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Design, synthesis and biological evaluation of glucose-containing scutellarein derivatives as neuroprotective agents based on metabolic mechanism of scutellarin in vivo

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ABSTRACT

Based on metabolic mechanism of scutellarin in vivo that scutellarin could be hydrolyzed into scutellarein by β-glucuronide enzyme, some glucose-containing scutellarein derivatives were designed and synthesized through the introduction of glucose moiety at C-7 position of scutellarein via a glucosidic bond. Biological activity evaluation showed that these glucose-containing scutellarein derivatives exhibited potent DPPH radical scavenging activities. Furthermore, the improvement of physicochemical properties such as anticoagulant and neuroprotective activities alongside with the water solubility was achieved by introducing glucose. These findings suggest that the introduction of the glucose moiety to scutellarein wattants further development of this kind of compounds as neuroprotective agents.

Traditional Chinese medicines (TCMs) have been used clinically for many years and can be regarded as potential sources for drug discovery. Scutellarin (**1**) (Fig. 1), which is the main effective constituent of breviscapine (>85%), a clinic natural drug consisting of total flavonoids of *Erigeron breviscapus* (Vant.) Hand-Mazz. (Compositae), has been used for the treatment of cerebral infarction, coronary heart disease, and angina pectoris in China.[1] Due to the distinguished efficacy of scutellarin in the clinical therapy, the research of scutellarin has become a hot topic in China in recent years. Pharmacological studies have demonstrated that scutellarin is associated with a wide range of benefits to brain injury caused by cerebral ischemia/reperfusion, these benefits are due to its antioxidant and anticoagulant activities to attenuate neuronal damage.[2–4]

Pharmacokinetic studies on scutellarin have been investigated in rats,[5–7] dogs[8] and humans[9] after oral administration, and the results showed that the oral bioavailability of scutellarin was quite poor.[10] One reason was its poor aqueous solubility and low lipophilicity,[11] its poor ability to penetrate cell membranes has long been a major impediment to its overall effectiveness as an oral drug. The other reason was that scutellarin is readily converted into scutellarein (**2**) (Fig. 2) before absorption, the latter is relatively easily absorbed into the blood and can metabolite into glucuronidated, sulfated or methylated forms.[12] Due to the low bioavailability after oral administration, direct administration of scutellarin by injection is the most common route of administration in clinical settings. Nonetheless, therapeutic effects elicited by breviscapine require repeated injection daily for a long time, this is highly inconvenient and results in low patient compliance.

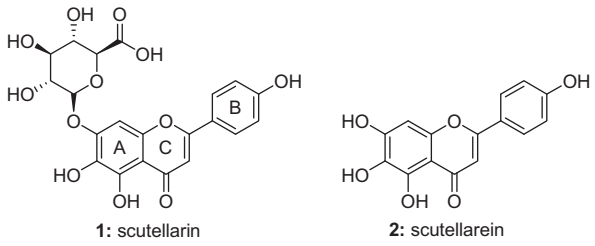

Figure 1. Chemical structures of scutellarin (**1**) and scutellarein (**2**).

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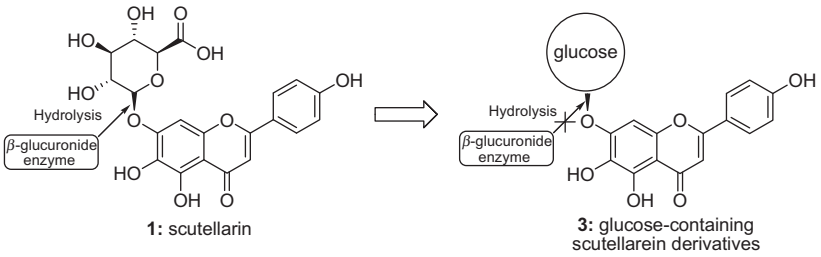
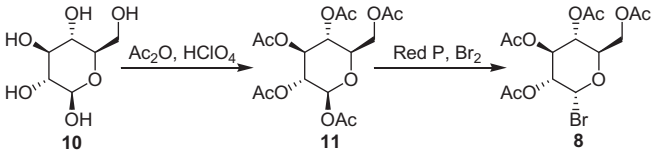


Figures 2. Design of glucose-containing scutellarein derivatives.

It has been reported that scutellarin (**1**) is readily hydrolyzed into scutellarein (**2**) by β-glucuronide enzyme and the microbial population in the intestine prior to absorption.[12] Since the glucose connected to scutellarein via a glucosidic bond is unlikely to be cleaved by β-glucuronide enzyme and the microbial population in the intestine, in the present study, the glucose moiety was introduced to scutellarein at C-7 position via a glucosidic bond (**3**) (Fig. 2). We assessed the anti-oxidation and anticoagulant activities, as well as the neuroprotective activities of **3a–3c** to investigate whether the biological activities of parent scutellarin **1** was retained in these glucose-containing scutellareins. Furthermore, the solubility of these glucose-containing scutellarein derivatives was also evaluated.

The regioselective D-glucose-containing scutellarein derivative (**3a**) was achieved using the Mitsunobu method,[13] which involved the coupling of protected scutellarein (**7**) with protected glucose (**8**) (Scheme 1). Scutellarin (**1**) was firstly hydrolyzed by refluxing with 6 N HCl in ethanol under a N_2 atmosphere to generate scutellarein (**4**) in 17.0% yield. Compound **4** was then converted into **5** (78.9% yield) after it was reacted with acetic anhydride and catalytic 4-*N*,*N*-dimethylaminopyridine (DMAP) in pyridine. Interestingly, when compound **5** reacted with BnBr using K_2CO_3 and catalytic KI in dry acetone, the desired intermediate **6** was obtained in 70% yield. Deprotection of the benzyl group in **6** was accomplished under hydrogenation conditions with 10% palladium on carbon as the catalyst in EtOH/CH_2Cl_2 gave **7** in 95% yield. Glycosylation of hydroxyl group took place completely at the position 7 using 2.5 equiv of K_2CO_3 and 2.0 equiv of AgO as bases in quinoline that led to **9**.[14] Finally, the hydrolysis of acetyl groups in **9** with a solution of sodium hydroxide afforded **3a** in 41% yield.

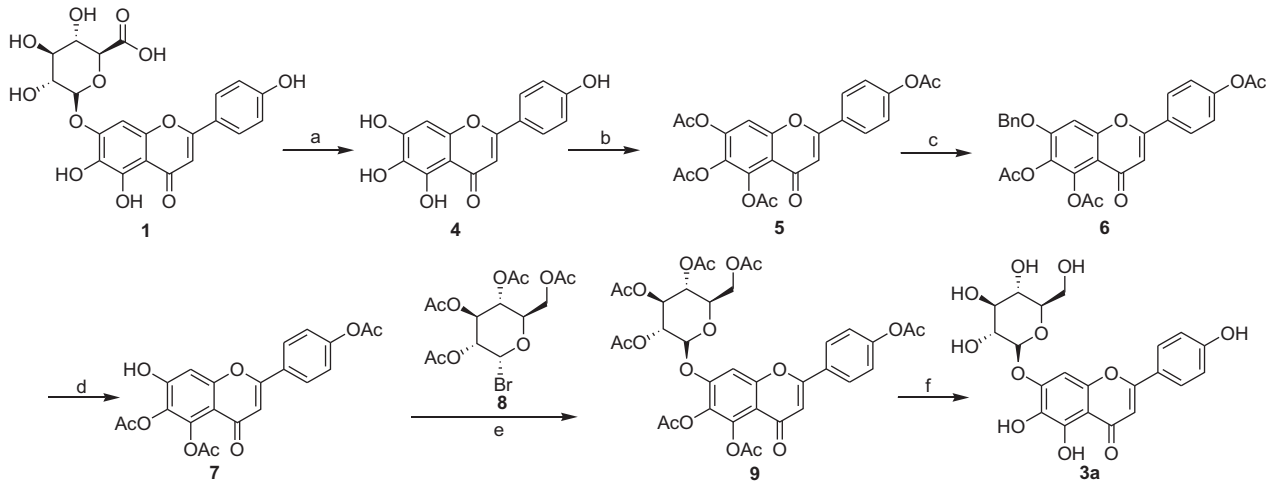


Scheme 2. Reagents and conditions: (a) Ac_2O (10.0 equiv, $HClO_4$ (0.05 equiv); (b) red phosphorus (0.2 equiv), Br_2 (10 equiv), H_2O, 25 °C, 40% over two steps.

O-Acetyl-D-glucosyl bromide **8** was synthesized from D-glucose (**10**) in two steps as shown in Scheme 2, firstly, penta-*O*-acetyl-D-glucose (**11**) was synthesized after D-glucose (**10**) was reacted with acetic anhydride under the catalyst of perchloric acid, then the reaction mixture was reacted with red phosphorus and liquid bromine directly without separation, and the target *O*-acetyl-D-glucosyl bromide **8** was obtained in 40% yield over these two steps.

The formation of **3b** and **3c** were obtained through the introduction of *O*-acetyl-D-manmosyl bromide and *O*-acetyl-D-galactopyranosyl bromide, respectively, using a procedure similar to that described above.

The antioxidant activities of the synthesized glucose-containing scutellarein derivatives **3a–3c** were evaluated by examining DPPH radical scavenging according to our previous procedure.[15] For comparison purposes, the antioxidant activity of scutellarin (**1**) was included as positive controls. As shown in Table 1, the synthesized compounds showed DPPH radical scavenging activities (IC_{50} = 25.31–34.86 μM) that were similar to those of the scutellarin (**1**) (IC_{50} = 26.78 μM), which indicated that the introduction of the glucose moiety had little effect on the change of DPPH radical



Scheme 1. Reagents and conditions: (a) 6 N Concentrated hydrochloric acid, EtOH, N_2, 120 °C, 17.0%; (b) Ac_2O (10.0 equiv), pyridine (10.0 equiv), DMAP (0.1 equiv), 25 °C, 12 h, 78.9%; (c) $PhCH_2Br$ (3.0 equiv), K_2CO_3 (7.0 equiv), KI (1.0 equiv), acetone, reflux, 6 h, 70%; (d) Pd/C (10 wt %), H_2 (1 atm), CH_2Cl_2/Et_2OH, 25 °C, 24 h, 95%; (e) **8** (4.0 equiv), $CuSO_4$ (2.5 equiv), AgO (2.0 equiv), quinoline, 25 °C, 12 h, 40%; (f) NaOH (2.5 M), N_2, $CHCl_3$, 0 °C, 41%.