40 (m, 1H), 4.01 (q, *J* = 6.9 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.17, 166.58, 166.06, 165.39, 165.26, 162.05, 161.95, 157.28, 156.31, 147.58, 143.72, 137.84, 133.82, 133.74, 133.67, 133.39, 130.02, 129.98, 129.78, 129.22, 128.87, 128.64, 128.57, 128.51, 122.66, 122.41, 115.83, 115.32, 107.22, 99.60, 98.26, 95.35, 77.36, 72.85, 72.78, 71.61, 69.46, 69.03, 63.26.

**3-O-n-Propyl-7-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)quercetin (V-c):** Yellow oil, yield 49%; *R<sub>f</sub>* 0.25 (1:60 MeOH–CHCl<sub>3</sub>); ESI-MS *m/z* 945.3 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.58 (s, 1H), 7.99–7.86 (m, 8H), 7.69 (s, 1H), 7.54–7.48 (m, 3H), 7.47–7.39 (m, 2H), 7.38–7.27 (m, 8H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.44 (s, 2H), 6.02 (t, *J* = 9.2 Hz, 1H), 5.81 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.79–5.74 (m, 1H), 5.53 (d, *J* = 7.3 Hz, 1H), 4.74 (dd, *J* = 12.0, 2.6 Hz, 1H), 4.54–4.39 (m, 2H), 3.89 (t, *J* = 6.9 Hz, 2H), 1.75–1.65 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.99, 166.43, 165.91, 165.25, 165.12, 161.96, 161.78, 156.97, 156.17, 147.30, 143.52, 137.98, 133.66, 133.58, 133.51, 133.24, 129.87, 129.83, 129.64, 129.10, 128.74, 128.49, 128.42, 128.37, 122.55, 122.37, 115.74, 115.15, 107.15,

99.42, 98.16, 95.20, 77.26, 77.01, 76.76, 74.81, 72.73, 72.65, 71.47, 69.33, 63.13, 23.22, 10.29.

**3-*O*-*i*-Butyl-7-*O*-(2,3,4,6-tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyl)quercetin (V-d):** Yellow oil, yield 84%;  $R_f$  0.15 (1:80 MeOH-CHCl<sub>3</sub>); ESI-MS  $m/z$  959.3 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 12.66 (s, 1H), 8.00–7.92 (m, 7H), 7.90–7.84 (m, 2H), 7.61–7.44 (m, 10H), 7.41–7.30 (m, 15H), 7.24 (s, 2H), 6.94 (d,  $J$  = 10.0 Hz, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 6.00 (t,  $J$  = 8.8 Hz, 1H), 5.81 (t,  $J$  = 7.6 Hz, 1H), 5.74 (t,  $J$  = 9.2 Hz, 1H), 5.56 (d,  $J$  = 6.2 Hz, 1H), 4.73 (d,  $J$  = 11.5 Hz, 1H), 4.52–4.38 (m, 2H), 3.80–3.63 (m, 2H), 2.09–1.97 (m, 1H), 0.91 (d,  $J$  = 6.7 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  179.05, 166.62, 166.01, 165.41, 165.29, 162.10, 161.83, 156.97, 156.26, 147.29, 143.63, 138.36, 133.82, 133.75, 133.66, 133.42, 130.02, 129.98, 129.96, 129.79, 129.19, 128.83, 128.64, 128.60, 128.56, 128.53, 122.68, 122.64, 115.90, 115.25, 107.32, 99.42, 98.26, 95.31, 79.63, 72.86, 72.75, 71.59, 69.43, 63.27, 29.05, 19.33.

**General Procedure<sup>21</sup> for the Synthesis of Compounds VI-a ~ VI-d.** To a solution of V-a (V-b, V-c or V-d) (0.089 mmol) in 4 mL EtOH and 1 mL CH<sub>2</sub>Cl<sub>2</sub>, a solution of MeONa (0.41 mg, 0.27 mmol, 3.0 eq.) in MeOH was added dropwise under argon. After stirring at room temperature for 30 min, the reaction mixture was neutralized with Amberlite IR-120 (HCl), filtered and concentrated. The resulting residue was purified by column chromatography on silica gel to afford VI-a (VI-b, VI-c or VI-d).

**3-*O*-Methyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (VI-a):**<sup>28</sup> Light yellow powder, yield 83%;  $R_f$  0.20 (1:5 MeOH-CHCl<sub>3</sub>); ESI-MS  $m/z$  501.1 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.69 (s, 1H), 8.16 (s, 1H), 7.57 (d,  $J$  = 2.2 Hz, 1H), 7.45 (dd,  $J$  = 8.5, 2.2 Hz, 1H), 6.91 (d,  $J$  = 8.4 Hz, 1H), 6.76 (d,  $J$  = 2.1 Hz, 1H), 6.42 (d,  $J$  = 2.1 Hz, 1H), 5.06 (d,  $J$  = 7.4 Hz, 1H), 3.78 (s, 3H), 3.71–3.66 (m, 1H), 3.50–3.41 (m, 2H), 3.32–3.22 (m, 2H), 3.16 (t,  $J$  = 8.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  178.15, 172.18, 163.57, 162.94, 160.93, 160.49, 156.32, 156.01, 148.99, 147.50, 145.33, 137.96, 136.86, 120.73, 120.68, 115.79, 115.67, 105.88, 99.88, 99.24, 94.53, 77.19, 76.43, 73.16, 69.58, 60.64, 59.76, 48.66, 27.34, 10.27.

**3-*O*-Ethyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (VI-b):** Light yellow powder, yield 92%;  $R_f$  0.15 (1:6.5 MeOH-CHCl<sub>3</sub>); ESI-MS  $m/z$  515.2 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.83 (s, 1H), 9.40 (br, 1H), 8.29 (br, 1H), 7.60 (d,  $J$  = 2.2 Hz, 1H), 7.47 (dd,  $J$  = 8.5, 2.2 Hz, 1H), 6.90 (d,  $J$  = 8.5 Hz, 1H), 6.75 (d,  $J$  = 2.1 Hz, 1H), 6.42 (d,  $J$  = 2.1 Hz, 1H), 5.41 (br, 1H), 5.13 (br, 1H), 5.06 (d,  $J$  = 7.3 Hz, 2H), 4.61 (br, 1H), 4.11 (br, 1H), 4.01 (q,  $J$  = 7.0 Hz, 2H), 3.73–3.65 (m, 1H), 3.49–3.45 (m, 1H), 3.30–3.23 (m, 2H), 3.17 (s, 1H), 1.26 (t,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  178.33, 162.90, 160.95, 156.60, 156.03, 148.86, 145.21, 136.85, 120.91, 120.79, 115.73, 115.67, 105.84, 99.86, 99.21, 94.48, 79.21, 77.18, 76.42, 73.15, 69.57, 67.81, 60.65, 48.66, 15.37.

**3-*O*-*n*-Propyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (VI-c):** Light yellow powder, yield 63%;  $R_f$  0.15 (1:8 MeOH-CHCl<sub>3</sub>); ESI-MS  $m/z$  529.2 [M + Na]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.72 (s, 1H), 8.29 (s, 1H), 7.55 (d,  $J$  = 2.2 Hz, 1H), 7.45 (dd,  $J$  = 8.5, 2.2 Hz, 1H), 6.89 (d,  $J$  = 8.5 Hz, 1H), 6.74 (d,  $J$  = 1.9 Hz, 1H), 6.42 (d,  $J$  = 2.0 Hz, 1H), 5.05 (d,  $J$  = 7.4 Hz, 2H), 4.63 (s, 1H), 3.89 (t,  $J$  = 6.6 Hz, 2H), 3.72–3.64

(m, 1H), 3.51–3.48 (m, 2H), 3.29–3.22 (m, 2H), 3.18–3.12 (m, 1H), 1.65 (h,  $J = 7.3$  Hz, 2H), 0.89 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  178.29, 162.91, 160.98, 156.68, 156.07, 148.88, 145.24, 137.06, 120.88, 115.84, 115.64, 105.91, 99.89, 99.24, 94.51, 79.23, 77.20, 76.44, 73.73, 73.17, 69.61, 60.67, 48.69, 22.85, 10.46.

**3-*O*-*i*-Butyl-7-*O*- $\beta$ -D-glucopyranosylquercetin (VI-d):** Light yellow powder, yield 68%;  $R_f$  0.15 (1:7 MeOH–CHCl<sub>3</sub>); ESI-MS  $m/z$  543.3 [M + Na]<sup>+</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.67 (s, 1H), 7.45 (d,  $J = 2.1$  Hz, 1H), 7.37 (dd,  $J = 8.4, 2.1$  Hz, 1H), 6.84 (d,  $J = 8.4$  Hz, 1H), 6.69 (d,  $J = 1.3$  Hz, 1H), 6.37 (d,  $J = 1.5$  Hz, 1H), 5.40 (br, 1H), 5.08 (br, 1H), 5.00 (d,  $J = 7.3$  Hz, 2H), 4.60 (br, 1H), 3.64 (d,  $J = 6.5$  Hz, 2H), 3.56 (s, 2H), 3.28–3.16 (m, 3H), 3.11 (t,  $J = 8.8$  Hz, 1H), 1.96–1.80 (m, 1H), 0.85 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  178.28, 162.93, 161.04, 156.80, 156.13, 148.87, 145.27, 137.29, 121.05, 120.89, 115.98, 115.63, 106.00, 99.93, 99.29, 94.56, 78.47, 77.24, 76.47, 73.21, 69.66, 60.71, 28.57, 19.22.

**Synthesis of Compounds V-a-1 and V-a-2.** The synthesis of compounds **V-a-1** and **V-a-2** was followed Jun's method.<sup>25</sup> To a mixture of compound **V-a** (180 mg, 0.2 mmol) and K<sub>2</sub>CO<sub>3</sub> (33 mg, 0.24 mmol, 1.2 eq.) in 8 mL dry DMF, BnBr (0.026 mL, 0.22 mmol, 1.1 eq.) was added under argon. After stirring at room temperature for 10 h, the resulting mixture was poured into water and extracted with EtOAc, the organic phase was washed with brine, dried over MgSO<sub>4</sub>. After removal of solvent, the obtained residue was purified by column chromatography on silica gel to afford **V-a-1**. To a mixture of anhydrous **V-a-1** (99 mg, 0.1 mmol) and anhydrous K<sub>2</sub>CO<sub>3</sub> (45 mg, 0.3 mmol, 3.0 eq.) in 600 mL of anhydrous DMF, *n*-propyl iodide (0.029 mL, 0.3 mmol, 3.0 eq.) was added under argon. After stirring at room temperature for 10 h, the resulting mixture was poured into water and extracted with EtOAc, the organic phase was washed with brine, dried over MgSO<sub>4</sub>. After removal of solvent, the obtained residue was purified by column chromatography on silica gel to afford **V-a-2**.

**3-*O*-Methyl-4'-*O*-benzyl-7-*O*-(2,3,4,6-tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyl)quercetin (V-a-1):** Light yellow powder, yield 78%;  $R_f$  0.30 (1:120 MeOH–CHCl<sub>3</sub>); ESI-MS  $m/z$  1007.1 [M + Na]<sup>+</sup>;  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  12.61 (s, 1H), 8.04–7.85 (m, 5H), 7.67–7.22 (m, 12H), 7.00 (d,  $J = 8.5$  Hz, 1H), 6.54 (s, 1H), 6.50 (s, 1H), 6.00 (t,  $J = 9.1$  Hz, 1H), 5.84–5.73 (m, 3H), 5.58 (d,  $J = 7.0$  Hz, 1H), 5.20 (s, 2H), 4.73 (d,  $J = 11.0$  Hz, 1H), 4.53–4.40 (m, 2H), 3.86 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  179.00, 166.25, 165.84, 165.32, 165.13, 162.35, 161.98, 156.36, 156.07, 148.22, 145.87, 139.36, 135.74, 133.77, 133.66, 133.57, 133.26, 130.05, 130.01, 129.97, 129.82, 129.41, 129.02, 128.99, 128.86, 128.79, 128.73, 128.64, 128.63, 128.55, 128.49, 128.01, 123.79, 121.62, 114.91, 111.90, 107.46, 99.51, 98.32, 95.36, 73.08, 72.71, 71.57, 71.31, 69.34, 63.14, 60.30.

**3-*O*-Methyl-3',5-di-*O*-*n*-propyl-4'-*O*-benzyl-7-*O*-(2,3,4,6-tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyl)-quercetin (V-a-2):** Yellow oil, yield 82%;  $R_f$  0.20 (1:80 MeOH–CHCl<sub>3</sub>); ESI-MS  $m/z$  1091.1 [M + Na]<sup>+</sup>;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01–7.93 (m, 4H), 7.90 (s, 2H), 7.88 (s, 2H), 7.67 (d,  $J = 2.0$  Hz, 1H), 7.56–7.51 (m, 2H), 7.50–7.45 (m, 4H), 7.42–7.29 (m, 11H), 7.16 (t,  $J = 7.8$  Hz, 2H), 6.94 (d,  $J = 8.6$  Hz, 1H), 6.62 (d,  $J = 2.1$  Hz, 1H), 6.36 (d,  $J = 2.1$  Hz, 1H), 6.02 (t,  $J = 9.1$  Hz, 1H), 5.84–5.74 (m, 2H), 5.62 (d,  $J = 7.2$  Hz, 1H), 5.23 (s, 2H), 4.75 (d,  $J = 9.4$  Hz, 1H), 4.55–4.44 (m, 2H), 4.07–4.00 (m, 2H), 3.94–3.87 (m, 2H), 3.83 (s, 3H), 1.97–1.81 (m, 4H), 1.11–1.03 (m, 6H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  177.83, 167.25, 166.94, 165.42, 165.18, 162.75, 162.08, 156.39, 156.17, 148.27, 145.77, 139.41, 135.84, 133.74, 133.68, 133.59, 133.27, 130.09, 130.03, 129.98, 129.85, 129.47, 129.06, 128.94, 128.86, 128.80, 128.74, 128.65, 128.60, 128.55, 128.49, 128.01, 123.89, 122.72, 114.81, 111.92, 108.46, 99.56, 98.42, 95.41, 73.18, 72.75, 71.61, 71.32, 69.35, 65.19, 61.50, 22.76, 22.58, 10.83, 10.61.

**Synthesis of Compounds V-d-1 and V-d-2.** To a mixture of compound **V-d** (120 mg, 0.128 mmol) and  $\text{K}_2\text{CO}_3$  (248 mg, 1.79 mmol, 14.0 eq.) in 4 mL dry DMF,  $\text{Br}(\text{CH}_2)_3\text{OH}$  (0.139 mL, 12.0 mmol, 1.1 eq.) was added under argon, the reaction mixture was stirred at room temperature for 10 h as Jun's method.<sup>25</sup> The resulting mixture was poured into water and extracted with EtOAc, the organic phase was washed with brine, dried over  $\text{MgSO}_4$ . After removal of solvent, the obtained residue was purified by column chromatography on silica gel to afford **V-d-1**. The synthesis of compound **V-d-2** was followed Qi's method.<sup>24</sup> To a solution of **V-d-1** (44 mg, 0.04 mmol) in 4 mL EtOH and 1 mL  $\text{CH}_2\text{Cl}_2$ , a solution of MeONa (0.18 mg, 0.12 mmol, 3.0 eq.) in MeOH was added dropwise under argon. After stirring at room temperature for 30 min, the reaction mixture was neutralized with Amberlite IR-120 (HCl), filtered and concentrated, the resulting residue was purified by column chromatography on silica gel to afford **V-d-2**.

**3-*O*-*i*-Butyl-3',4',5-tri-*O*-(3-hydroxypropyl)-7-*O*-(2,3,4,6-tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyl)-quercetin (V-d-1):** Yellow oil, yield 42%;  $R_f$  0.20 (1:75 MeOH– $\text{CHCl}_3$ ); ESI-MS  $m/z$  1133.4  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01–7.92 (m, 4H), 7.90 (s, 2H), 7.88 (s, 2H), 7.62–7.52 (m, 4H), 7.48 (t,  $J = 7.3$  Hz, 1H), 7.43–7.30 (m, 7H), 7.20 (t,  $J = 7.6$  Hz, 2H), 6.93 (d,  $J = 8.5$  Hz, 1H), 6.68 (s, 1H), 6.37 (s, 1H), 6.02 (t,  $J = 9.0$  Hz, 1H), 5.85–5.75 (m, 2H), 5.64 (d,  $J = 7.0$  Hz, 1H), 4.82–4.73 (m, 1H), 4.50 (s, 1H), 4.48 (s, 1H), 4.31–4.15 (m, 4H), 4.14–4.01 (m, 2H), 3.96–3.82 (m, 6H), 3.80–3.67 (m, 3H), 2.13–2.05 (m, 6H), 2.02–1.96 (m, 1H), 0.93 (d,  $J = 6.5$  Hz, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  175.03, 166.52, 166.31, 165.47, 165.39, 162.15, 162.03, 157.67, 156.46, 147.49, 143.73, 138.50, 133.81, 133.77, 133.65, 133.48, 130.12, 130.02, 129.88, 129.75, 129.39, 128.93, 128.84, 128.70, 128.56, 128.53, 122.68, 122.54, 115.90, 115.28, 107.35, 99.46, 98.32, 95.41, 79.73, 72.96, 72.85, 71.58, 70.43, 66.85, 65.75, 65.67, 60.67, 58.51, 57.45, 57.40, 32.51 32.34 32.18, 28.83, 19.43.

**3-*O*-*i*-Butyl-3',4',5-tri-*O*-(3-hydroxypropyl)-7-*O*- $\beta$ -D-glucopyranosylquercetin (V-d-2):** Light yellow powder, yield 84%;  $R_f$  0.15 (1:10 MeOH– $\text{CHCl}_3$ ); ESI-MS  $m/z$  717.2  $[\text{M} + \text{Na}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  7.64–7.59 (m, 2H), 7.12 (d,  $J = 9.2$  Hz, 1H), 6.85 (d,  $J = 2.1$  Hz, 1H), 6.56 (d,  $J = 2.1$  Hz, 1H), 5.41 (br, 1H), 5.17 (br, 1H), 5.10 (br, 1H), 5.07 (d,  $J = 7.3$  Hz, 1H), 4.72 (br, 1H), 4.68 (br, 1H), 4.57

(br, 2H), 4.17–4.04 (m, 6H), 3.74–3.68 (m, 1H), 3.70–3.62 (m, 4H), 3.62–3.53 (m, 4H), 3.32–3.23 (m, 5H), 3.15 (br, 2H), 1.98–1.81 (m, 7H), 0.89 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  172.59, 161.52, 159.69, 157.77, 152.25, 150.54, 147.89, 139.70, 122.63, 113.32, 109.19, 100.02, 78.08, 77.40, 76.62, 73.24, 69.81, 66.83, 65.85, 65.46, 60.76, 58.31, 57.51, 57.40, 32.30, 32.13, 31.82, 28.70, 19.23.

**Assay of  $\alpha$ -Glucosidase Inhibitory Activity.** The inhibitory activity against  $\alpha$ -glucosidase assay was performed on 96-well microplate with the PNPG as substrate and the acarbose as positive control according to Mei's method.<sup>29</sup> To a total of 70  $\mu\text{L}$  of reaction mixture containing 50  $\mu\text{L}$  of 0.1  $\text{mol}\cdot\text{L}^{-1}$  phosphate buffer (PB) and 20  $\mu\text{L}$  solution containing 200  $\text{U}\cdot\text{L}^{-1}$   $\alpha$ -glucosidase and 0.1% BSA in 0.1  $\text{mol}\cdot\text{L}^{-1}$  PB (pH 7.4), 10  $\mu\text{L}$  of 1  $\mu\text{mol}\cdot\text{L}^{-1}$  the test sample in 0.1  $\text{mol}\cdot\text{L}^{-1}$  PB was added. The resulted mixture was incubated for 10 min at 37  $^\circ\text{C}$ , then 20  $\mu\text{L}$  of 10  $\text{mmol}\cdot\text{L}^{-1}$  PNPG in 0.1  $\text{mol}\cdot\text{L}^{-1}$  PB was added. After incubation for 15 min at 37  $^\circ\text{C}$ , the reaction was stopped by adding 30  $\mu\text{L}$  of 3% sodium dodecyl sulfate (SDS) in 0.1  $\text{mol}\cdot\text{L}^{-1}$  PB. Then the optical density value (OD) at 405 nm was measured on microplate reader. The control sample was the mixture of test sample with solvent instead. The sample blank and control blank were the mixtures of sample and control, respectively, except  $\alpha$ -glucosidase was instead with buffer, respectively. The inhibition (%) of quercetin glycosides against  $\alpha$ -glucosidase were calculated according to the following formula:

$$\text{Inhibition (\%)} = (\text{OD}_S - \text{OD}_{\text{SB}}) / (\text{OD}_C - \text{OD}_{\text{CB}}) \times 100$$

Where  $\text{OD}_S$ ,  $\text{OD}_{\text{SB}}$ ,  $\text{OD}_C$ , and  $\text{OD}_{\text{CB}}$  are the optical density value of sample, sample blank, control, and control blank, respectively. Each sample was tested twice in triplicate, data are the average values of two individual experiments.

## ACKNOWLEDGEMENT

The authors are grateful to the staff of the analytical group of The Key laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Sciences for measurements of all spectra. This work was supported by Guizhou Bailing Group Pharmaceutical Co., Ltd., Guizhou province, P. R. China and The Special Fund for Outstanding Youth in Science and Technology, Guizhou Province, P. R. China (QKHRZ(2015)24).

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