Novel Cyanoglucosides from the Leaves of *Hydrangea macrophylla*

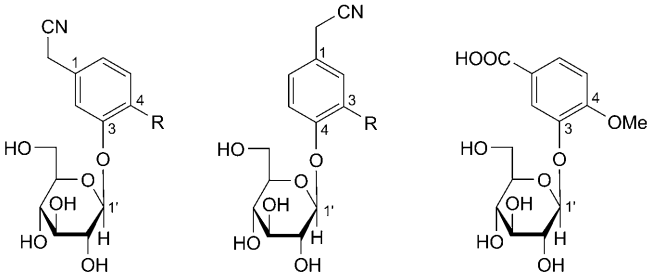
by **Zhi-Bin Wang**, **Hui-Yuan Gao**, **Chun-Juan Yang**, **Zhi Sun**, and **Li-Jun Wu***

School of Traditional Chinese Materia Medica 49#, Shenyang Pharmaceutical University, Wenhua Road No. 103, Shenhe District, Shenyang 110016, P. R. China
(phone: +86-24-23986481; e-mail: wulijun111@hotmail.com)

Four non-cyanogenic cyanoglucosides including hydranitrilosides A_1, A_2, B_1, and B_2 (**1**–**4**, resp.), together with a new phenolic glucoside, 3-hydroxy-4-methoxybenzoic acid 3-*O*-*β*-D-glucopyranoside (**5**), were isolated from the leaves of *Hydrangea macrophylla*. Their structures were determined on the basis of chemical and spectral evidence.

Introduction. – *Hydrangea macrophylla* (THUNB.) SER, a member of Saxifragaceae family, is widely cultivated in many countries including China and Japan. *Hydrangea dulcis folium*, which is the fermented and dried leaves of *H. macrophylla*, is listed in the Japanese Pharmacopoeia XV and extensively used in confectionery, drinks, and foods as a sweetener [1]. Dihydroisocoumarins [2][3] and secoiridoid glycosides [4][5] isolated from this plant have showed many pharmacological effects, such as antidiabetic [6], antiallergic, and antimicrobial activities [7].

Here, we report the isolation and structure elucidation of three new non-cyanogenic cyanoglucosides, hydranitriloside A_1 (**1**), hydranitriloside A_2 (**2**), and hydranitriloside B_1 (**3**), a related derivative isolated for the first time as a new natural product, hydrantriloside B_2 (**4**) [8], and a new phenolic glucoside, 3-hydroxy-4-methoxybenzoic acid 3-*O*-*β*-D-glucopyranoside (**5**) from the leaves of the plant.



1 R = OH
2 R = MeO

3 R = MeO
4 R = H

5

Results and Discussion. – Compound **1** was obtained as white amorphous powder and possessed a molecular formula $C_{14}H_{17}NO_7$, deduced from the HR-ESI-MS analysis ($[M+Na]^+$ at m/z 334.0901; $[M-H]^-$ at m/z 310.0929). The IR spectrum indicated the presence of OH (3380 cm^{-1}) and CN (2255 cm^{-1}) groups, and an aromatic ring (1608

© 2011 Verlag Helvetica Chimica Acta AG, Zürich

and 1518 cm^{-1}). The ^{1}H-NMR (*Table 1*) spectrum indicated the presence of a CH_2 group (δ(H) 3.75 (*s*)) bearing a CN group and an aromatic ring with an *ABX*-coupling system (δ(H) 7.17 (*d*, *J* = 2.0, 1 H), 6.82 (*d*, *J* = 8.2, 1 H), 6.89 (*dd*, *J* = 8.2, 2.0, 1 H)). The signal at δ(H) 4.76 (*d*, *J* = 7.6, 1 H) was assigned to an anomeric H-atom signal of the sugar unit. The acid hydrolysis of **1** with aqueous HCl (1M) yielded D-glucose, which was identified by HPLC analysis using an optical rotation detector [9]. The ^{13}C-NMR (*Table 2*) spectrum showed 14 C-atom signals including those of a cyano C-atom at δ(C) 120.0 and six aromatic C-atoms at δ(C) 148.2, 147.0, 124.3, 123.6, 118.8, and 117.6. As shown in the *Figure*, the DQF-COSY experiment on **1** indicated the presence of

Table 1. *^{1}H-NMR Data* (at 600 MHz, δ in ppm, *J* in Hz) *of Compounds* **1**–**4**

	1[a])	**2**[b])	**3**[a])	**4**[a])
H–C(2)	7.17 (*d*, *J* = 2.0)	7.56 (*d*, *J* = 2.0)	6.98 (*d*, *J* = 2.1)	7.28 (*d*, *J* = 8.5)
H–C(3)				7.11 (*d*, *J* = 8.5)
H–C(5)	6.82 (*d*, *J* = 8.2)	6.91 (*d*, *J* = 8.3)	7.16 (*d*, *J* = 8.3)	7.11 (*d*, *J* = 8.5)
H–C(6)	6.89 (*dd*, *J* = 8.2, 2.0)	7.00 (*dd*, *J* = 8.3, 2.0)	6.89 (*dd*, *J* = 8.3, 2.1)	7.28 (*d*, *J* = 8.5)
CH_2–C(1)	3.75 (*s*)	3.81 (*s*)	3.83 (*s*)	3.82 (*s*)
MeO		3.71 (*s*)	3.86 (*s*)	
H–C(1′)	4.76 (*d*, *J* = 7.6)	5.61 (*d*, *J* = 7.6)	4.90 (*d*, *J* = 7.6)	4.90 (*d*, *J* = 7.5)
H–C(2′)	3.48 (*dd*, *J* = 8.9, 7.6)	4.27–4.32 (*m*)	3.49 (*dd*, *J* = 8.9, 7.6)	3.46 (*dd*, *J* = 8.9, 7.5)
H–C(3′)	3.45 (*dd*, *J* = 8.9, 8.2)	4.27–4.32 (*m*)	3.45 (*dd*, *J* = 8.9, 9.7)	3.40–3.45 (*m*)
H–C(4′)	3.39–3.43 (*m*)	4.27–4.32 (*m*)	3.39–3.43 (*m*)	3.36–3.42 (*m*)
H–C(5′)	3.37–3.41 (*m*)	4.01–4.05 (*m*)	3.37–3.41 (*m*)	3.36–3.42 (*m*)
CH_2(6′)	3.90 (*dd*, *J* = 11.7, 2.0), 3.71 (*dd*, *J* = 11.7, 4.8)	4.49 (*dd*, *J* = 11.7, 2.0), 4.33 (*dd*, *J* = 11.7, 4.8)	3.88 (*dd*, *J* = 12.4, 1.9), 3.69 (*dd*, *J* = 12.4, 4.8)	3.90 (*dd*, *J* = 12.2, 2.0), 3.69 (*dd*, *J* = 12.2, 5.1)

[a]) Recorded in CD_3OD. [b]) Recorded in C_5D_5N.

Table 2. *^{13}C-NMR Data* (at 150 MHz, δ in ppm) *of Compounds* **1**–**4**

	1[a])	**2**[a])	**2**[b])	**3**[a])	**4**[a])
C(1)	124.3 (*s*)	125.0 (*s*)	123.9 (*s*)	126.9 (*s*)	126.0 (*s*)
C(2)	118.8 (*d*)	118.0 (*d*)	116.7 (*d*)	113.6 (*d*)	130.3 (*d*)
C(3)	147.0 (*s*)	148.2 (*s*)	148.2 (*s*)	151.2 (*s*)	118.4 (*d*)
C(4)	148.2 (*s*)	150.6 (*s*)	149.8 (*s*)	147.6 (*s*)	158.8 (*s*)
C(5)	117.6 (*d*)	114.0 (*d*)	113.5 (*d*)	118.3 (*d*)	118.4 (*d*)
C(6)	123.6 (*d*)	123.5 (*d*)	121.9 (*d*)	121.1 (*d*)	130.3 (*d*)
CH_2–C(1)	22.9 (*t*)	23.0 (*t*)	22.8 (*t*)	23.1 (*t*)	22.8 (*t*)
C(8)	120.0 (*s*)	119.9 (*s*)	119.1 (*s*)	119.8 (*s*)	119.9 (*s*)
MeO		56.8 (*q*)	56.2 (*q*)	56.8 (*q*)	
C(1′)	104.3 (*d*)	102.7 (*d*)	102.3 (*d*)	102.7 (*d*)	102.3 (*d*)
C(2′)	74.9 (*d*)	74.9 (*d*)	74.9 (*d*)	74.9 (*d*)	74.9 (*d*)
C(3′)	77.6 (*d*)	77.9 (*d*)	78.5 (*d*)	77.7 (*d*)	78.0 (*d*)
C(4′)	71.3 (*d*)	71.3 (*d*)	71.2 (*d*)	71.3 (*d*)	71.4 (*d*)
C(5′)	78.4 (*d*)	78.3 (*d*)	78.8 (*d*)	78.2 (*d*)	78.2 (*d*)
C(6′)	62.4 (*t*)	62.5 (*t*)	62.4 (*t*)	62.5 (*t*)	62.6 (*t*)

[a]) Recorded in CD_3OD. [b]) Recorded in C_5D_5N.

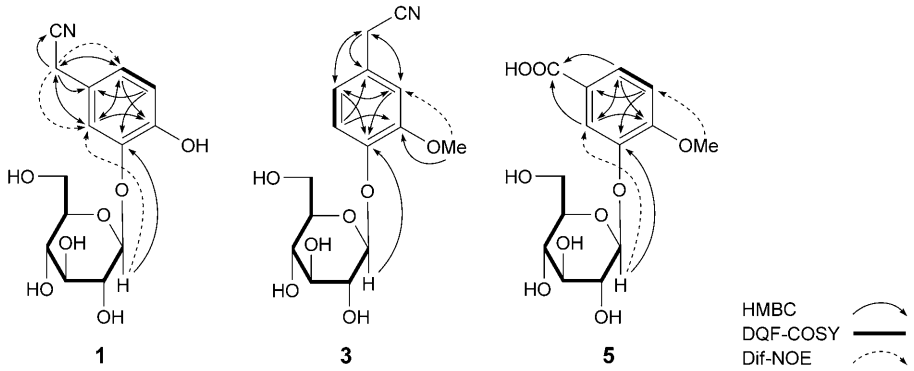


Figure. *Key HBMC, DQF-COSY, and Dif-NOE correlations of* **1**, **3**, *and* **5**

partial structures indicated in bold lines, and, in the HMBC experiment, long-range correlations were observed between the following H- and C-atoms: H–C(7) and C(1), C(2), C(6), and C(8); H–C(1′) and C(3). In addition, the position of glucose was confirmed by the observation of an NOE effect at δ(H) 7.17 (H–C(2)) upon irradiation of anomeric H-atom (δ(H) 4.76 (H–C(1′))). On the basis of the above analysis, the structure of hydranitriloside A_1 (**1**) was established as (3,4-dihydroxyphenyl)acetonitrile 3-*O*-β-D-glucopyranoside.

Compound **2** was obtained as white amorphous powder, and the molecular formula was determined as $C_{15}H_{19}NO_7$ on the basis of the HR-ESI-MS ($[M+Na]^+$ at *m*/*z* 348.1058). The IR spectrum indicated the presence of OH (3380 cm^{-1}) and CN (2255 cm^{-1}) groups, and an aromatic ring (1608 and 1518 cm^{-1}). In the ^{1}H-NMR spectrum, the signals of aromatic H-atoms overlapped when CD_3OD was used as solvent, and better resolution was achieved in C_5D_5N. The NMR data were very similar to those of compound **1**, with the exception of the presence of a MeO signal at δ(H) 3.71 in the ^{1}H-NMR (*Table 1*) spectrum and at δ(C) 56.2 in the ^{13}C-NMR spectrum (*Table 2*). In the HMBC spectrum, the cross-peaks between H–C(7) and C(1), C(2), C(6), and C(8); H–C(1′) and C(3); and MeO and C(4) were observed. The irradiation of the MeO group (δ(H) 3.71) resulted in an enhancement of the signal at δ(H) 6.91 (H–C(5)) in the difference NOE experiment. Therefore, compound hydranitriloside A_2 (**2**) was identified as (3-hydroxy-4-methoxyphenyl)acetonitrile 3-*O*-β-D-glucopyranoside.

Compound **3** was obtained as white amorphous powder with a molecular formula of $C_{15}H_{19}NO_7$, deduced from the HR-ESI-MS ($[M+Na]^+$ at *m*/*z* 348.1061). The presence of OH (3400 cm^{-1}) and CN (2249 cm^{-1}) functions, and of an aromatic ring (1597 and 1516 cm^{-1}) were suggested by its IR spectrum. The ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*) spectra of **3** indicated the presence of a CH_2 group (δ(H) 3.83 (*s*)) bearing a CN group, an aromatic ring with an *ABX*-coupling system (δ(H) 7.16 (*d*, J = 8.9, 1 H), 6.98 (*d*, J = 2.1, 1 H), 6.89 (*dd*, J = 8.9, 2.1, 1 H)), a MeO group (δ(H) 3.86 (*s*)), an anomeric H-atom (δ(H) 4.90 (*d*, J = 7.6)), and a CN C-atom (δ(C) 119.1). The acid hydrolysis of **3** liberated D-glucose, which was identified by HPLC analysis [9]. In the difference-NOE experiment, the irradiation of the MeO group (δ(H) 3.86) resulted in an enhancement

of the signal at δ(H) 6.98 (H–C(2)), which suggested that compound **3** was an isomer of compound **2** with respect to the MeO position. The 2D-NMR data, including HMQC, HMBC, and DQF-COSY experiments, indicated that in **3** the respective positions of the MeO and glucopyranosyloxy substituents reversed, compared to **2**. Thus, compound **3**, named hydranitriloside B_1, was elucidated as (4-hydroxy-3-methoxyphenyl)acetonitrile 4-*O*-β-D-glucopyranoside.

Compound **4** was obtained as white amorphous powder with a molecular formula of $C_{14}H_{17}NO_6$, on the basis of HR-ESI-MS ($[M+Na]^+$ at m/z 318.0956). The acid hydrolysis of **4** liberated D-glucose [9]. The ^{1}H- and ^{13}C-NMR spectra indicated the presence of a CH_2 group (δ(H) 3.82 (*s*)), an *AA′BB′*-coupling of an aromatic ring (δ(H) 7.28 (*d*, $J=8.5$, 2 H), 7.11 (*d*, $J=8.5$, 2 H)), a β-D-glucopyranosyl anomeric H-atom (δ(H) 4.90 (*d*, $J=7.5$)), and a CN group (δ(C) 119.9 (C(8))). Furthermore, long-range correlations in the HMBC spectra were observed between the following H- and C-atoms: H–C(7) and C(1), C(2), and C(8); and H–C(1′) and C(4). On the basis of this evidence, the structure of **4** was determined as (4-hydroxyphenyl)acetonitrile 4-*O*-β-D-glucopyranoside. This compound, for which we propose the name hydranitriloside B_2, was previously synthesized by *Helferich et al.* in 1935 [8], and it is reported here for the first time as a natural product.

Compound **5**, obtained as white amorphous powder, was found to possess a molecular formula of $C_{14}H_{18}O_9$, as evidenced by the HR-ESI-MS ($[M+Na]^+$ at m/z 353.0851). The IR spectrum indicated the presence of OH (3380 cm^{-1}) and CO (1698 cm^{-1}) groups, a benzene ring (1605 and 1509 cm^{-1}), and an ether (1074 cm^{-1}) function. The ^{1}H-NMR spectrum (*Table 3*) showed signals assignable to a trisubstituted aromatic system at δ(H) 8.55 (*d*, $J=2.0$, 1 H), 7.02 (*d*, $J=8.2$, 1 H), and 8.11 (*dd*, $J=$ 8.2, 2.0, 1 H), of a MeO group at δ(H) 3.73 (*s*), and of β-D-glucopyranosyl group at δ(H) 5.75 (*d*, $J=7.2$). The acid hydrolysis of **5** gave D-glucose [9]. The ^{13}C-NMR spectrum (*Table 3*) revealed 14 C-atom signals, including those of a CO C-atom (δ(C)

Table 3. *^{1}H- and ^{13}C-NMR Data* (at 600 and 150 MHz, resp., δ in ppm, J in Hz) *of Compound* **5**

	δ(H)[a])	δ(C)[a])	δ(C)[b])
C(1)		123.9 (*s*)	124.0 (*s*)
H–C(2)	8.55 (*d*, $J=2.0$)	117.5 (*d*)	119.2 (*d*)
C(3)		147.3 (*s*)	147.4 (*s*)
C(4)		153.7 (*s*)	155.1 (*s*)
H–C(5)	7.02 (*d*, $J=8.2$)	111.9 (*d*)	112.6 (*d*)
H–C(6)	8.11 (*dd*, $J=8.2$, 2.0)	125.2 (*d*)	126.7 (*d*)
COOH		168.8 (*s*)	170.0 (*s*)
MeO–C(4)	3.73 (*s*)	55.9 (*q*)	56.6 (*q*)
H–C(1′)	5.75 (*d*, $J=7.2$)	102.5 (*d*)	102.7 (*d*)
H–C(2′)	4.29–4.34 (*m*)	74.8 (*d*)	74.9 (*d*)
H–C(3′)	4.29–4.34 (*m*)	78.3 (*d*)	77.9 (*d*)
H–C(4′)	4.29–4.34 (*m*)	70.9 (*d*)	71.1 (*d*)
H–C(5′)	4.02–4.06 (*m*)	78.7 (*d*)	78.1 (*d*)
CH_2(6′)	4.46 (*dd*, $J=12.4$, 2.4), 4.35 (*dd*, $J=12.4$, 4.8)	62.1 (*t*)	62.3 (*t*)

[a]) Recorded in C_5D_5N. [b]) Recorded in CD_3OD.

168.8), a MeO group (δ(C) 55.9), and six aromatic C-atoms (δ(C) 123.9, 117.5, 147.3, 153.7, 111.9, and 125.2). In the HMBC spectrum, the cross-peaks were observed between H–C(2), and C(1) and C(7); H–C(6), and C(1) and C(7); and H–C(1′) and C(3). In addition, the irradiation of MeO (δ(H) 3.73) resulted in an enhancement of the signal at δ(H) 7.02 (H–C(2)) in the difference NOE spectrum. Based on the above evidence, compound **5** was established as 3-hydroxy-4-methoxybenzoic acid 3-*O*-β-D-glucopyranoside.

Non-cyanogenic glucosides are less common than their cyanogenic counterparts. They represent a small group of compounds comprising *ca.* 30 representatives with a scattered distribution in plants [10]. While their function in plants is not fully understood, they possess some interesting bioactivities. For example, they were found to enhance the antibiotic activity of rifampicin, tetracycline, and ampicillin against the *Gram*-positive and *Gram*-negative bacteria, and also to enhance the absorption of drugs, vitamins, and nutrients through the gastrointestinal membrane and increase their bioavailability [11].

To our knowledge, this is the first report on the presence of non-cyanogenic cyanoglucosides in the genus *Hydrangea*.

Experimental Part

General. Column chromatography (CC): normal-phase CC: silica gel (SiO_2; 200–300 mesh; *Qingdao Marine Chemical Inc.*, P. R. China); reversed-phase (RP) silica-gel CC: *ODS* (100–200 mesh; *Fuji Silysia Chemical, Ltd.*, Japan). HPLC pump and detector: *Shimadzu LC10AT* and *RID-6A* (refractive index detector), HPLC column: *ODS-A* (*C-18*, 10 mm × 25 cm, 5 μm, *YMC*), flow rate: 2.5 ml/min. IR Spectra: *Shimadzu FTIR-8100* spectrometer; KBr discs; in cm^{-1}. NMR Spectra: *JNM-ECA600* spectrometer; TMS as internal standard, δ in ppm, *J* in Hz. HR-ESI-MS: *Bruker micromass Q-Tof* mass spectrometer; in *m*/*z*.

Plant Material. The dried leaves of *H. macrophylla* were collected from Shizhu, Sichuan Province, P. R. China, in May 2009, and identified by associate Prof. *Jincai Lu* of School of Traditional Chinese Materia Medica of Shenyang Pharmaceutical University, P. R. China. A voucher specimen (HM 090505) was deposited with the Department of Natural Products Chemistry, Shenyang Pharmaceutical University, Shenyang, P. R. China.

Extraction and Isolation. The dried leaves of *H. macrophylla* (2.0 kg) were extracted with MeOH (3 × 8 l) for 3 h at 80° and evaporated *in vacuo*. The extract (452 g, 22.2%) was dissolved in H_2O (5 l) and partitioned into AcOEt/H_2O 1:1 (*v*/*v*) for three times, and removal of the solvent *in vacuo* yielded an AcOEt-soluble fraction (103.5 g, 4.3%) and an aq. phase. The aq. phase (5 l) was further extracted with BuOH (3 × 5 l) to give a BuOH-soluble fraction (125.5 g, 6.5%) and an H_2O-soluble fraction. The BuOH-soluble fraction was subjected to CC (SiO_2; $CHCl_3$/MeOH/H_2O) to give six fractions, *Frs. 1–6*. Compound **1** (7.1 mg, 0.000355%) was obtained from *Fr. 5* after CC (*ODS*; MeOH/H_2O 1:9 → 3:7) and HPLC (MeOH/H_2O 15:85; t_R 11.5 min). *Fr. 3* was separated by HPLC (MeOH/H_2O 20:80) to give compounds **2** (7.5 mg, 0.000375%; t_R 7.4 min) and **3** (26.6 mg, 0.001330%; t_R 10.4 min). *Fr. 2* was separated by CC (*ODS*; MeOH/H_2O 1:9 → 3:7) and HPLC (MeOH/H_2O 12:88) to afford compounds **4** (5.1 mg, 0.000255%; t_R 14.5 min) and **5** (220.3 mg, 0.011015%; t_R 20.5 min).

Acid Hydrolysis of **1**–**5**. A soln. of **1**–**5** (each 2.0 mg) in 1M HCl (1.0 ml) was heated under reflux for 3 h. After cooling, each mixture was neutralized with *Amberlite IRA-400* (OH^- form, *Alfa Aesar*, USA) and filtered, and the soln. was partitioned with AcOEt to give two layers. The aq. layer was evaporated and then subjected to HPLC analysis using NH_2 column (4.6 mm × 25 cm, *Tokyo Kasei Co., Ltd.*, Japan) and an optical-rotation detector (*Shodex OR-2*, *Showa Denko Co., Ltd.*, Japan). D-Glucose were confirmed by comparison of the t_R with that of the authentic sample (*NICPBP*, P. R. China; mobile phase: MeCN/H_2O 85:15 (*v*/*v*); flow rate: 0.8 ml/min; t_R 12.8 min (D-glucose, positive optical rotation)).

Hydranitriloside A_1 (=[3-(β-D-Glucopyranosyloxy)-4-hydroxyphenyl]acetonitrile; **1**). White amorphous powder (MeOH). $[\alpha]_D^{25} = -66.0$ ($c = 2.3$, MeOH). UV (MeOH): 204 (4.62), 224 (4.10), 279 (3.70). IR (KBr): 3380, 2924, 2255, 1609, 1518, 1439, 1287, 1236, 1075, 897, 804. ^{1}H-NMR (600 MHz, CD_3OD): *Table 1*. ^{13}C-NMR (150 MHz, CD_3OD): *Table 2*. HR-ESI-MS: 334.0901 ($[M+Na]^+$, $C_{14}H_{17}NNaO_7^+$; calc. 334.0903); 310.0929 ($[M-H]^-$, $C_{14}H_{16}NO_7^-$; calc. 310.0927).

Hydranitriloside A_2 (=[3-(β-D-Glucopyranosyloxy)-4-methoxyphenyl]acetonitrile; **2**). White amorphous powder (MeOH). $[\alpha]_D^{25} = -75.0$ ($c = 2.5$, MeOH). UV (MeOH): 205 (4.65), 227 (4.18), 278 (3.64). IR (KBr): 3380, 2919, 2251, 1595, 1518, 1458, 1267, 1233, 1080, 897, 806. ^{1}H-NMR (600 MHz, C_5D_5N): *Table 1*. ^{13}C-NMR (150 MHz, C_5D_5N): *Table 2*. HR-ESI-MS: 348.1058 ($[M+Na]^+$, $C_{15}H_{19}NNaO_7^+$; calc. 348.1059).

Hydranitriloside B_1 (=[4-(β-D-Glucopyranosyloxy)-3-methoxyphenyl]acetonitrile; **3**). White amorphous powder (MeOH). $[\alpha]_D^{25} = -65.1$ ($c = 8.3$, MeOH). UV (MeOH): 205 (4.64), 227 (4.13), 278 (3.66). IR (KBr): 3400, 2923, 2249, 1597, 1516, 1425, 1267, 1229, 1076, 895, 804. ^{1}H-NMR (600 MHz, CD_3OD): *Table 1*. ^{13}C-NMR (150 MHz, CD_3OD): *Table 2*. HR-ESI-MS: 348.1061 ($[M+Na]^+$, $C_{15}H_{19}NNaO_7^+$; calc. 348.1059).

Hydranitriloside B_2 (=[4-(β-D-Glucopyranosyloxy)phenyl]acetonitrile; **4**). White amorphous powder (MeOH). ^{1}H-NMR (600 MHz, CD_3OD): *Table 1*. ^{13}C-NMR (150 MHz, CD_3OD): *Table 2*. HR-ESI-MS: 318.0956 ($[M+Na]^+$, $C_{14}H_{17}NNaO_6^+$; calc. 318.0954).

3-(β-D-Glucopyranosyloxy)-4-methoxybenzoic Acid (**5**). White amorphous powder (MeOH). $[\alpha]_D^{25} = -68.0$ ($c = 2.3$, MeOH). UV (MeOH): 217 (4.46), 255 (4.15), 285 (3.77). IR (KBr): 3380, 2930, 1698, 1605, 1522, 1509, 1437, 1281, 1219, 1075, 891, 828. ^{1}H- and ^{13}C-NMR (600 and 150 MHz, resp., C_5D_5N): *Table 3*. HR-ESI-MS: 353.0851 ($[M+Na]^+$, $C_{14}H_{18}NaO_9^+$; calc. 353.0849); 329.0873 ($[M-H]^-$, $C_{14}H_{17}O_9^-$; calc. 329.0873).

REFERENCES

[1] M. Kikuchi, R. Kakuda, M. Kikuchi, Y. Yaoita, *Chem. Pharm. Bull.* **2008**, *56*, 610.
[2] H. Suzuki, T. Ikeda, T. Matsumoto, M. Noguchi, *Agric. Biol. Chem.* **1977**, *41*, 1815.
[3] T. Hashimoto, M. Tori, Y. Asakawa, *Phytochemistry* **1987**, *26*, 3323.
[4] H. Inouye, Y. Takeda, S. Uesato, K. Uobe, T. Hashimoto, *Tetrahedron Lett.* **1980**, *21*, 1059.
[5] S. Uesato, Y. Takeda, T. Hashimoto, K. Uobe, H. Inouye, H. Taguchi, T. Endo, *Helv. Chim. Acta* **1984**, *67*, 2111.
[6] H. Zhang, H. Matsuda, A. Kumahara, Y. Ito, S. Nakamula, M. Yoshikawa, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4972.
[7] M. Yoshikawa, E. Harada, Y. Naitoh, K. Inoue, H. Matsuda, H. Shimoda, J. Yamahara, N. Murakami, *Chem. Pharm. Bull.* **1994**, *42*, 2225.
[8] B. Helferich, H. E. Scheiber, R. Streeck, F. Vorsatz, *Ann. Chem.* **1935**, *518*, 211.
[9] S. Nakamula, X. Li, H. Matsuda, M. Yoshikawa, *Chem. Pharm. Bull.* **2008**, *56*, 536.
[10] K. Yamasaki, *Stud. Plant Sci.* **1999**, *6*, 335.
[11] S. P. S. Khanuja, J. S. Arya, R. S. K. Tiruppadiripuliyur, D. Saikia, H. Kaur, M. Singh, S. C. Gupta, A. K. Shasany, M. P. Darakar, S. K. Srivastava, M. M. Gupta, S. C. Verma, A. Pal, US Pat. US6858588 B2, 2005.

Received August 18, 2010