Regiospecific synthesis of three quercetin *O*-β-glucosides of *N*-acetylglucosamine

Zhiling Cao*, Jing Chen, Dandan Zhu, Zongnan Yang, Wenqi Teng, Gaofeng Liu, Bing Liu and Chuanzhou Tao

Jiangsu Key Laboratory of Marine Pharmaceutical Compound Screening, Jiangsu Institute of Marine Resources, Huaihai Institute of Technology, Lianyungang 222005, P.R. China

The regiospecific synthesis of three quercetin *O*-β-glucosides of *N*-acetylglucosamine has been achieved in good yield. Selective di- and tri-*O*-benzylation of quercetin followed by *O*-glycosylation with 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride under phase-transfer catalysis conditions yielded, after deacetylation and debenzylation, 3-, 3′- and 4′-glycosylated quercetin.

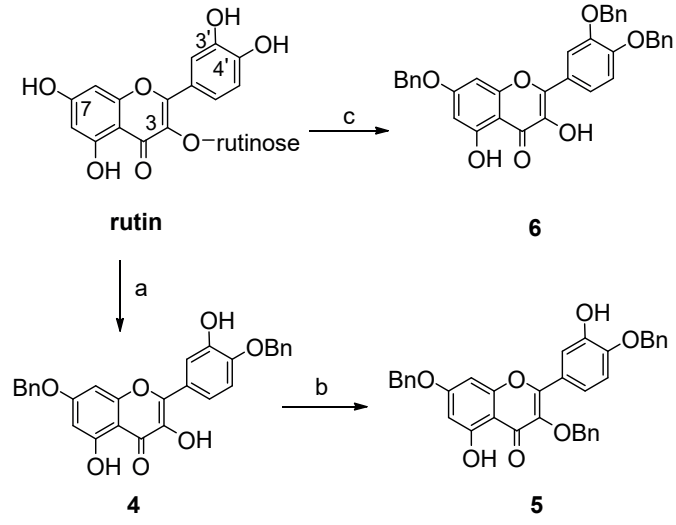
Keywords: glucosamine, quercetin, glycosylation, regiospecific synthesis, *N*-acetylglucosamine, phase-transfer catalysis

Many natural products that contain sugar residues have significant biological activity. Flavonoids are polyphenolic compounds that are widely distributed in plants. Quercetin (Fig. 1) and its glycosides are an important class of antioxidants and dietary flavonoids and some are known to be common components of traditional medicines.[1,2] Furthermore, some have exhibited pharmacological effects, such as anti-cancer,[3] anti-inflammatory,[4] and anti-ageing[5] activity, *in vivo* and *in vitro*. Quercetin can be linked to various sugars, including glucose, galactose, arabinose or rhamnose.[2] Both the structure and linking position of the sugar moiety attached to quercetin dramatically affect the biological activity.[6–8]

Recently, some natural and unnatural flavonoid amino sugar glycosides have been reported. Fenical and co-workers isolated a novel 3-amino-ribopyranose flavonoid from *Streptomyces* sp. that showed antibacterial activity against *Bacillus subtilis*[9] and Ahn and co-workers reported the biological synthesis of quercetin 3-*O*-*N*-acetylglucosamine glycoside (**1**) using engineered *Escherichia coli*.[10,11] Glucosamine and other amino sugars are common structural units found in various biological *O*-glycosides.[12,13] Most glucosamine glycosides are *N*-acetylated and characterised by β-glycosidic linkages.[14] Quercetin glycosides of glucosamine have interesting potential biological effects. However, the efficient regioselective and stereoselective synthesis of flavonoid glycosides remains challenging.[15,16] What is more, the production of them *via* biological synthesis has been limited by the diversity of sugar type and position of sugar links. This prompted us to develop a synthetic method for the preparation of unusual flavonoid glycosides of *N*-acetyl amino sugars. Here, we report the synthesis of three quercetin *O*-β-glycosides of *N*-acetylglucosamine (**1**–**3**) (Fig. 1).

Results and discussion

In this study, we aimed to introduce an *N*-acetylglucosamine moiety into quercetin at its C3, C3′ and C4′ hydroxyl groups by an *O*-glycosylation procedure. Obviously, the selective protection of four of the five hydroxyl groups of quercetin is crucial for the regiospecific *O*-glycosylation of one of them. The results showed that quercetin phenolic functions have a preferential reactivity in the order of 7 > 3 ≈ 4′ > 3′ > 5, which is in agreement with Rolando's tests.[17] In previous work from this laboratory, the C3 isomer (**1**) was synthesised by the direct glycosylation of 7,4′-di-*O*-benzylquercetin (**4**) (Scheme 1).[18] However, we found that it was difficult to avoid the concurrent formation of the 3,3′-di-*O*-glycosylated product. It was therefore clear that for the efficient synthesis of all three isomers (**1**–**3**) (Fig. 1), all OH groups except the one to be glycosylated should be protected to give the selectivity required.



Scheme 1 Synthesis of tri- (**5** and **6**), and a di-benzylated quercetin (**4**) from rutin. Path a: (i) BnBr (2 equiv.), K_2CO_3 (1.5 equiv.), DMF, 60 °C, 2 h; (ii) HCl/EtOH, reflux, 2 h. Path b: BnCl (1 equiv.), py, CH_2Cl_2, r.t., 12 h, 85%. Path c: (i) BnBr (8 equiv.), K_2CO_3, DMF, r.t., 16 h; (ii) HCl/EtOH, reflux, 2 h, 85%.

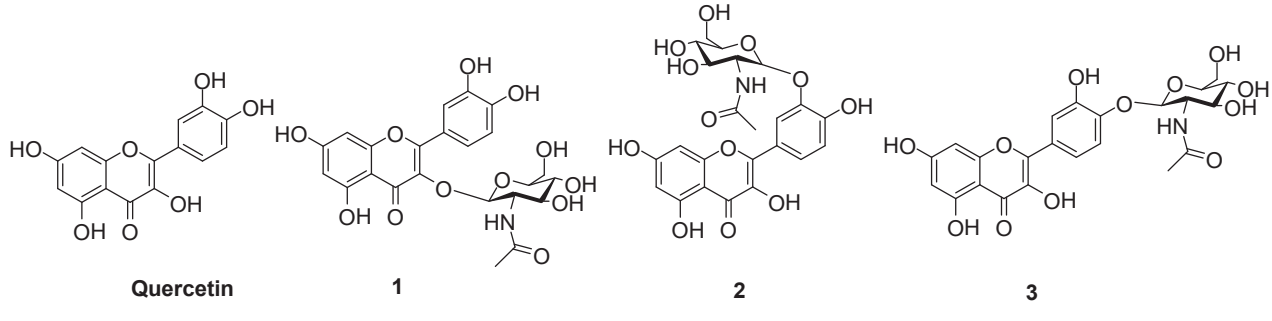


Fig. 1 Structure of quercetin and its 3- (**1**), 3′- (**2**) and 4′-*N*-acetylglucosamine glycosides (**3**).

* Correspondent. E-mail: zhilingcao@outlok.com

Accordingly, the selective glycosylation at the 3′-OH group required a 3,7,4′-*O*-protected quercetin and the desired tribenzoylated quercetin (**5**) was synthesised from the 3-*O*-glycosylated derivative of quercetin, rutin *via* the key intermediate **4** (Scheme 1). (There was no need to protect the 5-hydroxy group as hydrogen bonding with the adjacent C=O group rendered it inactive towards alkylation, except under forcing conditions.) In the first step (path a), dibenzylation of rutin was well controlled by the slow addition of 2 equiv. of benzyl bromide in DMF and subsequent hydrolysis of the rutinoside residue with HCl gave a good yield of the dibenzylated compound (**4**). Further selective benzylation of the 3-OH of **4** with 1 equiv. of benzyl chloride (path b) gave the tribenzylated compound (**5**) required as glycosyl acceptor.

7,3′,4′-Tri-*O*-benzylquercetin (**6**) was the glycosyl acceptor required for the synthesis of the quercetin 3-*O*-glycoside (**1**) and we prepared it *via* benzylation of rutin with an increase (>3 equiv.) in the amount of benzyl bromide, as described by Zhao and co-workers,[19] followed by the hydrolysis of the C3 rutinose residue (Scheme 1, path c).

3,7-Di-*O*-benzylquercetin (**9**), which has 3′- and 4′-OH groups, has been used previously for the synthesis of 4′-monomethylated quercetin[17] by taking advantage of the greater reactivity of the 4′ position compared with that of the 3′ position. We hoped a similar synthetic strategy would lead to selective glycosylation on 4′-OH. In the event, that proved to be the case (see below). First, to protect effectively and temporarily the 3′,4′-diols of quercetin, intermediate **7** was synthesised by reacting quercetin with dichlorodiphenylmethane in bis(2-methoxyethyl)ether (Scheme 2, path a). The subsequent benzylation afforded the 3,7-di-benzylated intermediate **8**, the diphenylmethane ketal moiety of which was deprotected with a mixture of HCl/EtOH to yield **9** (Scheme 2, paths b and c).

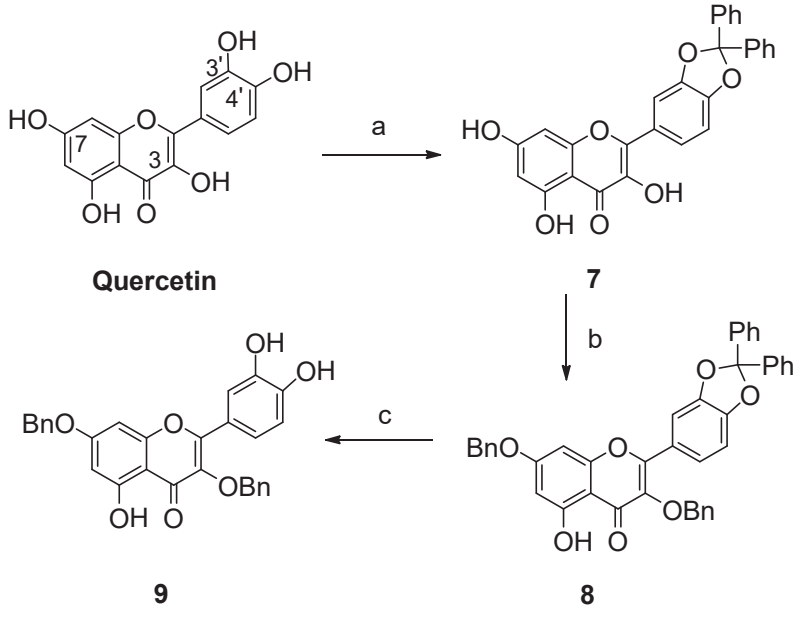
Of the many types of glycosyl donors,[20] 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**10**) was the most effective as its glycosylation of protected quercetins (**5**, **6** and **9**) can be controlled by C2 acetamide neighbouring participation to secure high 1,2-*trans* selectivity (Scheme 3).[21] The glycosylation synthesis was achieved under phase-transfer-catalysed conditions (K_2CO_3/$CHCl_3$ with tetrabutylammonium bromide (TBAB) as catalysts) and found to be practical as well as highly regioselective. In the aqueous two-phase reaction system, degradation of the glycosyl donor and glycosylation occurred at the same time. After optimisation of the stirring speed and reaction temperature, quercetin amino glucosides **11**, **12** and **13** were finally obtained in good yields (Scheme 3, path a).

Guo *et al.* reported a method using $FeCl_3$ to catalyse glycosylation of glucosamine pentaacetates with phenols.[22] However, our attempts to utilise $FeCl_3$ in our experiments were unsuccessful. We also tried the classic Schmidt's trichloroacetimidate method, but found that the phenolic hydroxyl groups of quercetin failed to react with glucosamine trichloroacetimidate donor in the presence of trifluoromethanesulfonate (TMSOTf) as catalyst.

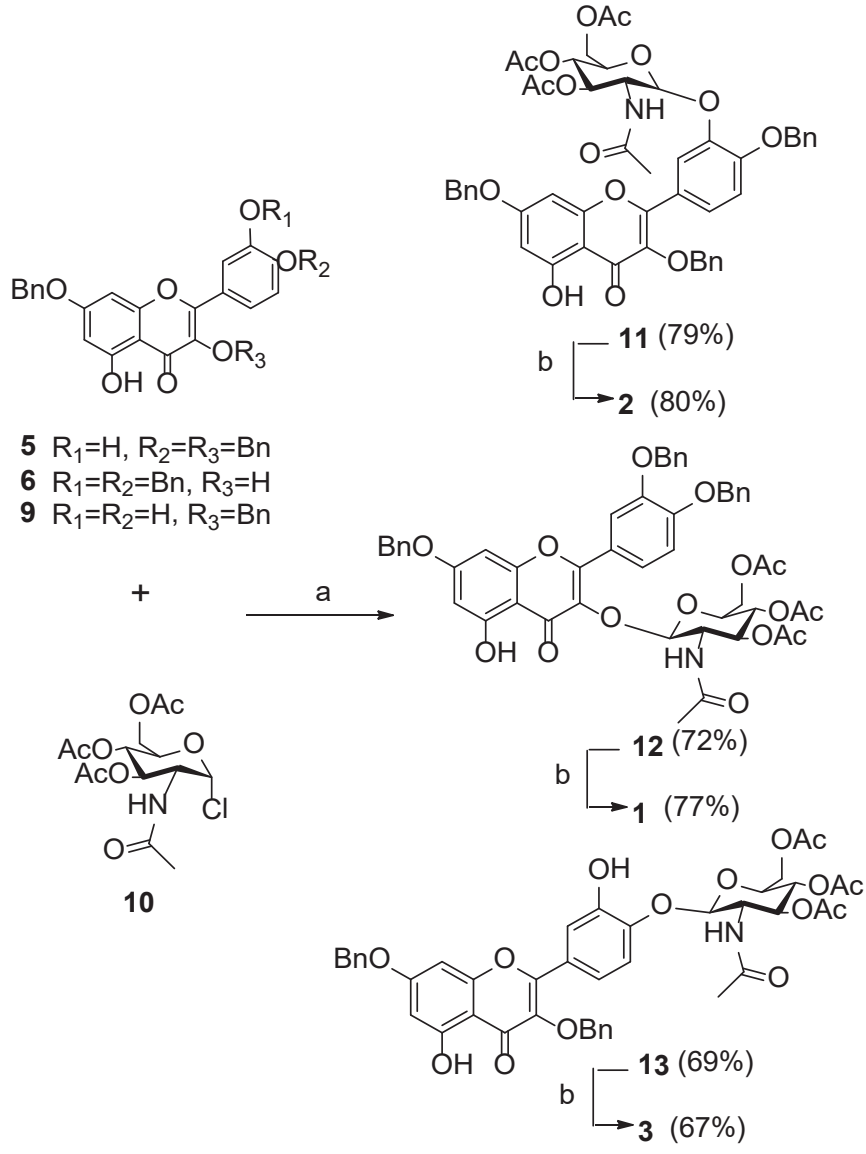
The resulting tribenzylated quercetin *N*-acetylamino glycoside triacetates (**11**–**13**) were first deacetylated by treatment with MeONa/MeOH and then debenzylated using 10% Pd–C/EtOH/THF to afford **2**, **1**, and **3** in high yield (Scheme 3, path b). Compounds **1**–**3** were identified as β-anomers because of the large $J_{1,2}$ value (7.5–7.8 Hz) observed for the anomeric proton of the glucose residue in their ^{1}H NMR spectra. In the HMBC spectrum of the *N*-acetyl amino glucoside **2**, the correlation between the glucose H1″ (δ 4.99) and quercetin C3′ (δ 146.1) showed a glycosidic linkage of quercetin at the C3′ position. The structural assignment of isomers **1** and **3** was also confirmed by the HMBC correlation of glucose H1 with C3 or C4′ carbon, respectively.[23]

Conclusion

We have achieved the regiospecific synthesis of three quercetin *O*-β-glucosides of *N*-acetylglucosamine. The three suitably protected glycosyl acceptors were 3,7,4′-di-*O*-benzylquercetin (**5**), 7,3′,4′-di-*O*-benzylquercetin (**6**) and 3,7-di-*O*-benzylquercetin (**9**) and they were synthesised from either quercetin or rutin by standard protecting-group methodology. Glycosylation of these protected quercetins with triacetylated glycosyl chloride **10** was efficiently achieved under phase-transfer-catalysed conditions using TBAB as catalyst and aqueous K_2CO_3 as base and the products (**11**–**13**) were deprotected to give the three quercetin *O*-β-glucosides of *N*-acetylglucosamine (**1**–**3**).



Scheme 2 Synthesis of 3,7-di-*O*-benzylquercetin (**9**). Path a: Ph_2CCl_2, bis(2-methoxyethyl)ether, reflux, 2 h, 56%. Path b: BnBr (2 equiv.), K_2CO_3, DMF, r.t., 3 h, 90%. Path c: HCl/EtOH, 70 °C, 5 h, 95%.



Scheme 3 Synthesis of quercetin *O*-β-glucosides of *N*-acetylglucosamine (**1**–**3**). Path a: 0.13 M K_2CO_3, $CHCl_3$, TBAB, 52 °C, 6 h. Path b: (i) NaOMe, MeOH, 30 °C, 10 h; (ii) H_2, Pd/C, THF/EtOH, 25 °C, 4 h.

Experimental

All reagents for synthesis were provided by J&K Scientific Co. unless otherwise specified. Melting points were measured on an XPR-400 melting point apparatus. NMR spectra were obtained on a Bruker AQS Avance spectrometer (^{1}H NMR at 400 or 300 Hz, ^{13}C NMR at 100 or 75 Hz) in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in Hz. Mass spectra were performed with an Agilent Technologies MSD SL Trap mass spectrometer with an ESI source coupled with a 1100 Series HPLC system.

*Synthesis of 7,4′-di-*O*-benzylquercetin* (**4**)

Rutin (1.22 g, 2.0 mmol) was dissolved in DMF (20 mL), and K_2CO_3 (0.41 g, 3.0 mmol) was added to this solution under stirring. The mixture was warmed to 60 °C and a solution of BnBr (0.48 mL, 4.0 mmol) in DMF (10 mL) was slowly added. After further stirring for 2 h, the reaction mixture was evaporated under reduced pressure. Ethanol (30 mL) and concentrated HCl (3 mL) were added to the residue, and the stirred solution was refluxed for 2 h. The solution was cooled and filtered, yielding a bright yellow precipitate, which was recrystallised from ethanol to give **4** as a yellow solid; yield 0.53 g (58%); m.p. 182–183 °C (lit.[17] 181–182 °C); ^{1}H NMR (300 MHz, DMSO): δ 12.43 (d, *J* = 9.0 Hz, 1H, 5OH), 9.61 (s, 1H, 3′OH), 9.42 (s, 1H, 3OH), 7.76 (d, *J* = 2.2 Hz, 1H, H2′), 7.63 (dd, *J* = 8.6, 2.2 Hz, 1H, H6′), 7.54–7.28 (m, 10H, 2 × Ph), 7.17 (d, *J* = 8.8 Hz, 1H, H5′), 6.81 (d, *J* = 2.1 Hz, 1H, H8), 6.44 (d, *J* = 2.1 Hz, 1H, H6), 5.23 (s, 2H, CH_2Ph), 5.21 (s, 2H, CH_2Ph).

*Synthesis of 3,7,4′-tri-*O*-benzylquercetin* (**5**)

A solution of **4** (1.00 g, 2.1 mmol), pyridine (0.41 g, 5.2 mmol), and BnCl (0.25 g, 2.1 mmol) in CH_2Cl_2 (10 mL) was stirred for 12 h at room temperature. The obtained solution was diluted with CH_2Cl_2 (15 mL) and washed with HCl (1 M, 3 × 50 mL). The organic layer was then dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was crystallised from ether to afford **5** as a yellow solid; yield 0.91 g (77%); m.p. 147–150 °C (lit.[17] 150–152 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.70 (s, 1H, 5OH), 7.67–7.58 (m, 2H, H2′, H6′), 7.49–7.33 (m, 12H, Ph), 7.27 (m, 3H, Ph), 6.97–6.93 (m, 1H, H5′), 6.50 (d, *J* = 2.1 Hz, 1H, H8), 6.44 (d, *J* = 2.2 Hz, 1H, H6), 5.76 (s, 1H, 3′OH), 5.19, 5.13, 5.07 (s, 3 × 2H, CH_2Ph).

*Synthesis of 7,3′,4′-tri-*O*-benzylquercetin* (**6**)

A mixture of rutin (1.22 g, 2.0 mmol), BnBr (1.9 mL, 16.0 mmol) and K_2CO_3 (2.20 g, 16.0 mmol) in DMF (20 mL) was stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure. Ethanol (30 mL) and concentrated HCl (3 mL) were added to the residue, and the solution was refluxed for 2 h. The solution

was cooled and filtered to give **6** as a yellow solid; yield 0.97 g (85%); m.p. 186–188 °C (lit.[17] 188–190 °C); ^{1}H NMR (300 MHz, DMSO): δ 12.42 (s, 1H, 5OH), 9.71 (s, 1H, 3OH), 7.89 (d, *J* = 2.0 Hz, 1H, H2′), 7.84 (dd, *J* = 8.7, 2.0 Hz, 1H, H6′), 7.51–7.30 (m, 15H, Ph) 7.26 (d, *J* = 8.7 Hz, 1H, H5′), 6.86 (d, *J* = 2.1 Hz, 1H, H8), 6.45 (d, *J* = 2.1 Hz, 1H, H6), 5.20–5.24 (m, 3 × 2H, CH_2Ph).

*Synthesis of 2-(2,2-diphenylbenzo[1,3]dioxol-5-yl)-3,5,7-trihydroxy-4*H*-chromen-4-one* (**7**)

Quercetin (2.0 g, 6.6 mmol) and 1,1-dichlorodiphenylmethane (2.0 mL, 10.4 mmol) were dissolved in bis(2-methoxyethyl) ether (20 mL). The mixture was warmed to reflux under an atmosphere of nitrogen for 2 h. The reaction solution was concentrated *in vacuo* to give a yellow solid which was purified on silica gel eluting with hexane/EtOAc to afford **7** as a yellow solid; yield 1.73 g (56%); m.p. 230–232 °C (lit.[17] 222–224 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.77 (s, 1H, 5OH), 7.83–7.75 (m, 2H, H6′, H2′), 7.66–7.52 (m, 4H, Ph), 7.47–7.32 (m, 6H, Ph), 7.02 (d, *J* = 8.2 Hz, 1H, H5′), 6.43 (d, *J* = 2.1 Hz, 1H, H8), 6.29 (d, *J* = 2.1 Hz, 1H, H6).

*Synthesis of 2-(2,2-diphenylbenzo[1,3]dioxol-5-yl)-3,7-dibenzyloxy-5-hydroxy-4*H*-chromen-4-one* (**8**)

A mixture of compound **7** (1.0 g, 2.1 mmol), BnBr (0.74 mL, 4.3 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) was stirred in DMF (20 mL) at room temperature until the reaction was complete (TLC). Then the solution was diluted with CH_2Cl_2 (20 mL), washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was recrystallised from ethanol/$CHCl_3$ to yield **8** as a yellow solid; yield 1.25 g (90%); m.p. 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.69 (s, 1H, 5OH), 7.65–7.54 (m, 5H, Ph), 7.50 (d, *J* = 1.6 Hz, 1H, H2′), 7.48–7.08 (m, 16H, Ph, H6′), 6.92 (d, *J* = 8.3 Hz, 1H, H5′), 6.48 (d, *J* = 2.2 Hz, 1H, H8), 6.45 (d, *J* = 2.1 Hz, 1H, H6), 5.13 (s, 2H, CH_2Ph), 5.04 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 164.1, 161.7, 156.3, 156.3, 148.9, 146.9, 139.4, 136.9, 135.8, 135.4, 129.0, 128.6, 128.4, 128.0, 127.8, 127.1, 125.9, 123.9, 123.7, 108.6, 108.0, 105.8, 98.3, 92.6, 74.1, 70.1. HRMS (ESI) *m/z* calcd for $C_{42}H_{30}O_7Na$ [M + Na]$^+$: 669.1884; found: 669.1895.

*Synthesis of 3,7-di-*O*-benzylquercetin* (**9**)

A mixture of **7** (0.5 g, 0.8 mmol), ethanol (15 mL) and concentrated HCl (2 mL) was refluxed for 5 h. After cooling, the precipitate was filtered off, washed with water and dried to yield **9** as a yellow solid; yield 0.35 g (95%); m.p. 206–208 °C (lit.[9] 202–204 °C); ^{1}H NMR (300 MHz, DMSO): δ 12.73 (s, 1H, 5OH), 9.83 (s, 1H, 4′OH), 9.35 (s, 1H, 3′OH), 7.54 (d, *J* = 2.1 Hz, 1H, H2′), 7.51–7.24 (m, 11H, H6′, Ph), 6.87 (d, *J* = 8.5 Hz, 1H, H5′), 6.80 (d, *J* = 2.1 Hz, 1H, H8), 6.47 (d, *J* = 2.1 Hz, 2H, H6), 5.24 (s, 2H, CH_2Ph), 5.01 (s, 2H, CH_2Ph).

Synthesis of glycosides **11**–**13***; general procedure*

A mixture of a protected quercetin **5**, **6** or **9** (2.0 mmol), tetrabutyl ammonium bromide (TBAB, 1.0 mmol) and 0.13 M K_2CO_3 (20 mL) in $CHCl_3$ (20 mL) was vigorously stirred at 52 °C for 1 h. Then 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **10** (4.0 mmol) was added in one portion, then stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water, dried and concentrated. The residue was purified by column chromatography (silica gel) to give compounds **11**–**13**.

*3′-*O*-(2″-acetamido-3″,4″,6′′-tri-*O*-acetyl-2″-deoxy)-*β*-D-glucopyranosyl-3,7,4′-tri-*O*-benzylquercetin* (**11**): Yellow solid; yield 1.42 g (79%); m.p. 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.64 (s, 1H, 5OH), 7.91 (d, *J* = 1.9 Hz, 1H, H2′), 7.78 (dd, *J* = 8.7, 1.9 Hz, 1H, H6′), 7.52–7.30 (m, 15H, Ph), 7.01 (d, *J* = 8.7 Hz, 1H, H5′), 6.55 (d, *J* = 1.9 Hz, 1H, H8), 6.44 (d, *J* = 1.9 Hz, 1H, H6), 5.34 (d, *J* = 8.8 Hz, 1H, H1″), 5.24–5.01 (m, 7H, 3 × CH_2Ph, H3″), 4.85–4.95 (m, 2H, H4″, NH), 4.21–4.08 (m, 2H, H2″, H6″), 4.02 (d, *J* = 10.3 Hz, 1H, H6″), 3.31 (dd, *J* = 7.1, 2.5 Hz, 1H, H5″), 2.05, 2.03, 1.94, 1.62 (s, 4 × 3H, CH_3C=O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 170.4, 170.3, 169.8, 169.0, 164.2, 161.6, 156.3, 155.2, 151.2, 145.5, 137.4, 136.3, 135.7, 135.4, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.4, 127.1, 125.0, 123.2, 120.3, 113.1, 105.8, 99.8, 98.4, 92.7, 74.0, 71.9, 71.6, 70.6, 70.1, 67.9, 61.4, 54.0, 22.5, 20.3, 20.2. HRMS (ESI) *m/z* calcd for $C_{50}H_{47}NO_{15}Na$ [M + Na]$^+$: 924.2838; found: 924.2847.

*3-*O*-(2″-acetamido-3″,4″,6′′-tri-*O*-acetyl-2″-deoxy)-*β*-D-glucopyranosyl-7,3′,4′-tri-*O*-benzylquercetin* (**12**): Yellow solid; yield 1.30 g (72%); m.p. 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.24 (s, 1H, 5OH), 7.82 (d, *J* = 2.1 Hz, 1H, H2′), 7.73 (dd, *J* = 8.7, 2.1 Hz, 1H, H6′), 7.55–7.28 (m, 15H, Ph), 6.95–7.05 (m, 2H, H5′, NH), 6.51 (d, *J* = 2.2 Hz, 1H, H8), 6.46 (d, *J* = 2.2 Hz, 1H, H6), 5.27–5.20 (m, 4H, 2 × CH_2Ph), 5.15 (s, 2H, CH_2Ph), 5.13–5.08 (m, 3H, H1′, H3′, H4′), 4.25–4.40 (m, 1H, H2′), 4.06 (dd, *J* = 12.3, 4.8 Hz, 1H, H6″), 3.91 (dd, *J* = 12.3, 2.5 Hz, 1H, H6″), 3.62–3.50 (m, 1H, H5″), 2.07, 2.02, 2.00, 1.81 (s, 4 × 3H, CH_3C=O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2, 170.6, 170.5, 170.1, 168.9, 164.5, 161.3, 156.9, 156.3, 151.4, 147.8, 136.6, 136.2, 135.2, 134.7, 128.4, 128.3, 128.1, 127.6, 127.6, 127.1, 127.0, 126.8, 123.1, 122.1, 115.4, 112.9, 105.4, 100.9, 98.6, 92.9, 73.5, 72.1, 71.1, 70.4, 70.2, 67.8, 61.4, 54.0, 23.1, 20.4, 20.2, 20.0. HRMS (ESI) *m/z* calcd for $C_{50}H_{47}NO_{15}Na$ [M + Na]$^+$: 924.2838; found: 924.2834.

*4′-*O*-(2″-acetamido-3″,4″,6″-tri-*O*-acetyl-2″-deoxy)-*β*-D-glucopyranosyl-3,7-tri-*O*-benzylquercetin* (**13**): Yellow solid; yield 1.12 g (69%); m.p. 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.62 (s, 1H, 5OH), 7.51–7.62 (m, 2H, H2′, H6′), 7.46–7.18 (m, 10H, Ph), 6.95 (d, *J* = 8.8 Hz, 1H, H5′), 7.60–7.71 (m, 1H, NH), 6.48 (s, 1H, H8), 6.44 (s, 1H, H6) 5.99 (d, *J* = 7.5 Hz, 1H, H1″), 5.27–5.16 (m, 1H, H4″), 5.13 (s, 2H, CH_2Ph), 5.05 (s, 2H, CH_2Ph), 4.93 (d, *J* = 8.1 Hz, 1H, H3″), 4.45–4.28 (m, 2H, H6″, H2″), 4.22 (d, *J* = 11.9 Hz, 1H, H6″), 3.79–3.95 (m, 1H, H5″), 2.18–1.91 (m, 12H, 4 × CH_3C=O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 172.0, 171.3, 170.2, 168.9, 164.2, 161.5, 156.2, 155.5, 146.2, 146.1, 137.4, 135.9, 135.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.1, 125.8, 120.8, 115.6, 114.1, 105.7, 101.6, 98.3, 92.6, 73.8, 71.8, 71.4, 70.1, 67.5, 61.5, 54.5, 23.1, 20.3, 20.3, 20.2. HRMS (ESI) *m/z* calcd for $C_{43}H_{42}NO_{15}$ [M + H]$^+$: 812.2549; found: 812.2559.

Synthesis of quercetin glycosides of N*-acetylglucosamine* (**1**–**3**)*; general procedure*

NaOMe (2.2 mmol) was added to a solution of a glucoside **11**–**13** (1.5 mmol) in MeOH (15 mL) and the resulting solution was stirred at 30 °C for 10 h. The solvent was removed under vacuum. Then ethanol (30 mL) and acetic acid (0.5 mL) were added to the residue. After refluxing for 0.5 h, the reaction was cooled to room temperature. The yellow precipitate was filtered off, washed with water, dried and dissolved in THF/EtOH (16 mL:16 mL). Then Pd/C 10% (0.19 g) was added to the solution and the mixture was stirred for 4 h in a hydrogen atmosphere at ambient pressure. The catalyst was filtered off, the filtrate evaporated and the residue recrystallised from acetone to give compounds **1**–**3**.

*3-*O*-(2″-acetamido-2″-deoxy)-*β*-D-glucopyranosylquercetin* (**1**): Yellow solid; yield 0.58 g (77%); m.p. 212–214 °C (lit.[18] 210–212 °C); ^{1}H NMR (400 MHz, DMSO): δ 12.71 (s, 1H, 5OH), 10.83 (s, 1H, 7OH), 9.71 (s, 1H, 3′OH), 9.09 (s, 1H, 4′OH), 8.03 (d, *J* = 9.3 Hz, 1H, NH), 7.71–7.57 (m, 2H, H2′, H6′), 6.84 (d, *J* = 8.4 Hz, 1H, H5′), 6.41 (d, *J* = 2.0 Hz, 1H, H8), 6.19 (d, *J* = 2.0 Hz, 1H, H6), 5.63 (d, *J* = 8.5 Hz, 1H, H1″), 5.03 (s, 2H, OH), 4.26 (s, 1H, OH), 3.75 (dt, *J* = 10.2, 8.9 Hz, 1H, H2″), 3.56 (dd, *J* = 11.3, 4.2 Hz, 1H, H6″), 3.44–3.24 (m, 2H, H6″, H3″), 3.14–3.03 (m, 2H, H4″, H5″), 1.86 (s, 3H, CH_3CO).

*4′-*O*-(2″-acetamido-2″-deoxy)-*β*-D-glucopyranosylquercetin* (**3**): Yellow solid; yield 0.51 g (67%); m.p. 218–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1H, 5OH), 7.97 (d, *J* = 8.3 Hz, 1H, NH), 7.70 (s, 1H, H2′), 7.61 (d, *J* = 8.4 Hz, 1H, H6′), 7.19 (d, *J* = 8.7 Hz, 1H, H5′), 6.40 (s, 1H, H8), 6.17 (s, 1H, H6), 5.14 (bs, 2H, OH), 5.02 (d, *J* = 8.4 Hz, 1H, H1″), 4.65 (bs, 1H, OH), 3.74 (d, *J* = 11.3 Hz, 1H, H6″), 3.67 (dd, *J* = 18.0, 8.8 Hz, 1H, H2″), 3.57–3.43 (m, 2H, H6″, H3″), 3.39–3.27 (m, 1H, H5″), 3.26–3.18 (m, 1H, H4″), 1.84 (s, 3H, CH_3C=O); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.0, 170.5, 165.2, 160.8, 156.4, 146.8, 145.7, 136.5, 125.4, 119.5, 116.2, 115.0, 102.8, 100.3, 98.6, 93.6, 77.4, 73.7, 70.3, 60.8, 56.1, 23.3. HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_{12}Na$ [M + Na]$^+$: 528.1112; found: 528.1117.

*3′-*O*-(2″-acetamido-2″-deoxy)-*β*-D-glucopyranosylquercetin* (**2**): Yellow solid; yield 0.61 g (80%); m.p. 210–212 °C; ^{1}H NMR

(400 MHz, DMSO-d_6): δ 12.45 (s, 1H, 5OH), 7.95 (d, J = 8.4 Hz, 1H, NH), 7.90 (d, J = 2.1 Hz, 1H, H2′), 7.83 (dd, J = 8.6, 2.1 Hz, 1H, H6′), 6.98 (d, J = 8.6 Hz, 1H, H5′), 6.48 (d, J = 2.0 Hz, 1H, H8), 6.20 (d, J = 2.0 Hz, 1H, H6), 5.12 (bs, 2H, OH), 4.99 (d, J = 8.4 Hz, 1H, H1″), 4.61 (s, 1H, OH), 3.79 (d, J = 11.3 Hz, 1H, H6″), 3.68 (dd, J = 18.5, 8.4 Hz, 1H, H2″), 3.60 (dd, J = 11.8, 4.5 Hz, 1H, H6″), 3.51 (t, J = 8.4 Hz, 1H, H3″), 3.39–3.23 (m, 2H, H4″, H5″), 1.87 (s, 3H, CH_3C=O); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.9, 170.4, 163.9, 160.6, 149.1, 146.1, 145.3, 135.9, 123.5, 122.14, 116.1, 115.8, 103.0, 101.0, 98.2, 93.6, 77.2, 73.7, 70.1, 60.6, 56.0, 48.6, 23.2. HRMS (ESI) m/z calcd for $C_{23}H_{23}NO_{12}Na$ [M + Na]$^+$: 528.1112; found: 528.1105.

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