Synthesis of Some Phenylpropanoid Glycosides (PPGs) and Their Acetylcholinesterase/Xanthine Oxidase Inhibitory Activities

Xiao-Dong Li 1, Shuai-Tao Kang 1, Guo-Yu Li 2,3, Xian Li 1,4 and Jin-Hui Wang 1,2,3,4,*

1 School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang 110016, China; E-Mail: lxdpharm@sina.com (X.-D. L.)
2 School of Pharmacy, Shihezi University, Shihezi 832002, China
3 Key Laboratory of Phytomedicine Resources & Modernization of TCM of Ministry of Education, Shihezi 832002, China
4 Key Laboratory of Structure-Based Drug Design & Discovery of Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, China

* Author to whom correspondence should be addressed; E-Mail: wjh.1972@yahoo.com.cn; Tel.: +86-24-23986478; Fax: +86-024-23986478.

Received: 16 March 2011; in revised form: 25 April 2011 / Accepted: 26 April 2011 / Published: 28 April 2011

Abstract: In this research, three categories of phenylpropanoid glycosides (PPGs) were designed and synthesized with PPGs isolated from Rhodiola rosea L. as lead compounds. Their inhibitory abilities toward acetylcholinesterase (AChE) and xanthine oxidase (XOD) were also tested. Some of the synthetic PPGs exhibited excellent enzyme inhibitory abilities.

Keywords: phenylpropanoid glycosides; Rhodiola rosea L.; acetylcholinesterase/xanthine oxidase inhibitory activity

1. Introduction

Rhodiola rosea L. has been used in Chinese herbal medicine to stimulate the nervous system, decrease depression, enhance work performance, resist anoxia, eliminate fatigue, prevent high altitude
sickness and improve sleep, etc. Clinical studies show that *Rhodiola rosea* extract has the ability to improve mental ability and learning behavior [1-3]. Recent literature indicates that it can improve resistance to cerebral ischemia and reduce myocardial infarction area. It also has therapeutical effects on coronary heart disease and hyperlipidemia [4-7]. Most of the reported activities were confined to the plant itself or its extract. Many trace components such as amino acids, polysaccharides, steroids and phenylpropanoid glycosides have been isolated from *Rhodiola rosea* L. and phenylpropanoid glycosides (Figure 1) are considered to be the major active components. However, the low content of PPGs in this plant has limited the further investigation of their activities.

**Figure 1.** Phenylpropanoid glycosides Isolated from *Rhodiola rosea* L.

| Compd.          | R    | R1  | Compd.          | R    | R1  |
|-----------------|------|-----|-----------------|------|-----|
| Rosin           | H    | H   | Rosavin         | H    | Arap-|
| ---             | OCH3 | H   | ---             | H    | Xylp-|
| Sachaliside1    | OH   | H   | ---             | OCH3 | Arap-|

Cholinesterase inhibitors are the only currently approved drugs for treating patients with mild to moderately severe Alzheimer’s disease, a disorder associated with progressive degeneration of memory and cognitive function. The cholinergic hypothesis postulates that memory impairment in patients with Alzheimer’s disease result from a deficit of cholinergic function in the brain [8,9]. The most important changes observed in the brain are a decrease in hippocampal and cortical levels of the neurotransmitter acetylcholine and associated enzyme choline transferase.

Acetylcholinesterase inhibitors can restore the level of acetylcholine by inhibiting acetylcholinesterase. Xanthine oxidase (XO) is a key enzyme in the purine metabolic pathway, catalyzing the oxidation of hypoxanthine to xanthine, and then to uric acid [10]. Xanthine oxidase and xanthine dehydrogenase (XDH) are the isomers of xanthine oxidoreductase (XOR). XO receives molecular oxygen resulting in superoxide anion \( \text{O}_2^- \) which causes serial harmful damages to vascular endothelial cell. The rise of XO protein level has been observed in heart failure models of both animal and human, which plays an important role in pathophysiological process of heart failure [11-15].

In order to provide the pharmacological basis for the usage of *Rhodiola rosea* L. in the therapy of nervous and cardiovascular diseases in Traditional Chinese Medicine, it was deemed necessary to synthesize these PPGs and evaluate their inhibitory activities towards acetylcholinesterase (AChE) as well as xanthine oxidase (XOD).

### 2. Results and Discussion

#### 2.1. Chemistry

The designed synthetic route of these PPGs is depicted in Scheme 1. Compound 4 was prepared via benzoylation of D-glucose followed by 1-O-bromination and sequential regioselective C-1
hydrolization with NaI as catalyst in a mixed solution of acetone-water (3:1). Treatment of the hemiacetal 4 with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and excess trichloroacetonitrile furnished the corresponding trichloroacetimidate donor 5.

Condensation of different benzaldehyde derivatives with [(ethoxycarbonylmethylene)triphenyl-phosphorane (6) afforded the target ethyl esters 7a-n in satisfactory yields. The latter were next reduced to the corresponding alcohol derivatives 8a-n using DIBAIH in toluene. Treatment of 8a-n with excess trichloroacetimidate under the influence of catalytic amounts of TMSOTf in CH₂Cl₂ at −20 °C to room temperature for 2 h afforded the tetrabenzoyl PPGs derivatives 9a-n. Finally, the protective groups were readily removed using NaOMe in MeOH to afford the desired PPGs 10a-n.

Scheme 1. The synthetic route of the target PPGs 10a-n

Reagents and conditions: (a) BzCl/Py, rt, 24 h; (b) 33% HBr-CH₂COOH/AC₂O, rt, 24 h; (c) NaI/H₂O/acetone, 30 °C, 48 h; (d) DBU/CCl₃CN, rt, 4 h; (e) PhMe 80 °C, 4 h; (f) DIBAIH, PhMe, -20 °C; (g) 5, TMSOTf, CH₂Cl₂, -20 °C, 2h; (h) NaOCH₂, CH₂OH, 0 °C.

In order to introduce the hydroxyl group onto the aromatic rings an alternative route was chosen and is depicted in Scheme 2. Coupling of benzaldehyde derivates with the same ylide reagent 6 gave compounds 11a-d, which were then hydrolyzed and acetylated to produce 13a-d, which in turn were treated with ethyl chloroformate in THF to form the corresponding anhydride intermediates. Reduction of the latter by adding sodium borohydride and a calculated amount of anhydrous methanol to the above solutions afforded the desired alcohols 14a-d, which were then glycosidated and deacylated using conditions similar to those used for 10a-n and we thus obtained 16a-d.
Scheme 2. The preparation of the target PPGs 16a-d.

Reagents and conditions: (i) PhMe 80 °C, 4 h; (j) 15% NaOH, MeOH, 70 °C, 4 h; (k) Ac₂O/Et₃N, 70 °C, 2 h; (l) ①. ethyl chloroformate, THF, 1.5 h; ②. NaBH₄/MeOH, 2 h; (m) 5, TMSOTf, CH₂Cl₂, −20 °C, 2 h; (n) NaOCH₃, CH₃OH, 0 °C.

Scheme 3. The synthetic approaches to the target disaccharide PPGs.

Reagents and conditions: (a) TrCl, DMAP, TEA, DMF, MS 4 Å. (b) BzCl, Py, 24 h. (c) 90% TFA, CH₂Cl₂. (d) TMSOTf, CH₂Cl₂, −20 °C 2 h. (e) NaOCH₃, CH₃OH, 0 °C.
The designed synthetic route for disaccharide PPGs was as shown in Scheme 3. Compounds 24a-c were prepared via a similar method to that used in the preparation of compound 5 [16]. Reaction of trityl chloride with 10m or 10a in N,N-dimethylformamide (DMF) solution for 36 h at room temperature in the presence of 4-N,N-dimethylaminopyridine (DMAP), powdered 4 Å molecular sieves and triethylamine cleanly produced 17a or 17b in high yields (56% and 64%, respectively) [17]. Compounds 17a and 17b were then converted to their tribenzoyl derivatives 18a and 18b by using benzoyl chloride in pyridine.

Compounds 18a and 18b were then treated with 90% aqueous TFA to selectively remove the trityl group and we thus acquired the key intermediates 19a and 19b. Treatment of 19a and 19b with excess trichloroacetimidates 24a-c under the influence of catalytic TMSOTf in CH₂Cl₂ at −20 °C to room temperature for 2 h afforded the corresponding hexabenzoyl derivatives. Finally, treatment of the coupling products with NaOMe in MeOH/CH₂Cl₂ provided the synthetic targets rosavin (20), cinnamyl 6-O-(β-D-xylopyranosyl)-β-D-glucopyranoside (21), 4-methoxycinnamyl 6-O-(α-L-arabinopyranosyl)-β-D-glucopyranoside (22) and cinnamyl 6-O-(α-L-rhamnopyranosyl)-β-D-glucopyranoside (23). The spectral data (¹H- and ¹³C-NMR) and specific rotation of the synthetic PPGs were consistent with those of the natural products reported in the literature [18-20].

2.2. AChE and XOD Inhibitory Activities of the Synthetic PPGs

In vitro inhibitory activity test of these glycosides against AChE and XOD was studied by using Acetylcholinesterase Detection Kit and Xanthine Oxidase Detection Kit. The results were summarized and shown in Table 1.

| Compd. | Structure | AChE inhibitory activity | XOD inhibitory activity |
|--------|-----------|--------------------------|-------------------------|
|        |           | % inhibition (1.5 mg/mL) | IC50 (µM)       | % inhibition (1.5 mg/mL) | IC50 (µM)       |
|        | R₁ | R      |                        |                |                        |                |
| 10a    | H  | 4-OCH₃ | 15 ± 3.27              | –              | 10 ± 2.22              | –              |
| 10b    | H  | 2-OCH₃ | 62 ± 4.53              | 15.5 ± 2.1     | 12 ± 3.12              | –              |
| 10c    | H  | 3,5-di-OCH₃ | 23 ± 0.85            | –              | 21 ± 1.21              | –              |
| 10d    | H  | 3,4-di-OCH₃ | 43 ± 1.35             | 43.5 ± 0.6     | 35 ± 3.22              | 73.5 ± 1.5     |
| 10e    | H  | 2,3-di-OCH₃ | 34 ± 4.36             | 71.2 ± 2.8     | 22 ± 0.85              | –              |
| 10f    | H  | 4-CF₃  | 22 ± 2.44              | –              | 5 ± 0.22               | –              |
| 10g    | H  | 3,4(-OCH₂O-) | 15 ± 3.55            | –              | 13 ± 1.43              | –              |
| 10h    | H  | 3,4,5-tri-OCH₃ | 17 ± 4.33           | –              | 33 ± 2.16              | 69.3 ± 1.3     |
| 10i    | H  | 2-F    | 18 ± 2.11              | –              | 24 ± 1.32              | –              |
| 10j    | H  | 4-Cl   | 42 ± 3.23              | 38.3 ± 1.4     | 50 ± 2.35              | 24.3 ± 1.4     |
| 10k    | H  | 3,4-di-F | 43 ± 2.31             | 35.5 ± 1.1     | 37 ± 2.78              | 55.4 ± 1.3     |
| 10l    | H  | 4-Br   | 57 ± 1.22              | 22.4 ± 0.6     | 55 ± 3.67              | 19.6 ± 1.5     |
| 10m    | H  | H      | 16 ± 0.44              | –              | 38 ± 2.83              | 93.2 ± 1.4     |
| 10n    | H  | 3-Br,4-OC₂H₅, 5-OCH₃ | 36 ± 3.55         | 87.3 ± 2.1     | 28 ± 1.74              | 97.3 ± 0.8     |
The data listed in Table 1 clearly show that most of the designed compounds such as 10b, 10l, 16b-d and compounds 20-23 exhibited moderate inhibitory activities toward cholinesterase. In the synthetic monosaccharide PPGs, compounds with sterically small substituents at position 4 (compounds 10b, 10j-l) were more potent than the corresponding unsubstituted compound 10m. The presence of a hydroxyl group at the aromatic ring caused a significant improvement in the activity. Disaccharide glycosides always possessed much stronger AChE inhibitory activities than the corresponding monosaccharide PPGs, with rosavin being the most potent (IC$_{50}$ = 1.72 μmol/L). Accordingly, the XOD inhibitory activity of these PPGs was generally lower than that against AChE. Compounds 10j, 10l, 16b, 16d and 20-23 have XOD inhibitory activity. Among them compound 21 showed the best such activity, with an IC$_{50}$ value of 4.56 μmol/L. The above results indicate that disaccharide glycosides and monosaccharide PPGs with a substitution of sterical small group at position 4 or hydroxyl at the aromatic ring are favorable for the enzymes inhibitory activities which are worthy of further study.

3. Experimental

3.1. General

Commercial reagents were used without further purification unless otherwise stated. The boiling range of petroleum ether was 60–90 °C. Preparative TLC was done on silica gel plates (GF254; Qingdao Haiyang Co.; China). Preparative column chromatography was performed with silica gel (200–300 mesh; supplier as above). Melting points were measured with a Yanaco apparatus and are uncorrected. NMR spectra were recorded on Bruker ARX 300 MHz or AV 600 MHz spectrometers; J values were given in Hertz, δ in ppm rel. to TMS used as internal standard. Optical rotations were measured at the sodium D-line at room temperature with a Perkin-Elmer 241 MC polarimeter. ESI mass spectra were obtained on a Finnigan TSQ 7000 mass spectrometer. High-resolution mass spectra (HR-ESI-MS) were obtained with Bruker micro TOF-Q 125 mass spectrometer.

2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranose (4). D-Glucose (10.0 g, 55.5 mmol) in pyridine (150 mL) was cooled to 0 °C, and then benzoyl chloride (38.5 mL, 333 mmol) was added dropwise over 30 min. The reaction mixture was raised to room temperature. After 24 h, water (100 mL) was added to the
reaction mixture, and stirring was continued for 30 min. The aq solution was extracted with CH$_2$Cl$_2$
(3 × 150 mL). The extract was washed with HCl (1 N) followed by saturated sodium bicarbonate
(2 × 150 mL), dried (Na$_2$SO$_4$) and concentrated to dryness to give a yellow solid which was directly
dissolved in a solution of anhydrous dichloromethane (230 mL) containing 33% HBr in glacial acetic
acid (50 mL) and acetic anhydride (7 mL). The reaction mixture was stirred for 24 h at 34 °C, and then
ice-cold water (200 mL) was added. The mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The
combined CH$_2$Cl$_2$ layers were washed with a saturated NaHCO$_3$ solution and brine, and the filtrate was
evaporated in vacuo to give a colorless white solid. The white solid was dissolved in acetone (144 mL)
and water (48 mL). After addition of sodium iodide dihydrate (2.22 g, 7.5 mmol) the mixture was
stirred at 30 °C for 2–3 days before removing the solvents in vacuo. The residue was resuspended in
water (100 mL) and the resulting water phase was extracted with dichloromethane (3 × 100 mL). The
combined organic layers were washed with 10% sodium thiosulfate, saturated sodium bicarbonate
and water, dried (Na$_2$SO$_4$). The filtrate was concentrated in vacuo to give the crude product (28.0 g,
47 mmol) as a white solid (85% yield for the three steps), m.p. 65–68 °C. $^1$H-NMR (600 MHz,
CDCl$_3$): δ 8.07–7.30 (20H, m, Ar-H × 20), 6.06 (1H, t, $J = 10.2$ Hz, CH), 5.62 (1H, t, $J = 10.2$ Hz,
CH), 5.53 (1H, t, $J = 3.6$ Hz, CH), 5.20 (1H, d, $J = 7.2$ Hz, CH), 4.62 (1H, d, $J = 10.0$ Hz, CH), 4.48
(1H, d, $J = 12.6$ Hz, CH), 4.42 (1H, dd, $J = 12.0, 4.2$ Hz, CH). HRMS (ESI-TOF) calcd. for
C$_{34}$H$_{28}$O$_{10}$Na (M+Na)$^+$ 619.1582 found 619.1580.

2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl trichloroacetimidate (5). The above product (19 g,
31.9 mmol) and trichloroacetonitrile (13.7 g, 95 mmol) were dissolved in CH$_2$Cl$_2$ (100 mL) and a
catalytic amount of DBU (0.48 mL) was added. The above solution was stirred for four hours at room
temperature, then concentrated and purified by Al$_2$O$_3$ column chromatography with pet.ether/EtOAc
(3:1) as eluent to give the product (20.0 g, 27.1 mmol) as a foamy white solid in 80% yield. $^1$H-NMR
(600 MHz, CDCl$_3$): δ 8.63 (s, 1H, NH), 8.10-7.87 (8H, m, Ar-H ×8), 7.58–7.30 (12H, m, Ar-H × 15),
6.80 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 6.26 (t, 1H, $J_{2,3} = J_{3,5} = 10.2$ Hz, H-3), 5.82 (t, 1H,
$J_{3,4} = J_{4,5} = 10.2$ Hz, H-4), 4.69 (dd, 1H, $J_{1,2} = 4.2$ Hz, $J_{2,3} = 9.6$ Hz, H-2), 4.65, 4.64, 4.49 (3H,
H-5, H-6, H-6'). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 165.4 (PhCO-), 165.2 (PhCO-), 164.7 (PhCO-), 164.7
(PhCO-), 163.0 (C=NH), 133.8 (Ar-C), 133.7 (Ar-C), 133.6 (Ar-C), 133.5 (Ar-C), 129.3 (8C, 8Ar-C),
128.8 (12C, 12Ar-C), 93.1 (C-1), 89.5 (CCl$_3$), 73.4(C-2), 70.5 (C-4), 68.2 (C-3), 66.7 (C-5), 62.4
(C-6). HRMS (ESI-TOF) calcd. for C$_{36}$H$_{28}$Cl$_3$NO$_{10}$ Na (M+Na)$^+$ 762.0676 found 762.0679.

General procedure for preparation of compounds 8. A mixture of the appropriate benzaldehyde
derivative (5 mmol) in anhydrous toluene (40 mL) and (carbethoxymethylene)triphenyl-phosphorane
(1.99 g, 6 mol) was refluxed for 4 h. The reaction was monitored by TLC using petroleum-ethyl
acetate (3:1) as the mobile phase. The solvent was removed and the residue was suspended in water
and the resulting water phase was extracted with ethyl acetate. The combined organic layers were dried
(Na$_2$SO$_4$) and filtered. The solvent was concentrated then purified by column chromatography with
pet.ether/EtOAc (3:1) to give compounds 7 which were then dissolved in CH$_2$Cl$_2$. Three equivalents of
DIBAIH in toluene were added dropwise to the above solution at −20 °C. After 2 h, water was added
and the mixture solution was extracted with EtOAc, concentrated. The crude products were purified
with a short silica gel column to afford compounds 8.
General procedure for preparation of compounds 14. 15% NaOH solution (20 mL) was added to the solution of compounds 11 (5 mmol) in MeOH. The mixture was refluxed for 3 h until the yellow oil disappeared and then cooled to room temperature. The organic solvent was removed. The residue was diluted with water and acidified by 10 N HCl to pH 1 to afford a white precipitate. The precipitate was collected and recrystallized from anhydrous ethanol, affording white needle-like crystals 12. To a 25 mL flask equipped with CaCl$_2$ drying tube, phenol 12, acetic anhydride (10 equiv) and triethylamine (2.0 equiv) were added. The mixture was refluxed at 70 °C for 4 h and water was added. The above solution was stirred until it became turbid. The precipitate was collected, washed with water and dried to give the product 13. To a solution of dry THF containing compounds 13 and triethylamine (1.1 equiv) was added dropwise ethyl chloroformate (1.1 equivalents) at 0 °C. After stirring for an additional 30 min, the reaction mixture was allowed to warm to r t and 4.0 equiv. of powdered sodium borohydride was added in one portion. To this suspension, 16 equiv. of absolute methanol was added dropwise over one hour at the same temperature. After being stirred at room temperature for an additional one hour, the reaction mixture was poured into saturated ammonium chloride solution (150 mL) and extracted with dichloromethane (2 × 150 mL). The combined organic layer were dried over anhydrous Na$_2$SO$_4$ and concentrated. Crude products were purified by silica gel column chromatography (pet. ether/EtOAc 3/1) to give the products 14.

Schmidt’s reaction to prepare the target PPGs 10a-n and 16a-d. Alcohols (1.5 mmol), the Schmidt donor 5 (6.0 mmol, 1.2 equiv), and powdered 4 Å molecular sieves (1.0 g) in dry CH$_2$Cl$_2$ (20 mL) were stirred for 30 min at −20 °C. A dry CH$_2$Cl$_2$ solution (0.5 mL) of TMSOTf (0.02 equiv) was added dropwise. The mixture was stirred for 1 h before a small amount of Et$_3$N was added to quench the reaction. The mixture was then diluted with CH$_2$Cl$_2$ and filtered. The resulting residue was dissolved in dry CH$_2$Cl$_2$-MeOH (1:2), to which NaOMe (4.0 equiv) was added. The solution was stirred at rt for 2 h and then neutralized with Dowex H$^+$ resin to pH 7 and filtered. The filtrate was concentrated and purified with a silica gel column to give the products as white powder.

4-Methoxycinnamyl β-D-glucopyranoside (10a). Yield: 41%. [$\alpha$]$_D^{25}$ = –35.9 (c = 1.0, MeOH). $^1$H-NMR (300 MHz, methanol-d$_6$): δ 7.34 (d, 2H, $J$ = 8.7 Hz, Ar-H), 6.85 (d, 2H, $J$ = 7.9 Hz, Ar-H), 6.60 (d, 1H, $J$ = 15.9 Hz, =CH), 6.21 (dt, 1H, $J$ = 6.6, 15.9 Hz, =CH-CH$_2$), 4.50 (dd, 1H, $J$ = 5.8, 12.4 Hz, =CH-CH$_2$), 4.36 (d, 1H, $J$ = 7.7 Hz, H-1), 4.29 (dd, 1H, $J$ = 6.8, 12.4 Hz), 3.87 (d, 1H, $J$ = 11.7 Hz), 3.78 (s, 3H, -OCH$_3$), 3.67 (dd, 1H, $J$ = 5.2, 11.9 Hz, =CH-CH$_2$), 3.35–3.24 (m, 4H). HRMS (ESI-TOF) calcd. for C$_{17}$H$_{23}$O$_9$ (M+HCOO)$^-$ 371.1342; found 371.1342.

2-Methoxycinnamyl β-D-glucopyranoside (10b). Yield: 45%. [$\alpha$]$_D^{25}$ = –25.5 (c = 1.0, MeOH). $^1$H-NMR (300 MHz, methanol-d$_6$): δ 7.45 (d, 1H, $J$ = 7.8 Hz, Ar-H), 7.22 (t, 1H, $J$ = 7.7 Hz, Ar-H), 6.94 (d, 1H, $J$ = 15.6 Hz, =CH), 6.93 (d, 1H, $J$ = 7.8 Hz, =CH), 6.90 (t, 1H, $J$ = 6.6 Hz, =CH), 6.36 (dt, 1H, $J$ = 6.3, 16.2 Hz, =CH-CH$_2$), 4.53 (dd, 1H, $J$ = 5.7, 13.5 Hz, =CH-CH$_2$), 4.40 (d, 1H, $J$ = 7.5 Hz, H-1), 4.32 (dd, 1H, $J$ = 6.0,12.3 Hz), 3.90 (dd, 1H, $J$ = 12.0, 2.0 Hz), 3.82 (s, 3H, -OCH$_3$), 3.72 (d, 1H, $J$ = 5.1, 12.0 Hz), 3.45–3.24 (m, 4H). HRMS (ESI-TOF) calcd. for C$_{16}$H$_{22}$O$_7$Na (M+Na)$^+$ 349.1263; found 349.1259.
3,5-Dimethoxycinnamyl β-D-glucopyranoside (10c). Yield: 53%. \([\alpha]_{D}^{25} = -38.7 \ (c = 1.0, \text{MeOH})\). \(^1\)H-NMR (300 MHz, methanol-\(d_6\)): \(\delta\) 6.60 (d, 1H, \(J = 16.5\) Hz, Ar-H), 6.36 (m, 2H), 4.51 (dd, 1H, \(J = 5.6, 13.3\) Hz, =CH-CH\(_3\)), 4.36 (d, 1H, \(J = 7.7\) Hz, =CH-CH\(_2\)), 4.31 (dd, 1H, \(J = 6.7, 12.9\) Hz, H-1), 3.88 (d, 1H, \(J = 11.6\) Hz), 3.76 (s, 3H, -OCH\(_3\) \(\times 2\)), 3.68 (dd, 1H, \(J = 5.2, 12.4\) Hz, H-1), 3.38–3.21 (m, 4H). HRMS (ESI-TOF) calcd. for \(\text{C}_{18}\text{H}_{20}\text{O}_{8}\text{Na} (\text{M}+\text{Na})^+\) 363.1056; found 363.1057.

2,3-Dimethoxycinnamyl β-D-glucopyranoside (10e). Yield: 53%. \([\alpha]_{D}^{25} = -34.8 \ (c = 1.0, \text{MeOH})\). \(^1\)H-NMR (300 MHz, methanol-\(d_6\)): \(\delta\) 7.05 (d, 1H, \(J = 1.8\) Hz, Ar-H), 6.95 (dd, 1H, \(J = 1.8, 8.4\) Hz, Ar-H), 6.88 (d, 1H, \(J = 8.4\) Hz, =CH), 6.60 (d, 1H, \(J = 15.9\) Hz, =CH), 6.25 (dt, 1H, \(J = 6.3, 15.9\) Hz, =CH), 4.51 (dd, 1H, \(J = 6.0, 12.9\) Hz, =CH-CH\(_2\)), 4.39 (d, 1H, \(J = 7.8\) Hz, =CH-CH\(_2\)), 4.33 (dd, 1H, \(J = 6.3, 12.6\) Hz, H-1), 3.91 (d, 1H, \(J = 11.4\) Hz), 3.84 (s, 3H, -OCH\(_3\)), 3.81 (s, 3H, -OCH\(_3\)), 3.71 (dd, 1H, \(J = 3.8, 11.7\) Hz, H-1), 3.44–3.23 (m, 4H). HRMS (ESI-TOF) calcd. for \(\text{C}_{17}\text{H}_{24}\text{O}_{9}\text{Na} (\text{M}+\text{Na})^+\) 379.1369; found 379.1372.

4-Trifluoromethycinnamyl β-D-glucopyranoside (10f). Yield: 49%. \([\alpha]_{D}^{25} = -29.9 \ (c = 1.0, \text{MeOH})\). \(^1\)H-NMR (300 MHz, methanol-\(d_6\)): \(\delta\) 7.60 (s, 4H, Ar-H \(\times 4\)), 6.77 (d, 1H, \(J = 16.0\) Hz, =CH), 6.52 (dt, 1H, \(J = 5.6, 16.0\) Hz, =CH), 4.57 (dd, 1H, \(J = 13.4, 5.0\) Hz, =CH-CH\(_2\)), 4.39 (d, 1H, \(J = 7.5\) Hz, H-1), 4.36 (dd, 1H, \(J = 5.3, 13.4\) Hz, =CH-CH\(_2\)), 3.91 (d, 1H, \(J = 12.5\) Hz), 3.70 (dd, 1H, \(J = 5.2, 11.8\) Hz), 3.45–3.18 (m, 4H). HRMS (ESI-TOF) calcd. for \(\text{C}_{14}\text{H}_{48}\text{O}_{16}\text{Na} (2\text{M}+\text{Na})^+\) 735.2840; found 735.2833.

3,4-Methylenedioxyxycinnamyl β-D-glucopyranoside (10g). Yield: 51%. \([\alpha]_{D}^{25} = -36.8 \ (c = 1.0, \text{MeOH})\). \(^1\)H-NMR (300 MHz, methanol-\(d_6\)): \(\delta\) 8.10 (d, 1H, \(J = 3.9\) Hz, 1H), 7.47 (t, 1H, \(J = 3.9\) Hz, =CH), 6.97 (d, 1H, \(J = 0.6\) Hz), 6.83 (dd, 1H, \(J = 3.9, 0.6\) Hz), 6.74 (d, 1H, \(J = 3.9\) Hz), 6.58 (d, 1H, \(J = 8.1\) Hz), 6.20 (dt, 1H, \(J = 3.0, 8.1\) Hz), 5.92 (s, 2H, -CH\(_2\)-), 4.90 (dd, 1H, \(J = 0.3, 2.7\) Hz, =CH-CH\(_2\)), 4.37 (d, 1H, \(J = 3.9\) Hz, H-1), 4.29 (dd, 1H, \(J = 3.6, 6.3\) Hz), 3.89 (d, 1H, \(J = 3.0\) Hz), 3.69 (dd, 1H, \(J = 6.0, 2.7\) Hz), 3.40–3.23 (m, 4H). HRMS (ESI-TOF) calcd. for \(\text{C}_{16}\text{H}_{20}\text{O}_{8}\text{Na} (\text{M}+\text{Na})^+\) 363.1056; found 363.1057.

3,4,5-Trimethoxycinnamyl β-D-glucopyranoside (10h). Yield: 57%. \([\alpha]_{D}^{25} = -38.2 \ (c = 1.0, \text{MeOH})\). \(^1\)H-NMR (300 MHz, methanol-\(d_6\)): \(\delta\) 6.71 (s, 2H), 6.60 (d, 1H, \(J = 15.9\) Hz, Ar-H), 6.30 (dt, 1H, \(J = 6.0, 9.7\) Hz, =CH), 4.51 (dd, 1H, \(J = 5.0, 12.9\) Hz, =CH-CH\(_2\)), 4.37 (d, 1H, \(J = 7.7\) Hz, =CH-CH\(_2\)), 4.31 (dd, 1H, \(J = 6.5, 13.0\) Hz, H-1), 3.88 (d, 1H, \(J = 11.8\) Hz), 3.82 (s, 3H, -OCH\(_3\) \(\times 2\)), 3.73 (s, 3H, -OCH\(_3\)), 3.69 (dd, 1H, \(J = 5.0, 11.9\) Hz, H-1), 3.40–3.22 (m, 4H). HRMS (ESI-TOF) calcd. for \(\text{C}_{18}\text{H}_{26}\text{O}_{6}\text{Na} (\text{M}+\text{Na})^+\) 409.1475; found 409.1455.
2-Fluorocinnamyl β-D-glucopyranoside (10i). Yield: 55%. [α]_D²⁵ = -39.0 (c = 1.0, MeOH). ¹H-NMR (300 MHz, methanol-d₆): δ 7.47 (t, 1H, J = 7.8 Hz, Ar-H), 7.16 (q, 1H, J = 7.8 Hz, Ar-H), 7.06 (t, 1H, J = 7.5 Hz, =CH), 6.98 (t, 1H, J = 8.4 Hz, =CH), 6.76 (d, 1H, J = 16.2 Hz, =CH), 6.40 (dt, 1H, J = 6.0, 16.2 Hz, =CH-CH₃), 4.50 (dd, 1H, J = 5.4, 12.9 Hz, =CH-CH₃), 4.32 (d, 1H, J = 7.8 Hz, H-1), 4.28 (dd, 1H, J = 4.8, 11.4 Hz), 3.83 (d, 1H, J = 11.4 Hz), 3.63 (dd, 1H, J = 5.1, 12.0 Hz), 3.36–3.17 (m, 4H). HRMS (ESI-TOF) calcd. for C₁₅H₂₀O₆F (M+HCOO⁻) 359.1142; found 359.1145.

4-Chlorocinnamyl β-D-glucopyranoside (10j). Yield: 81%. [α]_D²⁵ = -35.5 (c = 1.0, MeOH). ¹H-NMR (300 MHz, methanol-d₆): δ 7.39 (d, 2H, J = 8.4 Hz, Ar-H × 2), 7.29 (d, 2H, J = 8.5 Hz, Ar-H × 2), 6.66 (d, 1H, J = 16.0 Hz, =CH), 6.38 (dt, 1H, J = 6.0, 16.0 Hz, =CH), 4.52 (dd, 1H, J = 5.3, 12.8 Hz, =CH-CH₃), 4.36 (d, 1H, J = 7.7 Hz, H-1), 4.30 (dd, 1H, J = 5.3, 12.8 Hz, =CH-CH₃), 3.88 (d, 1H, J = 12.5 Hz), 3.67 (dd, 1H, J = 11.8, 5.2 Hz), 3.35–3.18 (m, 4H). HRMS (ESI-TOF) calcd. for C₁₆H₂₀O₈Cl (M+HCOO⁻) 375.0847; found 375.0857.

3,4-Difluorocinnamyl β-D-glucopyranoside (10k). Yield: 49%. [α]_D²⁵ = -40.0 (c = 1.0, MeOH). ¹H-NMR (300 MHz, methanol-d₆): δ 7.28 (dd, 1H, J = 7.3, 10.6 Hz, Ar-H), 7.14-7.09 (m, 2H), 6.58 (d, 1H, J = 16.0 Hz, =CH), 6.28 (dt, 1H, J = 5.9, 16.0 Hz, =CH), 4.45 (dd, 1H, J = 5.3, 13.2 Hz, =CH-CH₃), 4.28 (d, 1H, J = 7.7 Hz, H-1), 4.25 (dd, 1H, J = 6.2, 14.7 Hz), 3.81 (d, 1H, J = 11.5 Hz), 3.61 (dd, 1H, J = 5.2, 11.9 Hz), 3.30–3.14 (m, 4H). HRMS (ESI-TOF) calcd. for C₁₆H₂₀O₆Na (M+Na⁺) 415.1497; found 415.1493.

4-Bromocinnamyl β-D-glucopyranoside (10l). Yield: 70%. [α]_D²⁵ = -31.2 (c = 1.0, MeOH). ¹H-NMR (300 MHz, methanol-d₆): δ 7.45 (d, 2H, J = 8.4 Hz, Ar-H), 7.34 (d, 2H, J = 8.4 Hz, Ar-H), 6.67 (d, 1H, J = 16.0 Hz, =CH), 6.41 (dt, 1H, J = 5.8, 15.9 Hz, =CH), 4.53 (dd, 1H, J = 5.2, 13.2 Hz, =CH-CH₃), 4.37 (d, 1H, J = 7.8 Hz, =CH-CH₃), 4.33 (dd, 1H, J = 6.8, 13.8 Hz, H-1), 3.90 (d, 1H, J = 11.5 Hz), 3.69 (dd, 1H, J = 4.8, 11.9 Hz, H-1), 3.39–3.22 (m, 4H). HRMS (ESI-TOF) calcd. for C₁₆H₂₀O₈Br (M+HCOO⁻) 479.0342; found 479.0340.

Cinnamyl β-D-glucopyranoside (10m). Yield: 61%. [α]_D²⁵ = -24.2 (c = 1.0, MeOH). ¹H-NMR (300 MHz, DMSO-d₆): δ 7.85 (d, 2H, J = 7.2 Hz, Ar-H), 7.74 (t, 2H, J = 7.1 Hz, Ar-H), 7.66 (d, 1H, J = 7.2 Hz, =CH), 7.18 (d, 1H, J = 16.0 Hz, =CH), 5.50 (d, 1H, J = 4.9 Hz, =CH), 5.35 (dd, 2H, J = 4.4, 12.8 Hz, =CH-CH₃), 4.95 (t, 1H, J = 5.8 Hz, H-1), 4.83 (dd, 1H, J = 6.6, 12.3 Hz, =CH-CH₃), 4.63 (d, 2H, J = 7.7 Hz), 3.87 (m, 1H), 3.48 (m, 4H). (ESI-TOF) calcd. for C₁₅H₂₀O₆Na (M+Na⁺) 319.1158; found 319.1158.

3-Bromo-4-ethoxy-5-methoxycinnamylcinnamyl β-D-glucopyranoside (10n). Yield: 43%. [α]_D²⁵ = -31.2 (c = 1.0, MeOH). ¹H-NMR (300 MHz, methanol-d₆): δ 7.18 (d, 1H, J = 1.7 Hz, Ar-H), 7.03 (d, 1H, J = 1.7 Hz, Ar-H), 6.59 (d, 1H, J = 15.9 Hz, =CH), 6.32 (dt, 1H, J = 6.0, 15.9 Hz, =CH-CH₃), 4.54 (dd, 1H, J = 5.5, 13.0 Hz, =CH-CH₃), 4.36 (d, 1H, J = 7.7 Hz, H-1), 4.31 (dd, 1H, J = 6.5, 13.3 Hz), 4.02 (q, 2H, J = 7.1 Hz), 3.86 (s, 3H, -OCH₃), 3.67 (dd, 1H, J = 5.2, 11.9 Hz, =CH-CH₃), 3.40-3.20 (m, 4H), 1.35 (t, 3H, J = 7.2 Hz, -CH₃). HRMS (ESI-TOF) calcd. for C₁₉H₂₆O₁₆Br (M+HCOO⁻) 493.0709; found 493.0700.
4-Hydroxycinnamyl β-D-glucopyranoside (16a). Yield: 46%. [α]_D^25 = −32.6 (c = 1.0, MeOH). 1H-NMR (300 MHz, methanol-d6): δ 7.23 (d, 2H, J = 8.6 Hz, Ar-H), 6.72 (d, 2H, J = 8.5 Hz, Ar-H), 6.55 (d, 1H, J = 15.9 Hz, =CH), 6.15 (dt, 1H, J = 5.8, 15.9 Hz), 4.47 (dd, 1H, J = 6.0, 12.8 Hz, =CH-CH₂), 4.36 (d, 1H, J = 7.7 Hz, H-1), 4.26 (dd, 1H, J = 6.8, 12.4 Hz), 3.89 (d, 1H, J = 12.9 Hz), 3.69 (dd, 1H, J = 5.2, 12.0 Hz), 3.39–3.21 (m, 4H). HRMS (ESI-TOF) calcd. for C_{15}H_{20}O_{7} Na (M+Na)^+ 335.1107; found 335.1088.

3-Hydroxycinnamyl β-D-glucopyranoside (16b). Yield: 51%. [α]_D^25 = −35.2 (c = 1.0, MeOH). 1H-NMR (300 MHz, methanol-d6): δ 7.12 (t, 1H, J = 7.8 Hz, Ar-H), 6.88 (d, 2H, J = 9.2 Hz, Ar-H), 6.61 (d, 1H, J = 15.9 Hz, =CH), 6.32 (dt, 1H, J = 6.3, 15.9 Hz, =CH), 4.51 (dd, 1H, J = 6.0, 13.3 Hz, =CH-CH₂), 4.39 (d, 1H, J = 7.5 Hz, H-1), 3.95 (d, 1H, J = 10.8 Hz), 3.71 (s, 3H, -OCH₃), 3.66 (dd, 1H, J = 5.1, 11.7 Hz, =CH-CH₂), 3.40–3.19 (m, 4H). HRMS (ESI-TOF) calcd. for C_{16}H_{21}O₉ (M+HCOO)^− 357.1186; found 357.1173.

4-Hydroxy-3-methoxycinnamyl β-D-glucopyranoside (16c). Yield: 51%. [α]_D^25 = −36.2 (c = 1.0, MeOH). 1H-NMR (300 MHz, methanol-d6): δ 7.01 (d, 1H, J = 1.5 Hz, Ar-H), 6.85 (dd, 1H, J = 1.5, 8.1 Hz, Ar-H), 6.72 (d, 1H, J = 8.1 Hz, =CH), 6.57 (d, 1H, J = 15.9 Hz, =CH), 6.18 (dt, 1H, J = 6.3, 15.9 Hz, =CH), 4.49 (dd, 1H, J = 6.0, 13.3 Hz, =CH-CH₂), 4.37 (d, 1H, J = 7.5 Hz, H-1), 4.29 (dd, 1H, J = 6.6, 12.3 Hz, =CH-CH₂), 3.91 (d, 1H, J = 10.8 Hz), 3.86 (s, 3H, -OCH₃), 3.40–3.20 (m, 4H). HRMS (ESI-TOF) calcd. for C_{17}H_{23}O_{10} (M+HCOO)^− 387.1291; found 387.1284.

3-Hydroxy-4-methoxycinnamyl β-D-glucopyranoside (16d). Yield: 61%. [α]_D^25 = −35.7 (c = 1.0, MeOH). 1H-NMR (300 MHz, methanol-d6): δ 6.96 (d, 1H, J = 1.5 Hz, Ar-H), 6.87 (dd, 1H, J = 1.5, 8.0 Hz, Ar-H), 6.73 (d, 1H, J = 8.1 Hz, =CH), 6.57 (d, 1H, J = 15.9 Hz, =CH), 6.18 (dt, 1H, J = 6.3, 15.9 Hz, =CH), 4.44 (dd, 1H, J = 6.0, 13.3 Hz, =CH-CH₂), 4.33 (d, 1H, J = 7.5 Hz, H-1), 4.29 (dd, 1H, J = 6.6, 12.3 Hz, =CH-CH₂), 3.91 (d, 1H, J = 10.8 Hz), 3.86 (s, 3H, -OCH₃), 3.46 (dd, 1H, J = 6.3, 15.9 Hz, =CH-CH₂), 3.40–3.19 (m, 4H). HRMS (ESI-TOF) calcd. for C_{17}H_{23}O_{10} (M+HCOO)^− 387.1291; found 387.1283.

Cinnamyl 6-trityl-O-β-D-glucopyranoside (17a). A solution of 10m (1.25 g, 3.8 mmol), trityl chloride (2.24 g, 8.1 mmol), triethylamine (0.98 g, 9.8 mmol), DMAP (0.31 g, 2.5 mmol) and powered 4 Å molecular sieves (2.5 g) in DMF (12 mL) was stirred overnight at room temperature under nitrogen. After another 12 h stirring, the yellow cloudy solution was poured into ice-water and extracted with CH₂Cl₂. The organic extracts were washed with saturated ammonium chloride solution and water, dried (Na₂SO₄). After removal of the solvents, the yellowish solid was subjected to column chromatography on silica gel with petroleum-ethyl acetate (3:1) and ethyl acetate as eluents. Concentrating the ethyl acetate part gave the product as a white amorphous solid. Yield: 1.14 g (56%). m.p. 68–70 °C; [α]_D^25 = −48.8 (c 1.0, MeOH); 1H-NMR (600 MHz, DMSO-d₆): δ 7.50–7.20 (m, 20H, Ar-H × 20), 6.70 (d, 1H, J = 16.2 Hz, =CH), 6.44 (dt, 1H, J = 16.2, 6.0 Hz, =CH), 5.15 (d, 1H, J = 4.8 Hz), 4.98 (d, 1H, J = 4.8 Hz), 4.86 (d, 1H, J = 5.4 Hz), 4.52 (dd, 1H, J = 5.4, 13.2 Hz, =CH-CH₂), 4.35 (dd, 1H, J = 5.4, 13.2 Hz, =CH-CH₂), 4.34 (d, 1H, J = 7.8 Hz), 3.28 (d, 1H, J = 9.6 Hz),
3.15 (m, 1H), 3.07 (m, 3H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$ 144.1 (3C, 3Ar-C), 136.5 (Ar-C), 131.6 (=CH)), 128.8 (4C, 4Ar-C), 128.5 (4C, 4Ar-C), 128.0 (4C, 4Ar-C), 127.8 (=CH), 127.1 (4C, 4Ar-C), 126.5 (4C, 4Ar-C), 102.2 (C-1), 85.7 (Ph3C), 77.0 (C-3), 75.3 (C-5), 73.6 (C-2), 70.4 (C-4), 68.6 (=C-CH2), 63.8 (C-6). HRMS (ESI-TOF): calcd. for C$_{35}$H$_{35}$O$_8$ (M+HCOO)$^-$ 583.2332; found 583.2332.

4-Methoxycinnamyl 6-trityl-2,3,4-tri-O-benzoyl-$\beta$-D-glucopyranoside (17b). Prepared according to synthetic method of 17a from 10a (1.23 g, 3.8 mmol). Yield: 1.15 g (64%). m.p. 58–60 °C; $[\alpha]_D^{25}$ = –25.4 (c 1.0, MeOH); $^1$H-NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.90 (d, 2H, $J = 7.8$ Hz, Ar-H × 2), 7.73 (d, 2H, $J = 7.2$ Hz, Ar-H × 2), 7.66 (d, 2H, $J = 7.8$ Hz, Ar-H × 2), 7.58 (m, 2H, Ar-H × 2), 7.49 (t, 1H, $J = 7.2$ Hz, Ar-H), 7.43 (t, 2H, $J = 7.8$ Hz, Ar-H × 2), 7.40–7.35 (m, 11H, Ar-H × 11), 7.20–7.15 (m, 8H, Ar-H × 8), 7.15–7.10 (m, 4H, Ar-H × 4), 6.81 (d, 2H, $J = 8.4$ Hz, Ar-H × 2), 6.62 (d, 1H, $J = 16.2$ Hz, =CH), 6.16 (dt, 1H, $J = 16.2, 5.4$ Hz, =CH), 5.13 (d, 1H, $J = 4.8$ Hz), 4.98 (d, 1H, $J = 4.8$ Hz), 4.85 (d, 1H, $J = 5.4$ Hz), 4.49 (dd, 1H, $J = 5.4, 13.2$ Hz, =CH-CH$_2$), 4.33 (d, 1H, $J = 7.8$ Hz), 4.32 (dd, 1H, $J = 5.4, 13.2$ Hz, =CH-CH$_2$), 3.73 (s, 3H, -OCH$_3$), 3.27 (d, 1H, $J = 9.6$ Hz), 3.15 (m, 1H), 3.07 (m, 3H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$ 165.3 (PhCO-), 164.9 (PhCO), 164.5 (PhCO-), 143.5 (3C, 3Ar-C), 136.2 (3C, 3Ar-C), 132.9 (3C, 3Ar-C), 114.2 (2C, 2Ar-C ), 102.1 (C-1), 85.7 (Ph3C), 77.0 (C-3), 75.3 (C-5), 73.7 (C-2), 70.5 (C-4), 68.8 (=C-CH$_3$), 63.9 (C-6), 55.2 (OCH$_3$). HRMS (ESI-TOF): calcd. for C$_{56}$H$_{47}$O$_{11}$Na (M+HCOO)$^-$ 613.2438; found 613.2433.

Cinnamyl 6-trityl-2,3,4-tri-O-benzoyl-$\beta$-D-glucopyranoside (18a). Cinnamyl 6-trityl-$\beta$-D-glucopyranoside (4.4 g, 8.16 mmol) in pyridine (50 mL) was cooled to 0 °C, and then benzoyl chloride (5.71 g, 40.8 mmol) was added dropwise over 30 min. The reaction temperature was raised to room temperature. After 24 h water (50 mL) was added to the reaction mixture and stirring was continued for 30 min. The aq. solution was extracted with CH$_2$Cl$_2$ (3 × 50 mL) and the extracts were washed with saturated NaHCO$_3$. The solution was evaporated under vacuum to give a yellow sticky solid which was dissolved in toluene and dehydrate by repeated azeotropic distillation to give the crude product (6.7 g). The product was purified using a short silica gel column eluted with petroleum-ethyl acetate (10:1), to give the title compound as a yellow oil (6.0 g, yield 87%). $[\alpha]_D^{25}$+4.9 (c 1.0, CDCl$_3$); $^1$H-NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.99–7.14 (m, 35H, Ar-H × 35), 6.59 (d, 1H, $J = 16.2$ Hz, =CH), 6.35 (dt, 1H, $J = 16.2, 5.4$ Hz, =CH), 5.93 (t, 1H, $J = 9.6$ Hz), 5.74 (t, 1H, $J = 9.6$ Hz), 5.49 (d, 1H, $J = 9.0$ Hz), 5.27 (d, 1H, $J = 7.8$ Hz), 4.56 (dd, 1H, $J = 5.4, 13.2$ Hz, =CH-CH$_2$), 4.42 (dd, 1H, $J = 6.0, 13.8$ Hz, =CH-CH$_2$) 4.29 (d, 1H, $J = 10.2$ Hz), 3.35 (d, 1H, $J = 10.2$ Hz), 3.06 (dd, 1H, $J = 3.0, 10.2$ Hz). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$ 165.3 (PhCO-), 164.9 (PhCO), 164.5 (PhCO-), 143.5 (3C, 3Ar-C), 136.2 (Ar-C), 133.8 (3C, 3Ar-C), 129.2 (2C, 2Ar-C), 127.1 (3C, 3Ar-C), 114.2 (2C, 2Ar-C ), 102.1 (C-1), 85.7 (Ph3C), 77.0 (C-3), 75.3 (C-5), 73.7 (C-2), 70.5 (C-4), 68.8 (=C-CH$_3$), 63.9 (C-6), 55.2 (OCH$_3$). HRMS (ESI-TOF): calcd. for C$_{56}$H$_{47}$O$_{11}$Na (M+HCOO)$^-$ 613.2438; found 613.2433.
4-Methoxycinnamyl 6-trityl-2,3,4-tri-O-benzoyl-β-D-glucopyranoside (18b). Prepared according to the synthetic method used for the preparation of 18a from 17b (5.7 g, 10 mmol). Yield: 7.93 g (90%). m.p. 88–90 °C; [α]25D +21.5 (c 1.0, CDCl3); 1H-NMR (600 MHz, DMSO-d6): δ 7.90–7.10 (m, 32H, Ar-H × 32), 6.82 (d, 2H, J = 9.0 Hz, Ar-H × 2), 6.51 (d, 1H, J = 16.2 Hz, =CH), 6.17 (dt, 1H, J = 16.2, 5.4 Hz, =CH), 5.90 (t, 1H, J = 9.6 Hz), 5.70 (t, 1H, J = 9.6 Hz), 5.47 (t, 1H, J = 9.0 Hz), 5.24 (d, 1H, J = 7.8 Hz, H-1), 4.51 (dd, 1H, J = 5.4, 13.2 Hz, =CH-CH2), 4.42 (dd, 1H, J = 6.0, 13.2 Hz, =CH-CH2), 4.26 (dt, 1H, J = 2.4, 9.6 Hz), 3.33 (d, 1H, J = 9.0 Hz), 3.03 (dd, 1H, J = 3.6, 10.2 Hz). 13C-NMR (75 MHz, DMSO-d6): δ 165.3 (PhCO-), 164.9 (PhCO-), 164.5 (PhCO-), 159.0 (2C, 2Ar-C), 143.5 (3C, 3Ar-C), 133.7 (3C, 3Ar-C), 131.8 (3C, 3Ar-C), 129.3 (2C, 2Ar-C), 129.2 (3C, 3Ar-C), 128.9 (3C, 3Ar-C), 128.8 (3C, 3Ar-C), 128.6 (=CH), 128.2 (6C, 6Ar-C), 127.9 (3C, 3Ar-C), 127.7 (3C, 3Ar-C), 127.0 (3C, 3Ar-C), 122.9 (=CH), 114.0 (2C, 2Ar-C), 99.2 (C-1), 86.0 (Ph2C), 73.7 (C-3), 72.3 (2C, C-5, 2), 69.1 (2C, C-4, =C-CH2), 61.7 (C-6), 55.1 (OCH3). HRMS (ESI-TOF): calcd. for C56H49O10 (M+H)+ 881.3320; found 881.3347.

Cinnamyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (19a). Cinnamyl 6-trityl-2,3,4-tri-O-benzoyl-β-D-glucopyranoside (18b, 5.0 g, 5.9 mol) was dissolved in CH2Cl2 (30 mL) followed by the addition of 90% aq TFA (3.0 mL) and the solution was allowed to stir for 30 min at room temperature. Then the solution was poured into a separating funnel and washed successively with water (50 mL), saturated NaHCO3 (2 × 50 mL) and brine (50 mL). The organic layer was collected, dried (Na2SO4) and filtered. The filtrate was evaporated and the resulting crude material was purified by silica gel chromatography using petroleum-ethyl acetate (3:1) as eluent, affording pure compound (3.0 g, 84%) as a light yellow solid. m.p. 108–110 °C; [α]25D +2.9 (c 1.0, CDCl3); 1H-NMR (600 MHz, DMSO-d6): δ 7.87–7.15 (m, 20H, Ar-H × 20), 6.51 (d, 1H, J = 16.2 Hz, =CH), 6.23 (dt, 1H, J = 5.4, 16.2 Hz, =CH), 5.93 (t, 1H, J = 9.6 Hz), 5.49 (d, 1H, J = 9.0 Hz), 5.36 (d, 1H, J = 9.0 Hz), 5.18 (d, 1H, J = 7.8 Hz), 5.06 (s, 1H, OH), 4.48 (dd, 1H, J = 5.4, 13.2 Hz, =CH-CH2), 4.32 (dd, 1H, J = 6.0, 13.8 Hz, =CH-CH2), 4.09 (m, 1H), 3.66 (m, 2H), 3.06 (dd, 1H, J = 3.0, 10.2 Hz). 13C-NMR (75 MHz, DMSO-d6): δ 165.4 (PhCO-), 165.0 (2C, 2PhCO-), 136.3 (Ar-C), 133.9 (3C, 3Ar-C), 131.8 (=CH), 129.4 (3C, 3Ar-C), 129.2 (2C, 2Ar-C), 129.0 (3C, 3Ar-C), 128.9 (3C, 3Ar-C), 128.6 (=CH), 128.2 (6C, 6Ar-C), 127.9 (3C, 3Ar-C), 127.7 (3C, 3Ar-C), 127.0 (3C, 3Ar-C), 122.9 (=CH), 114.0 (2C, 2Ar-C), 99.2 (C-1), 86.0 (Ph2C), 73.7 (C-3), 72.3 (2C, C-5, 2), 69.1 (2C, C-4, =C-CH2), 61.7 (C-6), 55.1 (OCH3). HRMS (ESI-TOF): calcd. for C37H33O11 (M+HCOO)– 653.2023; found 653.2028.

4-Methoxycinnamyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (19b). Prepared according to synthetic method described for preparation of 19a from 18b (6.0 g, 6.8 mmol). Yield: 3.73 g (86%). m.p. 125–127 °C; [α]25D +6.8 (c 1.0, CDCl3); 1H-NMR (600 MHz, CDCl3): δ 8.10–7.10 (m, 17H, Ar-H × 17), 6.80 (d, 2H, J = 9.0 Hz, Ar-H × 2), 6.49 (d, 1H, J = 15.6 Hz, =CH), 6.00 (dt, 1H, J = 6.0, 15.0 Hz, =CH), 5.93 (t, 1H, J = 9.6 Hz), 5.55 (t, 1H, J = 9.0 Hz), 5.51 (t, 1H, J = 9.0 Hz), 4.94 (d, 1H, J = 7.8 Hz, H-1), 4.51 (dd, 1H, J = 5.4, 13.2 Hz, =CH-CH2), 4.34 (dd, 1H, J = 6.0, 13.8 Hz, =CH-CH2), 3.87 (m, 1H), 3.79 (s, 3H, OCH3), 3.82–3.78 (m, 2H), 3.48 (s, 1H, -OH). 13C-NMR (75 MHz, CDCl3): δ 166.0 (PhCO-), 165.8 (PhCO-), 165.1 (PhCO-), 159.3 (Ar-C), 133.6 (Ar-C), 133.2 (Ar-C), 132.8 (Ar-C), 130.1 (2C, 2Ar-C), 129.8 (2C, 2Ar-C), 129.7 (2C, 2Ar-C), 129.6 (2C, 2Ar-C), 129.2 (Ar-C), 128.8 (3C, 3Ar-C), 128.2 (2C, 2Ar-C), 127.8 (2C, 2Ar-C), 127.2 (2C, 2Ar-C), 126.9 (Ar-C), 122.1 (Ar-C), 113.9 (2C, 2Ar-C), 99.6 (C-1), 74.6 (C-3), 72.7 (C-5), 71.8 (C-2), 70.1 (C-4), 69.5
Rosavin (20). A suspension of cinnamyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (100 mg, 0.164 mmol), 2,3,4-tri-O-benzoyl-α-L-arabinopyranosyl trichloroacetimidate (119 mg, 0.197 mmol) and powdered 4 Å molecular sieves (1.0 g) in dry CH₂Cl₂ (20 mL) was stirred for 30 min at −20 °C. A dry CH₂Cl₂ solution (0.2 mL) containing TMSOTf (1.8 µL, 0.01 mmol) was added dropwise. The mixture was stirred for 1 h before Et₃N (0.1 mL) was added to quench the reaction, and then the mixture was diluted with CH₂Cl₂ (20 mL) and passed through a sintered-glass funnel. The resulting solution was concentrated and the resulting residue was dissolved in dry CH₂Cl₂-MeOH (1:2, 30 mL). NaOMe (108 mg, 2.0 mmol) was added. The solution was stirred at room temperature for 2 h and then neutralized with Dowex H⁺ resin to pH 7. The resin was filtered and the filtrate was concentrated. The residue was subjected to a silica gel PTLC to give the product as a white powder. Yield: 69 mg (79%). m.p. 170–173 °C; [α]₂⁰D -54.2 [c 0.7, CHCl₃:MeOH (1:1)]. Lit. [19] [α]₂⁰D -56.5 [c 0.7, CHCl₃:MeOH (1:1)]; ¹H-NMR (600 MHz, MeOH-d₄): δ 7.36 (d, 2H, J = 7.2 Hz, Ar-H × 2), 7.26 (t, 2H, J = 7.2 Hz, Ar-H × 2), 7.15 (t, 1H, J = 7.2 Hz, Ar-H), 6.61 (d, 1H, J = 15.6 Hz, =CH), 6.31 (dt, 1H, J = 6.0, 16.2 Hz, =CH), 4.45 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH₂), 4.37 (d, 1H, J = 7.8 Hz, H-1'), 4.36 (d, 1H, J = 6.8 Hz, H-1′′), 4.35 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH₂), 4.11 (d, 1H, J = 10.9 Hz), 3.94 (dd, 1H, J = 1.8 Hz, 9.6 Hz), 3.77 (d, 1H, J = 6.0, 12.6 Hz, =CH), 3.7 (d, 1H, J = 6.0, 12.6 Hz, =CH), 3.75 (m, 2H), 3.61 (t, 1H, J = 7.2 Hz), 3.55 (m, 2H), 3.35 (m, 1H), 3.25 (m, 1H), 3.20 (t, 1H, J = 7.0 Hz). ¹³C-NMR (150 MHz, MeOH-d₄): δ 138.3 (Ar-C), 133.8 (=CH), 129.7 (2C, 2Ar-C), 128.7 (Ar-C), 127.6 (2C, 2Ar-H), 126.7 (=CH), 105.2 (C-1′′), 103.4 (C-1′), 78.1 (C-3′), 76.9 (C-5′), 75.1 (C-2′), 74.3 (C-3′), 72.5 (C-2′′), 71.8 (C-4′), 70.9 (-CH₂-), 69.6 (C-4′′), 66.7 (C-5′′). HRMS (ESI-TOF): calcd. for C₂₁H₂₉O₁₂ (M+HCOO)− 473.1659; found 473.1656.

Cinnamyl 6-O-(β-D-xylopyranosyl)-β-D-glucopyranoside (21). Prepared according to the synthetic method described for the preparation of 20 from 19a (100 mg, 0.164 mmol). Yield: 68 mg (78%). m.p. 173–175 °C; [α]₂⁰D -67.9 [c 1.0, MeOH]. ¹H-NMR (600 MHz, MeOH-d₄): δ 7.33 (d, 2H, J = 7.8 Hz, Ar-H × 2), 7.29 (t, 2H, J = 7.8 Hz, Ar-H × 2), 7.20 (t, 1H, J = 7.2 Hz, Ar-H), 6.68 (d, 1H, J = 15.6 Hz, =CH), 6.36 (dt, 1H, J = 6.0, 16.2 Hz, =CH), 4.51 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH₂), 4.37 (d, 1H, J = 7.8 Hz, H-1′), 4.36 (d, 1H, J = 7.2 Hz, H-1′′), 4.35 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH₂), 4.11 (d, 1H, J = 1.8, 9.6 Hz), 3.86 (dd, 1H, J = 5.6, 11.4 Hz), 3.77 (d, 1H, J = 6.0, 11.4 Hz), 3.55–3.45 (m, 1H), 3.40–3.32 (m, 3H), 3.28–3.13 (m, 3H). ¹³C-NMR (75 MHz, MeOH-d₄): δ 138.3 (Ar-C), 133.9 (=CH), 129.5 (2C, 2Ar-C), 128.7 (Ar-C), 127.5 (2C, 2Ar-H), 126.7 (=CH), 105.2 (C-1′′), 103.4 (C-1′), 78.1 (C-3′), 76.9 (C-5′), 75.1 (C-2′), 74.3 (C-3′), 72.5 (C-2′′), 71.8 (C-4′), 70.9 (-CH₂-), 69.6 (C-4′′), 66.7 (C-5′′). HRMS (ESI-TOF): calcd. for C₂₁H₂₉O₁₂ (M+HCOO)− 473.1659; found 473.1656.

4-Methoxycinnamyl 6-O-(α-L-arabinopyranosyl)-β-D-glucopyranoside (22). Prepared according to synthetic method described for the preparation of 20 from 19b (100 mg, 0.156 mmol). Yield: 71 mg (81%). m.p. 93–95 °C; [α]₂⁰D -40.2 (c 1.0, MeOH). ¹H-NMR (600 MHz, MeOH-d₄): δ 7.37 (d, 2H, J = 8.3 Hz), 6.83 (d, 2H, J = 8.3 Hz), 6.60 (d, 1H, J = 15.9 Hz), 6.20 (td, 1H, J = 6.8, 15.9 Hz), 4.48
Cinnamyl 6-O-(α-L-rhamnopyranosyl)-β-D-glucopyranoside (23). Prepared according to synthetic method described for the preparation of 20 from 19a (100 mg, 0.164 mmol). Yield: 74 mg (83%). m.p. 111–112 °C; [α]D−59.2 (c 1.0, MeOH); 1H-NMR (600 MHz, MeOH-d4): δ 7.35 (d, 2H, J = 7.2 Hz, Ar-H × 2), 7.25 (t, 2H, J = 7.2 Hz, Ar-H × 2), 7.17 (t, 1H, J = 7.2 Hz, Ar-H), 6.62 (d, 1H, J = 15.6 Hz, =CH), 6.31 (dt, 1H, J = 6.0, 16.2 Hz, =CH), 4.45 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH2), 4.74 (d, 1H, J = 1.2 Hz, H-1), 4.32 (d, 1H, J = 7.8 Hz, H-1′), 4.35 (dd, 1H, J = 6.0, 12.6 Hz, =CH-CH3), 3.94 (dd, 1H, J = 1.8 Hz, 11.4 Hz, H-6), 3.86 (t, 1H, J = 1.8 Hz, H-2′), 3.77 (d, 1H, J = 2.0, 3.0 Hz, H-5″), 3.67 (m, 1H, H-3″), 3.60 (1H, dd J = 6.0, 11.4 Hz, H-6′), 3.39 (m, 1H, H-5″), 3.37 (m, 1H, H-4″), 3.35 (m, 1H, H-4′), 3.33 (m, 1H, H-6′), 3.25 (1H, m, H-3′), 3.20 (t, 1H, J = 9.0 Hz, H-2′′), 1.24 (d, 3H, J = 7.8 Hz, CH3). 13C-NMR (75 MHz, MeOH-d4): δ 138.0 (Ar-C), 133.9 (=CH), 129.5 (2C, 2Ar-C), 128.7 (Ar-C), 127.5 (2C, 2Ar-H), 126.4 (=CH), 103.1 (C-1′), 102.2 (C-1″), 77.9 (C-5′), 76.7 (C-4′), 74.9 (C-2′), 73.9 (C-4″), 72.2 (C-3″), 72.1 (C-2″), 71.5 (C-3′), 70.7 (-CH2-), 69.7 (C-5″), 68.1 (C-6″), 18.0 (-CH3). HRMS (ESI-TOF): calcd. for C22H31O12 (M+HCOO)− 487.1816; found 487.1828.

Assay of the in vitro AChE/XOD inhibitory activity: The tests of in vitro inhibitory activity of these PPGs against AChE (from drosophila, Jing Peng Bio-Pesticide Co., Ltd. Shandong, P. R. China) and Xanthine Oxidase (from buttermilk, Sigma Co., Ltd. X4875) were carried out by using AChE (or XOD) Detection Kits (Jian Cheng Bioengineering Institute, Nan Jin, Jiangsu, P. R. China), following the manufacturer’s protocol. All the compounds were dissolved in 1% DMSO. The test compounds were initially assayed for their inhibition of AChE and XOD at a concentration of 1.5 mg/mL. If an inhibition of more than 30% was observed, the compound was classified as active. The active compounds were consequently tested at seven concentrations. The results were read on a microplate reader at the wavelength of 450 nm/530 nm. All the assays were performed in triplicate with three independent experiments. The IC50 values were calculated using XLfit software.

4. Conclusions

In summary, by using active ingredients from Rhodiola rosea L. as lead compounds, we adopted three routes to synthesize three categories of natural and synthetic PPGs and tested their AChE and XOD inhibitory activity. Several PPGs were found to have potential inhibitory effects on AChE and XOD which are worthy of further study. This result suggested PPGs may be the active ingredients of Rhodiola rosea L. in the therapy of nervous and cardiovascular diseases and also provided some pharmacological basis for the usage of this plant in Traditional Chinese Medicine.
Acknowledgments

This research project was supported by grant No. 30960493 and 20762008 from the National Natural Science Foundation of PR China and No. 2009ZX09501-011 supported by National Key Technologies R & D Program of China during the 11th Five-Year Plan Period.

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Sample Availability: Samples are available from the authors.