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Studies on the Constituents of *Scutellaria* Species (X)[1] On the Flavonoid Constituents of the Leaves of *Scutellaria baicalensis* GEORGI[2]

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Two new flavanones (I and II) were isolated from the leaves of *Scutellaria baicalensis* GEORGI, together with chrysin, wogonin, apigenin, salvigenin, scutellarein, isoscutellarein, apigenin 7-*O*-glucuronide and isoscutellarein 8-*O*-glucuronide. The structures of I and II were shown to be (2*S*)-5,7,8,4′-tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside and (2*S*)-5,6,7,4′-tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside, respectively, on the basis of the chemical and spectral data.

Keywords——*Scutellaria baicalensis*; Labiatae; leaves; flavonoid; flavone; flavanone; structure elucidation

In the previous papers,[3] we reported the isolation and characterization of twenty flavonoids from the root of *Scutellaria baicalensis* GEORGI (Labiatae). As regards the constituents of the leaves of this plant, only three flavonoids, scutellarin,[4] carthamidin[5] and isocarthamidin,[5] have been isolated by this time. As a part of our studies on the flavonoid constituents of *Scutellaria* species, we now examined the constituents of the leaves.

As described in the experimental section, two new flavanones (**I** and **II**) were isolated together with eight known flavones (**III**–**X**) from the ethanol extract of the leaves of this plant which had been cultivated in the botanical garden of our university. This paper deals with their structural identification.

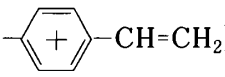
Compound **I** was obtained as pale yellow needles, mp 208°C (dec.), $C_{21}H_{20}O_{12}$, Mg-HCl test (+). It gave the infrared (IR) absorption bands of hydroxyl, carboxyl and conjugated carbonyl groups and benzene rings and the ultraviolet (UV) spectrum characteristic of flavanones.[6] The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **I** showed the signals of one chelated hydroxyl (11.70 ppm), sugar protons (3.30–5.16 ppm) and an ABX type grouping due to the C-2 (5.50 ppm) and C-3 protons (2.71 and 3.40 ppm). In the aromatic region of the spectrum were one singlet (6.29 ppm, 1H) ascribable to the A-ring proton and two doublets of A_2B_2 type (7.35 ppm, 2H, J = 8.0 Hz and 6.81 ppm, 2H, J = 8.0 Hz) ascribable to the B-ring protons.

On methanolysis, **I** gave 5,6,7,4′-tetrahydroxyflavanone (isocarthamidin),[5] 5,7,8,4′-tetrahydroxyflavanone (carthamidin)[5] and sugars which were identified as methyl glucuronopyranoside methyl ester and methyl glycoside of glucurono-6, 3-lactone by gas-liquid chromatography (GLC). In the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **I**, the carbon signals caused by the sugar moiety including the anomeric carbon signal at 99.9 ppm (d, J = 161.8 Hz) indicated the presence of a *β*-glucuronopyranosyl unit. **I** was methylated with CH_2N_2 to give its trimethyl ether monomethyl ester (**I a**), mp 196°C (dec.), $C_{25}H_{28}O_{12}$. Reduction of **Ia** with $NaBH_4$ followed by hydrolysis gave D-glucose, the absolute configuration of which was established by the method reported by Oshima *et al.*[7] The glucuronic acid in **I** was, therefore, proved to be of D-form.

From these results, **I** was considered to be the *β*-D-glucuronopyranoside of either carthamidin or isocarthamidin. The latter was ruled out by the long range selective proton decoupling (LSPD)[8] in the ^{13}C-NMR spectrum of **I**, as follows. In the ^{1}H non-decoupling ^{13}C-NMR spectrum of **I**, the signal of the carbon having an isolated aromatic hydrogen was observed at 95.1 ppm as a double doublet (J = 164.8 and 6.0 Hz). This signal became a doublet when the chelated hydroxyl proton at the C-5 position was selectively irradiated, indicating that no substituent was present at the C-6 position. The aglycone of **I** is, therefore, carthamidin,

and the formation of isocarthamidin was considered to be due to the ring isomerization between 5-hydroxy-7,8-oxygenated flavanone and 5-hydroxy-6,7-oxygenated flavanone.[1]

The glucuronic acid in **I** was determined to be linked to the 7-hydroxyl group of the aglycone in the following way. (1) The mass spectrum of **Ia** exhibited a fragment ion peak originating from the B-ring at

m/z 134  , indicating that no sugar moiety attached to the B-ring. (2) The

^{1}H-NMR spectrum of **I** showed the presence of a free chelated hydroxyl (5-hydroxyl). (3) In the ^{13}C-NMR spectrum of **Ia**, one of the methoxyl carbon signals was observed at 60.5 ppm. This signal is considered to be of the methoxyl on the C-8 carbon with both *ortho* positions being substituted by oxygen functions.[9] This indicated that the 8-hydroxyl in **I** was free.

It is known that flavanones having (2*S*)-configuration exhibit a positive Cotton effect due to n-π^* transition (~330 nm) and a negative Cotton effect due to π-π^* transition (270–290 nm) in the circular dichroism (CD) spectra.[10] The CD curve of **I** exhibited positive and negative maxima at 311 and 284 nm, respectively, which confirmed that it has (2*S*)-configuration.

On the basis of the above findings, compound **I** was determined to be (2*S*)-5,7,8,4′-tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside.

Compound **II** was obtained as pale yellow needles, mp 201°C (dec.), $C_{21}H_{20}O_{12}$, Mg-HCl test (+), and gave carthamidin,[5] isocarthamidin,[5] methyl glucuronopyranoside methyl ester and methyl glycoside of glucurono-6,3-lactone on methanolysis. The presence of a substituent at the C-6 position in **II** was confirmed by the LSPD method.[8] The aglycone of **II** is, therefore, isocarthamidin.

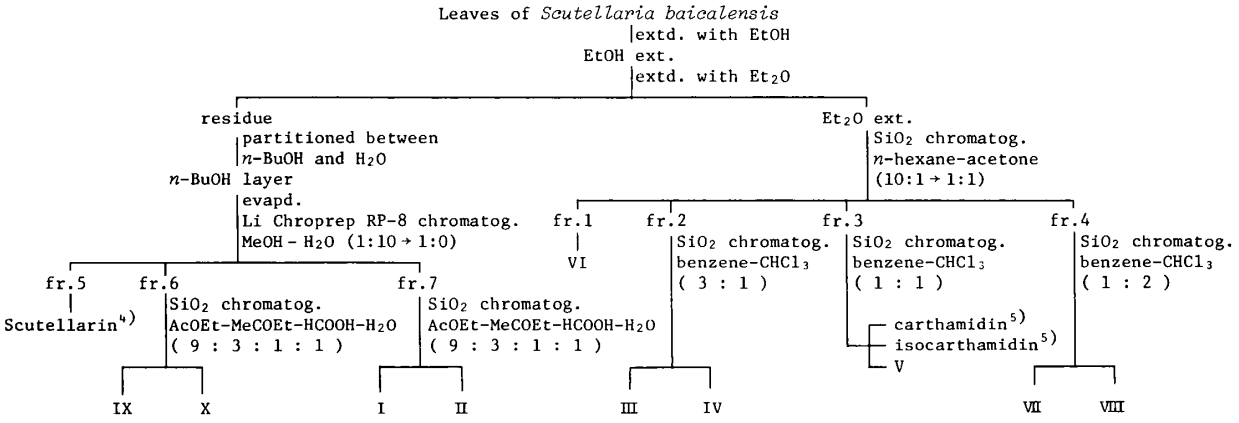
In the ^{13}C-NMR spectrum of **II**, the signals assignable to the sugar moiety were in good accord with those of **I**, and the signal patterns of the A-ring and the B-ring were almost superimposable on those of dihydrobaicalin (5,6,7-trihydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside)[3a] and **I**, respectively. The *β*-configuration of glycosidic linkage and the (2*S*)-configuration were confirmed in the same way as in the case of **I**.

Thus, the structure of **II** was established as (2*S*)-5,6,7,4′-tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside.

Compounds **III**–**X** were identified as chrysin,[11] wogonin,[1] apigenin,[12] salvigenin,[13] scutellarein,[14] isoscutellarein,[15] apigenin 7-*O*-glucuronide[16] and isoscutellarein 8-*O*-glucuronide,[17] respectively, by direct comparison with authentic samples.

Experimental

General procedures——The instruments used to obtain the physical data were the same as those described in the previous paper.[1] GLC was run on a Shimadzu GC-6AM unit with a flame ionization detector. GLC-1: column, a glass column (2m × 4mm i.d.) packed with 5% SE-30 on Chromosorb W (60–80 mesh); column temperature, programed from 150°C (20 min hold) to 240°C at 5°C/min. GLC-2: column, a fused-silica WCOT column with Carbowax 20M (Shinwa Kako Co., 25m × 0.2 mm); column temperature, programed from 110°C (1 min hold) to 170°C



I: 2(*S*)-5,7,8,4'-tetrahydroxyflavanone 7-O-β-D-glucuronopyranoside
II: 2(*S*)-5,6,7,4'-tetrahydroxyflavanone 7-O-β-D-glucuronopyranoside
III: chrysin IV: wogonin V: apigenin VI: salvigenin VII: scutellarein
VIII: isoscutellarein IX: apigenin 7-O-glucuronide X: isoscutellarein 8-O-glucuronide

Chart 1.

(10 min hold) at 2°C/min [lit.,[7] 158°C]. Thin layer chromato-graphy (TLC) was carried out on Kieselgel $60F_{254}$ (Merck) with the following solvent systems: $CHCl_3$–MeOH–H_2O–HCOOH(25:8:1:1) (TLC-1), AcOEt-methyl ethyl ketone–H_2O–HCOOH (60:30:8:1) (TLC-2). Spots were detected by spraying dil. H_2SO_4 followed by heating.

Extraction and separation——As shown in Chart 1, ten flavonoids, **I**(40 mg), **II**(30 mg), **III**(20 mg), **IV**(20 mg), **V** (30 mg), **VI**(20 mg), **VII**(15 mg), **VIII**(30 mg), **IX**(20 mg) and **X**(15 mg) were obtained from 500g of the dried leaves of *Scutellaria baicalensis* GEORGI, cultivated in the botanical garden of Hokuriku University for two years.

I ((2*S*)-5,7,8,4′-Tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside)——Pale yellow needles (MeOH/H_2O) mp 208°C. (dec.). $[\alpha]_D^{15}$ − 117.0° (*c* = 0.08, MeOH). *Anal.* Calcd for $C_{21}H_{20}O_{12}$: C, 54:31; H, 4.34. Found: C 54.42 H, 4.27. Mg-HCl (+). *Rf*: 0.07 (TLC-1), 0.51 (TLC-2). UV λ_{max}^{MeOH} nm (log ε): 244 sh(4.02), 285 (4.08), 365 (3.57); $\lambda_{max}^{MeOH-NaOMe}$ nm (log ε): 246 (4.12), 290 (3.92), 390 (4.10); $\lambda_{max}^{MeOH-AlCl_3}$ nm (log ε): 256 sh (3.80), 314 (4.28), 425 (3.64); $\lambda_{max}^{MeOH-AlCl_3-HCl}$ nm (log ε): 255 sh (3.89), 312 (4.26), 420 (3.63); $\lambda_{max}^{MeOH-NaOAc}$ nm (log ε): 306 (4.22), 317 sh (4.23), 344 (4.27); $\lambda_{max}^{MeOH-NaOAc-H_3BO_3}$ nm (log ε): 247 sh (4.15), 266 (3.64), 285 (4.16). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1731 (COOH), 1650 (conjugated CO), 1610 (arom. C = C). ^{1}H-NMR: 2.71 (1H, brd, *J* = 16.9 Hz, *cis* 3-H), ca. 3.40 (m, *trans* 3-H), 5.50 (1H, brd, *J* = 10.0 Hz, 2-H), 3.3–4.1 (m, sugar moiety), 5.16 (1H, brs, anomeric H of glucuronic acid unit), 6.81 (2H, d, *J* = 8.0 Hz, 3′, 5′-H), 7.35 (2H, d, *J* = 8.0 Hz, 2′, 6′-H), 6.29 (1H, s, 6-H), 11.70 (1H, s, 5-OH), ^{13}C-NMR: 78.8 (C-2), 42.5 (C-3), 198.0 (C-4), 153.8 (C-5), 95.1 (C-6, $J_{(C-6)-(6-H)}$ = 164.8 Hz, $J_{(C-6)-(5-H)}$ = 6.0 Hz), 155.1 (C-7), 127.4 (C-8), 149.2 (C-9), 103.7 (C-10), 129.1 (C-1′), 128.5 (C-2′, 6′), 115.4 (C-3′, 5′), 158.0 (C-4′), 99.9 (C-1″, *J* = 161.8 Hz), 72.9 (C-2″), 75.2 (C-3″), 71.4 (C-4″), 75.4 (C-5″), 170.2 (C-6″). MS *m*/*z* (%): 288 ($C_{15}H_{12}O_6$, 100), 168 ($C_7H_4O_5$, 65). CD (*c* = 0.0001, MeOH) $[\theta]^{15}$ (nm): +1920 (311) (positive maximum), –45112 (284) (negative maximum).

Methanolysis of **I**: A solution of **I** (10 mg) in 10% HCl-MeOH (2 ml) was heated under reflux on a water bath for 3h. The reaction mixture was neutralized with Ag_2CO_3. The precipitate was filtered off and the filtrate was concentrated to give the residue. The residue was crystallized from MeOH/H_2O to give a mixture of two types of crystals, which was chromatographed on silica gel (10 mg) using benzene as an eluent to give pale yellow needles (benzene-AcOEt), mp 226°C (dec.) and pale yellow needles (benzene-AcOEt), mp 244°C (dec.). They were identified as carthamidin[5] and isocarthamidin,[5] respectively, by direct comparisons (TLC, UV, IR, ^{1}H- and ^{13}C-NMR, mixed fusion) with authentic specimens. The mother liquor of crystallization was shown to contain methyl glucuronopyranoside methyl ester [t_R 13′24″ (both *α* and *β*)] and the methyl glycoside of glucurono-6,3-lactone [t_R 6′05″ (*α*, trace), 6′48″ (*β*)] by GLC-1 (as trimethylsilylether derivatives).

Methylation of **I**: MeOH solution (10 ml) of **I** (25 mg) was treated with ethereal CH_2N_2 (3 ml) for a short time. After the removal of the solvent, the residue was chromatographed on silica gel (10 g) using $CHCl_3$–MeOH(10:1) as an eluent and recrystallized from MeOH to give **Ia** (yield 15 mg) as colorless needles, mp 196°C (dec.). $[\alpha]_D^{15}$ –81.8° (*c* = 0.03, MeOH). *Anal.* Calcd for $C_{25}H_{28}O_{12}$: C, 57.69; H, 5.42. Found: C, 57.74; H, 5.53. Mg-HCl (+). *Rf*: 0.61 (TLC-1), 0.70 (TLC-2). UV λ_{max}^{MeOH} nm (log ε): 275 (4.13), 329 (3.54). No change was observed in the spectrum when NaOMe, NaOAc or $AlCl_3$ was added to the solution. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 ($COOCH_3$), 1670 (conjugated CO), 1600 (arom. C = C). ^{1}H-NMR: 3.39 ($COOCH_3$), 3.70 (3H, s, 8-OCH_3), 3.82 (6H, s, 5,4′-OCH_3 × 2), 2.71 (1H, dd, *J* = 16.4, 3.0 Hz, *cis* 3-H), 3.14 (1H, dd, *J* = 16.4,11.6 Hz, *trans* 3-H), 5.56 (1H, dd, *J* = 11.6, 3.0 Hz, 2-H), 3.4–4.2 (m, sugar moiety), 5.37 (1H, brs, anomeric H of glucuronic acid unit), 7.04 (2H, d, *J* = 9.0 Hz, 3′, 5′-H), 7.51 (2H, d, *J* = 9.0 Hz, 2′, 6′-H), 6.48 (1H, s, 6-H). ^{13}C- NMR: 78.2 (C-2), 44.6 (C-3), 188.5 (C-4), 156.7 (C-5), 93.2 (C-6), 156.3 (C-7), 131.3 (C-8), 155.7 (C-9), 107.0 (C-10), 131.1 (C-1′), 128.1 (C-2′, 6′), 114.1 (C-3′, 5′), 159.5 (C-4′), 99.8 (C-1″), 72.8 (C-2″), 75.2 (C-3″), 71.2 (C-4″), 75.8 (C-5″), 169.2 (C-6″), 52.0 (-$COOCH_3$), 55.2 (C-4′-OCH_3), 56.0 (C-5-OCH_3), 60.5 (C-8-OCH_3). EI-MS *m*/*z* (%): 134 ($C_9H_{10}O_1$, 20), 196 ($C_9H_8O_5$, 100), 330 ($C_{18}H_{18}O_6$, 85). FAB-MS *m*/*z* (%): 197 ($C_9H_8O_5$ + 1, 62), 331 ($C_{18}H_{18}O_6$, + 1,100), 521 (M^+ + 1, 6). CD (*c* = 0.0001, MeOH) $[\theta]^{15}$ (nm): +10947(340) (positive maximum), −18246 (285) (negative maximum).

Reduction of **I** a followed by hydrolysis: $NaBH_4$(5 mg) was added to a solution of **I** a (10 mg) in MeOH (5 ml) under cooling in an ice-bath, which was left for 30 min with stirring. After neutralization with dil. AcOH, the reaction mixture was extracted with AcOEt. The AcOEt-soluble portion was washed with water, passed through a silica gel column and evaporated to dryness in *vacuo*. The residue was hydrolyzed with 2N HCl(2 ml) under reflux for 2 h. The reaction mixture was neutralized with Ag_2CO_3 and the precipitate was filtered off. The filtrate was passed through Sephadex LH-20 with MeOH to give a syrup, which was shown to contain D-glucose by GLC-2 [sugars were converted to the TMS-ether of 1-(L-*α*-methylbenzylamino)-1-deoxyalditol (TMS-MBA-alditol) according to the Oshima's method],[7] t_R 25′ 00″ (TMS-MBA-D-glucitol, t_R 25′ 00″; TMS-MBA-L-glucitol, t_R 24′ 52″).

II ((2*S*)-5,6,7,4′-Tetrahydroxyflavanone 7-*O*-*β*-D-glucuronopyranoside)——Pale yellow needles (MeOH/H_2O), mp 201°C. (dec.). $[\alpha]_D^{15}$ —98.0° (*c* = 0.08, MeOH). *Anal.* Calcd for $C_{21}H_{20}O_{12}$: C, 54.31; H, 4.34. Found: C, 54.27; H, 4.27. Mg-HCl (+). *Rf*: 0.07 (TLC-1), 0.55 (TLC-2). UV λ_{max}^{MeOH} nm (log ε): 248 sh (4.08), 286 (4.13), 362 (3.60); $\lambda_{max}^{MeOH-NaOMe}$ nm (log ε): 246 (4.17), 288 (3.96), 388 (4.15); $\lambda_{max}^{MeOH-AlCl_3}$ nm (log ε): 255 sh (3.85), 314 (4.32), 423 (3.67); $\lambda_{max}^{MeOH-AlCl_3-HCl}$ nm (log ε): 255 sh (3.93), 313 (4.29), 414 (3.66); $\lambda_{max}^{MeOH-NaOAc}$ nm (log ε): 297 (4.98), 344 (4.11); $\lambda_{max}^{MeOH-NaOAc-H_3BO_3}$ nm (log ε): 247 sh (4.19), 285 (4.21), 366 (3.64). IR ν_{max}^{KBr} cm^{-1}: 3376 (OH), 1737 (COOH), 1662 (conjugated CO), 1622, 1598 (arom. C = C). ^{1}H-NMR: 2.71 (1H, brd, *J* = 16.9 Hz, *cis* 3-H), ca. 3.40 (m, *trans*

3-H), 5.50 (1H, brd, J = 10.0 Hz, 2-H), 3.3–4.1 (m, sugar moiety), 5.16 (1H, brs, anomeric H of glucuronic acid unit), 6.81 (2H, d, J = 8.0 Hz, 3′, 5′-H), 7.35 (2H, d, J = 8.0 Hz, 2′, 6′-H), 6.36 (1H, s, 8-H), 11.85 (1H, s, 5-OH). ^{13}C-NMR (*; may be reversed): 78.8 (C-2), 42.5 (C-3), 198.3 (C-4), 153.2 (C-5*), 128.1 (C-6), 149.7 (C-7*), 94.2 (C-8), 154.8 (C-9*), 103.6 (C-10), 129.1 (C-1′), 128.5 (C-2′, 6′), 115.3 (C-3′, 5′), 157.9 (C-4′), 99.9 (C-1″, J = 161.8 Hz), 72.9 (C-2″), 75.2 (C-3″), 71.4 (C-4″), 75.4 (C-5″), 170.2 (C-6″). MS m/z (%): 288 ($C_{15}H_{12}O_6$, 100), 168 ($C_7H_4O_5$, 60). CD (c = 0.0001, MeOH) $[\theta]^{15}$ (nm): +1853 (335) (positive maximum), −27791 (284) (negative maximum).

Methanolysis of **II**: **II** was methanolyzed and worked up in the same way as that described for **I**, to give carthamidin[5], isocarthamidin[5] (confirmed by TLC, UV, IR, ^{1}H- and ^{13}C-NMR, mixed fusion), methyl glucuronopyranoside methyl ester and methyl glycoside of glucurono-6,3-lactone (GLC-1).

Methylation of **II**: **II** was methylated in the same manner as that described for **I** to give **IIa** as colorless needles, mp (206°C (dec.). $[\alpha]_D^{15}$ −83.3° (c = 0.03, MeOH). *Anal.* Calcd for $C_{25}H_{28}O_{12}$ C, 57.69; H, 5.42. Found: C, 57.77; H, 5.51. Mg-HCl (+). *Rf*: 0.62 (TLC-1), 0.77 (TLC-2). UV λ_{max}^{MeOH} nm (log ε): 275 (4.13), 329 (3.54). No change was produced in the UV spectrum by the addition of NaOMe, NaOAc or $AlCl_3$.IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 ($COOCH_3$), 1670 (conjugated CO), 1600 (arom. C = C). ^{1}H-NMR: 3.39 ($COOCH_3$), 3.72 (3H, s, 6-OCH_3), 3.77 (6H, s, 5,4′-OCH_3 × 2), 2.59 (1H, brd, J = 16.9 Hz, *cis* 3-H), 3.16 (1H, brt, J = 14.0 Hz, *trans* 3-H), 5.53 (1H, brd J = 13.7 Hz, 2-H), 3.4–4.2 (m, sugar moiety), 5.30 (1H, brs, anomeric H of glucuronic acid unit), 6.98 (2H, d, J = 8.0 Hz, 3′, 5′-H), 7.46 (2H, d, J = 8.0 Hz, 2′, 6′-H), 6.67 (1H, s, 8-H). ^{13}C-NMR(*; may be reversed): 78.5 (C-2), 44.7 (C-3), 189.1 (C-4), 156.5 (C-5*), 137.4 (C-6), 159.1 (C-7*), 99.2 (C-8), 154.0 (C-9*), 110.0 (C-10), 130.9 (C-1′), 128.5 (C-2′, 6′), 114.1 (C-3′, 5′), 159.7 (C-4′), 99.2 (C-1″), 73.0 (C-2″), 75.2 (C-3″), 71.4 (C-4″), 75.7 (C-5″), 169.4 (C-6″), 52.1 (-$COO\underline{C}H_3$), 55.3 (C-4′-$O\underline{C}H_3$), 61.2, 61.5 (C-5, 6-$O\underline{C}H_3$ × 2).

EI-MS m/z (%): 134 ($C_9H_{10}O_1$, 45), 196 ($C_9H_8O_5$, 100), 330 ($C_{18}H_{18}O_6$, 85). FAB-MS m/z (%): 197 ($C_9H_8O_5$ + 1, 100), 331 ($C_{18}H_{18}O_6$, + 1, 90), 521 (M^+ + 1, 8). CD (c = 0.0001, MeOH) $[\theta]^{15}$ (nm): + 11545(310) (positive maximum), −11545 (268) (negative maximum).

Reduction of **IIa** followed by hydrolysis: **II** was treated with $NaBH_4$ and then hydrolyzed with 2N HCl in the same way as that described for **Ia**, to give D-glucose.

Identification of III-X——**III** (mp 285°C), **IV** (mp 203°C), **V** (mp 350°C), **VI** (mp 190°C (dec.), **VII** (mp 345°C (dec.)), **VIII** (mp 300°C (dec.)), **IX** (mp 227°C (dec.)), **X** (mp 195°C (dec.)) were identified as chrysin,[11] wogonin,[1] apigenin,[12] salvigenin,[13] scutellarein,[14] isoscutellarein,[15] apigenin 7-*O*-glucuronide,[16] isoscutellarein 8-*O*-glucuronide[17] respectively, by direct comparisons with their respective authentic specimens (UV, IR, ^{1}H- and ^{13}C-NMR).

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