NEW FLAVONOID GLYCOSIDES FROM *SCUTELLARIA AMOENA*

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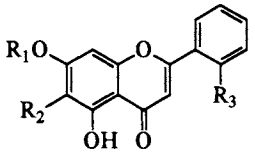
Key Word Index -- Labiatae; *Scutellaria amoena*; flavonoids.

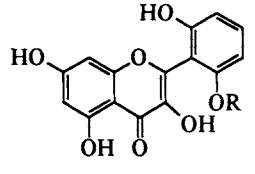
Abstract -- Three new flavonoid glycosides, 5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide methyl ester, 5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucoside and 5,7,2',6'-tetrahyroxyflavonol 2'-O-β-D-glucoside, along with eleven known flavonoids and two known phenyl ethanoid glycosides, were isolated from the roots of *Scutellaria amoena*. Their structures were determined by spectral and chemical methods.

Introduction

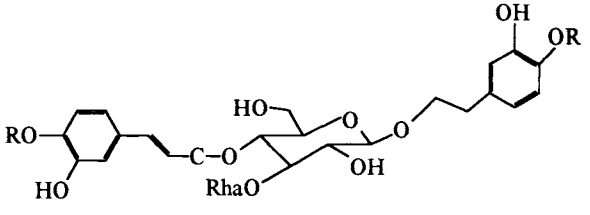
Scutellaria amoena C. H. Wright as a labiataeous herb is natived in the southwest of China. Its roots as one of the original material of "Huang-qin" has been used for the treatment of suppurative dermatitis, diarrhea and inflammatory diseases in traditional chinese medicine. Some chemical studies have been reported on this plant and several flavonoids were obtained[1-3]. As a part of our research work on important traditional medicinal herbs in Yunnan, we re-investigated the chemical constitutents of this plant, and sixteen phenolic compounds were obtained. Among them, compounds **1-3** are new flavonoid glycosides.



	R_1	R_2	R_3
1	glcUA-6-Me	OMe	OH
2	glc	OMe	OH
4	glcUA	OMe	OH
5	glcUA	OMe	H
6	glcU-6-Me	OMe	H
7	glcUA	H	H
8	glc	OH	H
9	glcUA	OH	H
10	H	OH	H
11	H	OMe	H
12	H	H	H
13	H	OMe	OH



	R
3	glc
14	H



	R
15	Me
16	H

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Table 1. ^{13}C NMR data of compound **1-7**

	1	2	3	4	5	6	7
2	161.96	161.85	146.63	161.74	163.54	163.73	163.56
3	108.77	108.75	130.03	108.57	104.95	104.95	105.37
4	182.39	182.39	177.20	182.32	182.32	182.39	181.94
5	152.25	152.25	161.01	152.25	152.31	152.53	161.50
6	132.46	132.46	97.60	132.62	132.78	132.66	99.65
7	155.98	156.52	163.42	156.40	156.64	156.09	163.15
8	93.89	94.30	93.35	94.18	94.24	94.05	94.77
9	152.43	152.25	158.13	152.25	152.31	152.19	157.02
10	105.87	105.69	103.95	105.76	106.50	106.12	105.37
1'	117.16	117.11	109.32	116.69	130.61	130.58	130.51
2'	156.67	156.67	156.48	157.40	126.34	126.35	126.35
3'	117.05	117.04	110.48	117.30	129.10	129.05	129.02
4'	132.88	132.84	131.16	132.62	132.05	132.07	132.00
5'	119.33	119.36	104.71	118.82	129.10	129.05	129.02
6'	128.43	128.43	157.20	128.11	126.34	126.35	126.35
Sugar-1	99.41	100.15	100.46	99.87	99.98	99.46	99.65
2	72.77	73.15	73.30	73.02	73.02	72.77	72.88
3	75.20	76.66	76.63	74.40	74.49	75.25	74.29
4	71.18	69.60	69.74	71.81	71.50	71.21	71.74
5	75.60	77.18	77.00	76.45	76.57	75.61	76.25
6	168.98	60.62	60.78	172.89	172.66	169.00	172.15
OMe	60.21	60.20		60.15	60.23	60.23	
OMe	51.81					51.85	

Table 2. ^{13}C NMR data of compound **8-14**

	8	9	10	11	12	13	14
2	163.61	163.54	162.85	163.15	163.00	161.38	146.62
3	104.76	104.65	104.40	104.57	104.96	108.53	130.95
4	182.61	182.50	182.01	182.13	181.56	182.27	177.21
5	146.61	146.71	146.95	152.45	157.32	152.62	160.82
6	130.71	130.79	130.91	131.43	104.96	131.29	97.65
7	149.30	149.17	149.79	157.44	164.22	157.39	163.37
8	94.38	94.17	93.93	99.30	93.77	94.19	93.19
9	151.68	151.57	153.55	152.63	161.44	152.62	157.09
10	106.16	106.12	104.23	104.29	103.94	104.12	103.64
1'	130.88	130.79	129.25	130.68	130.72	119.47	106.66
2'	126.43	126.33	126.19	126.26	125.91	156.64	157.23
3'	129.21	129.11	128.99	129.11	128.67	117.03	106.66
4'	132.11	131.96	131.68	131.84	130.72	132.76	130.95
5'	129.21	129.11	128.99	129.11	128.67	117.31	106.66
6'	126.43	126.33	126.19	126.26	125.91	128.50	157.23
Sugar-1	101.07	100.59					
2	73.25	72.91					
3	75.98	74.79					
4	69.84	71.81					
5	77.39	75.64					
6	60.78	171.74					
OMe						59.93	

Results and Discussion

MeOH extract of the roots of *S. amoena* was repeatedly chromatographed on Silica gel , Sephadex LH-20, MCI gel CHP 20P, RP-18 and TSK gel columns to yield sixteen compounds. Compounds **4-16** were identified by comparing their spectral data with those of reported values and authentic sample as eleven known flavonoids and two known phenyl ethanoid glycosides, i.e. 5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide (**4**)[3], oroxylin A 7-O-β-D-glucuronide(**5**)[4] , oroxylin A 7-O-β-D-glucuronide methyl ester (**6**)[5], chrysin 7-O-β-D-glucuronide(**7**)[6], baicalein 7-O-β-D-glucoside (**8**)[7], baicalin (**9**)[4,6], baicalein (**10**)[4], oroxylin A (**11**)[2], chrysin (**12**)[6], 5,7,2'-trihydroxy-6-methoxyflavone (**13**)[3], 5,7,2',6'-tetrahydroxyflavonol (**14**)[3], 3-hydroxy-4-methoxyphenyl ethyl 1-O-α-L-rhamnosyl-(1→3)-β-D-(4-feruloyl) glucoside(**15**)[8], acteoside(**16**).

Compound **1** was obtained as pale yellow powder. Its molecular formula was analysed as $C_{23}H_{22}O_{12}$ from its negative FAB mass spectrum, in which there appeared a quasi-molecular ion peak at *m/z* 489[M-H]$^-$, in conjunction with its ^{13}C NMR spectrum. Combining with its chemical shifts of ^1H and ^{13}C NMR spectra, it could be considered as a flavone skeleton. Its ^1H NMR spectrum showed that there were six aromatic protons at δ 7.88(d, J=8.0Hz), 7.42(t, J=7.6Hz) and 7.00-7.10 (4H, m), two hydroxyl proton at δ 12.88 and 10.88, and two methyl groups at δ 3.75 (3H, s) and 3.65 (3H, s). The ^1H and ^{13}C NMR signals of **1** due to sugar moiety indicated the presence of a β-D-glucuronopyranosyl unit [δ_C 168.98 (COO), 99.41(anomeric C) and δ_H 5.51(d, J=5.6Hz, anomeric H)], and the signals for the aglycone were very similar to those of 2',5,7-trihydroxy-6-methoxyflavone[3], but **1** has one more methoxy group at δ_C 51.81 and δ_H 3.65(s). The HMBC spectrum of **1** showed that there are correlation signals between the protons of methoxyl (δ 3.75) and C-6 (δ 132.46), between the protons of methyl (δ 3.65) and the carbonyl carbon (δ 168.98) of glucuronide, and between anometic proton (δ 5.51) and C-7 (δ 155.98). This indicated that the carboxyl group of β-D-glucuronopyranosyl unit which was linked at C-7 position of aglycone was esterified by the methyl group at δ 3.65, and the another methyl group at δ 3.75 was attached at C-6 position of aglycone, as a methoxyl form. Therefore, compound **1** was assigned as 5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide methyl ester.

Compound **2** was obtained as pale yellow powder. Its molecular formula was analysed by negative FAB mass spectrum, in which there appeared a quasi-molecular ion peak at *m/z* 461[M-H]$^-$. Comparing its ^1H and ^{13}C NMR spectra with those of **1** indicated that both compounds were very similar, but instead of a β-D-glucuronopyranosyl methyl ester attached at C-7 position in **1**, **2** has a β-D-glucopyranosyl unit attached at C-7 position of aglycone. This assignment was also comletely supported by the COLOC spectrum of **2** that there are correlaiton signals between the anomeric proton of β-D-glucopyranosyl unit at δ 5.12 and C-7 (δ 156.32) position of aglycone and between the methoxyl group at δ 3.77 and C-6 (δ 132.46) position of aglycon. Thus, **2** was determined as 5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucoside.

Compound **3** was obtained as brown powder. Its molecular formula was analysed as $C_{21}H_{20}O_{12}$ from its negative FAB mass spectrum, in which there appeared a quasi-molecular ion peak at *m/z* 463[M-H]$^-$, in conjunction with its ^{13}C NMR spectrum. Combining with its chemical shifts of ^1H and ^{13}C NMR spectra, it could be considered as a flavonoid compound. Its ^1H NMR spectrum showed a hydroxyl proton signal at δ 12.79 (C_5-OH), and five aromatic protons at δ 7.21(t, J=8.4Hz), 6.63(d, J=8.4Hz), 6.54(d, J=8.4Hz), 6.28(d, J=1.2Hz) and 6.14(d, J=1.2Hz). The latter two aromatic proton signals which were coupled *via* a ^4J coupling should be assigned as H-6 and H-8. The former three aromatic proton signals exhibited as an ABC-type coupling system, which indicated that they were at B-ring. The ^1H and ^{13}C NMR

signals of **3** due to sugar moiety indicated the presence of a β-glucopyranosyl unit [δ_C 100.46 (anomeric C) and δ_H 4.86(d, J=7.6Hz, anomeric H)]. Acid hydrolysis of **3** yielded **14** as its aglycone, which is identified with authentic sample. Thus, **3** should be a glucoside of **14**. The β-D-glucopyranosyl group should be attached at C-2' position of B-ring in **3**, according to the glycosylation effect in B-ring, which the chemical shift of C-1', 3' were shifted to downfield from 106.66 in **14** to 109.32 and 110.48 in **3**, C-5' was shifted to upfield from 106.66 in **14** to 104.71 in **3**. This elucidation was also supported by the results of comparing the ^1H and ^{13}C NMR signals of **3** with those of 5,7,2',6'-tetrahydroxy-flavone 2'-O-β-D-glycopyranoside[9] that both compound had a same B-ring substituence. Therefore, compound **3** was determined as 5,7,2',6'-tetrahydroxyflavanol 2'-O-β-D-glucoside.

Experimental

Genera. Mps were determined on a Kofler hot stage apparatus and are corrected by authentic sample of caffeine(237 ^{0}C). UV and IR were recorded on Shimadzu UV-210A and IR-450 spectrophotometers, in MeOH and KBr pellets, respectively. ^1H, ^{13}C and COLOC NMR spectras were measured on a Bruker AM-400 NMR spectrometer and HMBC NMR spectras on a Bruker AM-500 NMR spectrometer in DMSO-d_6 using TMS as internal standards. FAB and EI Mass spectra were obtained using a VG Autospec mass spectrometer. CC was carried out on silica gel (200-300 mesh), Sephadex LH-20, MCI-gel CHP 20P and TSK-gel Toyopearl HW-40F, Lichroprep RP_8 (40-63 μ, merck). TLC was conducted on precoated silica gel plates. Spots were detected by spraying with $FeCl_3$.

Extraction and isolation. Dried roots (18.0 kg) of *Scutellaria amoena* were extracted with MeOH under reflux. After removal of the solvent in vacuo, the residue was suspended in H_2O and then successively extracted with petroleum ether, $CHCl_3$, EtOAc and n-BuOH. After concentrated, it gave petroleum ether extract (49 g), $CHCl_3$ extract (64 g), EtOAc extract (54.5 g), n-BuOH extract (328 g) and H_2O layer fraction (600 g). $CHCl_3$ extract (40g) was chromatographed on silica gel column, eluting with different proportional solution of $CHCl_3$-MeOH, to give **11**(80mg), **12** (200mg), **13**(25mg). The EtOAc extract (54.5g) was repeatedly chromatographed on silica gel column with different proportional solution system of $CHCl_3$-MeOH, Sephadex LH-20 and MCI-gel CHP 20P column with different concentration of aq. MeOH to afford **3**(50mg), **4**(100mg), **10**(85mg) and **14** (40mg). The n-BuOH extract (50g) was repeatedly chromatographed on MCI-gel CHP 20P, Sephadex LH-20 and reverse phase column of RP_8, eluting with different proportional solution system of MeOH-H_2O to give **2** (100mg), **7** (25mg, **9** (40mg), **15** (45mg) and **16** (50mg),. The water layer fraction (600g) was chromatographed on macroporous resin D101, eluting with H_2O and MeOH. After concentrated, it gave MeOH fraction (150g). The MeOH fraction (18g) was chromatographed on MCI-gel CHP 20P, TSK gel and reverse phase column of RP_8, eluting with different proportional solution system of MeOH-H_2O to give **1** (200mg), **5** (150mg), **6** (40mg), **8** (40mg).

5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide methyl ester (**1**). Pale Yellow powder. mp: 279-281 ^{0}C; $[\alpha]_D^{25.8}$ -85.18^0 (pyridine; c 0.0026). UVλ_{max}nm (MeOH): 304.5, 274.5, 245.5. IR ν_{max} cm^{-1}: 3500-3100, 2900, 1645, 1600, 1450, 1375, 1275, 760. FAB-MS: *m/z* 489[M-H]$^-$, 299[M-glcUAMe]$^-$. ^1H NMR(DMSO-d_6): δ 12.88(C5-OH), 10.88, 7.88(d, J=8.0Hz, H-3'), 7.42(t, J=7.6Hz, H-4'), 7.00-7.10(m, H-5',6', 3, 8), 5.51(d, J=5.6Hz, anomeric H), 3.75(s, OMe), 3.65(s, OMe). ^{13}C NMR: see Table 1.

5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucoside (**2**). Yellow powder.$[\alpha]_D^{26.0}$ -12.33^0 (pyridine; c 0.00223). FAB-MS: *m/z* 461[M-H]$^-$ (100). ^1H NMR(DMSO-d_6): δ 12.86 (C5-OH), 7.88(d, J=7.6Hz, H-3'), 7.41(m, H-4'), 7.11-6.98(m, H-3, 8, 3', 5'), 5.12(d, J=7.2Hz, anomeric H) 3.77(s, OMe). ^{13}C NMR: see Table 1.

5,7,2',6'-tetrahydroxyflavanol 2'-O-β-D-glucoside (**3**). Brown powder. mp:199-201 ^{0}C; $[\alpha]_D^{25.9}$-79.68^0 (pyridine; c 0.00251). UVλ_{max}nm(MeOH): 297, 270, 239, 210.5. IR ν_{max} cm^{-1}: 3500-3100, 2900, 1725, 1600. FAB-MS: *m/z* 463 [M-H]$^-$(100). ^{1}H NMR (DMSO-d_6): δ 12.79(C5-OH), 7.21(t, J=8.4Hz, H-4'), 6.63(d, H- 5'), 6.54(d, J=8.4, H-3'), 6.28(d, J=1.2Hz, H-6), 6.14(d, J=1.2Hz, H-8), 4.86(d, J=7.6Hz, anomeric H). ^{13}C NMR: see Table 1.

Acid hydrolysis of **3**. A solution of **3** (3 mg) in 2N HCl/H_2O (5 ml) was heated at 98 ^{0}C for 40 minutes. From the reaction mixture, its aglycone was identified as 2',6',5,7-tetrahydroxyflavanol by comparing with an authentic sample on TLC (silica gel plates; solvent system: benzene-ethyl formate-formic acid (2:7:1); detected by spraying with $FeCl_3$. Rf = 0.6).

5,7,2'-trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide (**4**). Pale Yellow crystals. FAB-MS: *m/z* 475[M-H]$^-$ (100). UVλ_{max}nm(MeOH): 335, 271, 212. IR ν_{max} cm^{-1}: 3400, 1650, 1600, 1440, 1340, 1280, 1240, 1180, 1080. ^{1}H NMR(DMSO-d_6):12.85(C5-OH), 7.77(d, J=8.0Hz, H-3'), 7.31(t, J=8.0Hz, H-4'), 7.10(s, H-3), 7.05(d, J=8.0Hz, H-6'), 6.95(s, H-8), 6.87(t, J=7.8Hz, H-5'), 5.17(d, J=6.4Hz, anomeric H), 3.75(s, OMe). ^{13}C NMR see Table 1.

oroxylin A-7-O-β-D-glucuronide (**5**). Yellow powder. FAB-MS: *m/z* 459[M-H]$^-$(100). UVλ_{max}nm(MeOH): 287, 273, 245.5, 214, 204. IR ν_{max} cm^{-1}: 3500-3200, 1650, 1600, 1450, 1400, 1350, 1290. ^{1}H NMR(DMSO-d_6): 8.06(d, J=7.2Hz, H-2', 6'), 7.54-7.62(m, H-3', 4', 5'), 7.04(s, H-3), 7.02(s, H-8), 5.17(d, J=6.4Hz, anomeric), 3.75(OMe). ^{13}C NMR see Table 1.

oroxylin A-7-O-β-D-glucuronide methyl ester (**6**). Yellow powder. FAB-MS: *m/z* 473[M-H]$^-$(100). UVλ_{max}nm(MeOH): 213.5, 242, 272.5, 309. IR ν_{max} cm^{-1}: 3380, 1730, 1655, 1610, 1580, 1075. ^{1}H NMR(DMSO-d_6): 12.82(C5-OH), 8.07(d, J=7.2Hz, H-2', 6'), 7.56-7.62(m, H-3', 4', 5'), 7.12(s, H-3), 7.04(s, H-8), 5.53(d, J=5.6Hz, anomeric H), 3.76(s, OMe), 3.65(OMe).

chrysin 7-O-β-D-glucuronide (**7**). Yellow powder. FAB-MS: *m/z* 429[M-H]$^-$ (100). IR ν_{max} cm^{-1}: 3500-3100, 1650, 1600, 1475, 1450, 1400, 1175, 1050. ^{1}H NMR(DMSO-d_6): 8.08(d, J=8.0Hz, H-2', 6'), 7.6-7.50(m, H-3', 4', 5'), 7.04(s, H-3), 6.67(s, H-6), 6.46(s, H-8), 5.11(d, J=7.2Hz, anomeric H). ^{13}C NMR see Table 1.

Baicalein 7-O-β-D-glucoside (**8**). Yellow powder. FAB-MS: *m/z* 431[M-H]$^-$ (100). UVλ_{max}nm(MeOH): 314.5, 277.5, 242.5, 215. IR ν_{max} cm^{-1}: 3500-3100, 1650, 1600, 1475, 1445, 1400, 1350, 1300, 1230, 1175. ^{1}H NMR(DMSO-d_6): 8.04(d, J=8.0Hz, H-2', 6'), 7.55-7.60(m, H-3', 4', 5'), 7.04(s, H-3), 6.96(s, H-8). ^{13}C NMR see Table 2.

baicalin (**9**). Yellow and green powder. FAB-MS: *m/z* 445[M-H]$^-$ (100). UVλ_{max}nm (MeOH): 312.5, 278.5, 243.5, 215, 203. IR ν_{max} cm^{-1}: 3500-3100, 1700, 1600, 1475, 1350, 1075. ^{1}H NMR (DMSO-d_6): 8.04(d, J=8.0Hz, H-2', 6'), 7.59-7.50(m, H-3', 4', 5'), 7.04(s, H-3), 6.97(s, H-8). ^{13}C NMR see Table 2.

baicalein (**10**). Brown and green powder. EI-MS: *m/z* 270[M]$^+$(100). UVλ_{max}nm (MeOH): 324.5, 270, 215, 204. IR ν_{max} cm^{-1}: 3360, 1640,1605, 1585, 1525, 1300, 1220. ^{1}H NMR (DMSO-d_6): 12.65(C5-OH), 8.03(d, J=7.8Hz, H-2', 6'), 7.570-7.52(m, H-3', 4', 5'), 6.90(s, H-3), 6.62(s, H-8). ^{13}C NMR see Table 2.

oroxylin A (**11**). Yellow powder. EI-MS: *m/z* 284[M]$^+$ (100). ^{1}H NMR(DMSO-d_6): 12.91(C5-OH), 8.04(d, J=7.2Hz, H-2', 6'), 7.60-5.52(m, H-3', 4', 5'), 6.94(s, H-3), 6.61(s, H-8), 3.71(s, OMe). ^{13}C NMR see Table 2.

chrysin (**12**). Yellow powder. EI-MS: *m/z* 254[M]$^+$ (100). ^{1}H NMR(DMSO-d_6): 13.57(C5-OH), 7.93(d, J=7.2Hz, H-2', 6'), 7.45(m, H-3', 4', 5'), 7.19(s, H-3), 6.82(d, J=2.4Hz, H-6), 6.74(d, J=2.4Hz, H-8). ^{13}C NMR see Table 2.

5,7,2'-trihydroxy-6-methoxyflavone (**13**). Yellow powder. EI-MS: *m/z* 300[M]$^+$ (100). UVλ_{max}nm(MeOH): 337, 270.5, 212. IR ν_{max} cm^{-1}: 3450, 3100-2975, 1650, 1600, 1550, 1425,

1350, 1235, 1075. ^{1}H NMR(DMSO-d_6): 12.99(C5-OH), 7.85(d, J=7.6Hz, H-3'), 7.38(m, H-4'), 7.04(m, H-3, 6'), 6.97(m, H-5'), 6.57(s, H-8), 3.69(s, OMe). ^{13}C NMR see Table 2.

5,7,2',6'-tetrahydroxyflavanol (**14**). Brown powder. FAB-MS: *m/z* 301[M-H]$^-$ (100). ^{1}H NMR(DMSO-d_6): 12.64(C5-OH), 7.06(t, J=8.0Hz, H-4'), 6.34(m, H-3', 5'), 6.27(s, H-6), 6.16(s, H-8). ^{13}C NMR see Table 2.

3-hydroxy-4-methoxyphenyl-ethyl 1-O-α-L-rhamnosyl-(1-3)-β-D-(4-feruloyl) glucoside (**15**). Yellow powder. FAB-MS: *m/z* 651[M-H]$^-$ (100). UVλ_{max}nm(MeOH): 328.5, 295, 285.5, 213, 204. IR ν_{max} cm^{-1}: 3500-3000, 1600. ^{13}C NMR: 131.11(C-1), 112.45(C-2), 144.98(C-3), 146.06(C-4), 116.27(C-5), 119.35(C-6), 69.97(C-α), 34.90(C-β), 125.52 (C-1'), 111.22(C-2'), 147.92(C-3'), 149.48(C-4'), 115.55(C-5'), 123.02(C-6'), 146.29 (C-α'), 114.08(C-β'), 55.75(OMe), 55.65(OMe), glu.: 101.12(C-1), 74.54(C-2), 79.09 (C-3), 69.17(C-4), 74.54(C-5), 60.74(C-6), rha.: 102.30(C-1), 7.49(C-1), 70.40(C-2), 71.70(C-3), 68.69(C-5), 17.98(C-6). ^{1}H NMR(DMSO-d_6): 7.52(d, J=15.84Hz, H-Ar-C=CH), 6.62-7.30(m, Ar-H), 6.43(d, J=15.84Hz, Ar-CH=C), 3.79(s, OMe), 3.76(OMe), 0.96(d, J=6.0Hz, Me).

acteoside (**16**). Pale yellow powder. FAB- MS: *m/z* 623[M-H]$^-$ (100). UVλ_{max}nm (MeOH): 333, 296.5, 289, 242, 219. IR ν_{max} cm^{-1}: 3500-3000, 1975, 1680, 1600, 1500.

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