New Quassinoids from Indonesian *Picrasma Javanica*. Structures of Javanicins E, F, G and M

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Four new des-4-methylated picrasane type quassinoids, javanicins E, F, G and M, were isolated from the bark of Indonesian *Picrasma javanica* (Simaroubaceae). In addition, the known quassinoid, quassin, was also identified. The structures were determined by spectroscopic data and chemical evidence.

Keywords *Picrasma javanica*; Simaroubaceae; quassinoids; javanicin E; javanicin F; javanicin G; javanicin M

Quassinoids, bitter principles of simaroubaceous plants, have been extensively investigated from the standpoint of structure determination and their useful biological activities.[1] Particularly, recent studies of Simaroubaceae plants have received renewed attention because of antimalarial[2] and antitumor[1,3] activities shown by some quassinoids. In previous papers,[4-6] we have reported the isolation and determination of seven novel des-4-methylated picrasane type quassinoids from the methanolic extract of the bark of Indonesian *Picrasma javanica* BL. Further investigation led to the isolation of four new same-type quassinoids named javanicins E, F, G and M (**1**, **2**, **3** and **4**), all isolated from the same plant.

Results and Discussion

The methanolic extract of the bark of *P. javanica* was partitioned between chloroform and water. The aqueous layer was further extracted with *n*-BuOH. The chloroform soluble fraction was chromatographed on silica gel, low-pressure liquid chromatography (LC) and high-performance LC (HPLC) to afford four new quassinoids, javanicins E, F, G and M (**1**, **2**, **3** and **4**), along with the known quassin (**5**).[7]

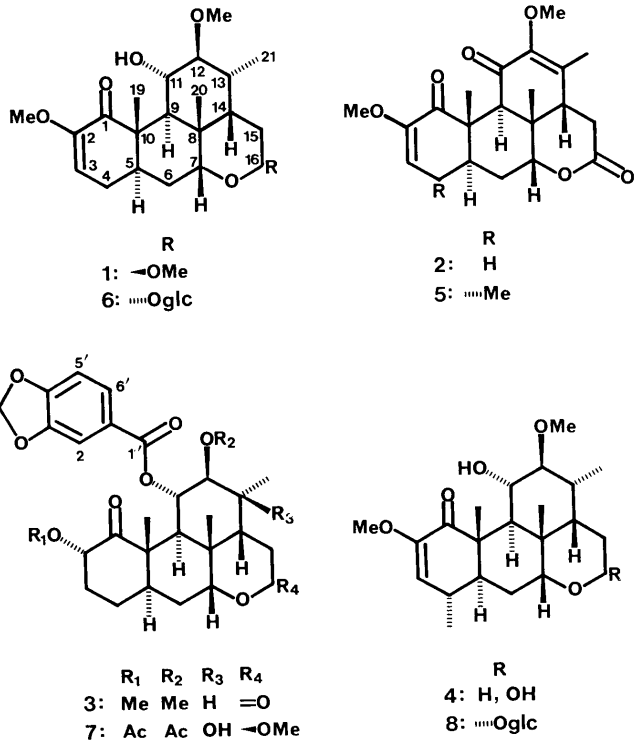

Chart 1

Javanicin E (**1**) was obtained as colorless needles, mp 105 °C, $[\alpha]_D$ +78.0 (c=0.9, $CHCl_3$), and its molecular formula was determined to be $C_{22}H_{34}O_6$ by high-resolution mass spectrometry (HRMS). The infrared (IR) and ultraviolet (UV) spectra of **1** indicated the presence of hydroxyl (ν_{max} 3450 cm^{-1}) and α,β-unsaturated carbonyl (ν_{max} 1675 cm^{-1} and λ_{max} 270 nm) groups. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** showed signals due to one secondary methyl at δ 0.96 (d, J=7 Hz, Me-13), two tertiary methyls at δ 1.11 (s, Me-8) and 1.38 (s, Me-10), three methoxyls at δ 3.30 (s, OMe-16), 3.58 (s, OMe-2) and 3.61 (s, OMe-12), a hemiacetal proton at δ 4.74 (d, J=3 Hz) and an olefinic proton at δ 5.62 (dd, J=6 and 2 Hz). The ^{1}H- and carbon-13 (^{13}C)-NMR chemical shift values and J_{HH} coupling constants of **1** were similar in most respects to those of the aglycone moiety of javanicinoside A (**6**).[5] Acid hydrolysis of javanicinoside A (**6**) with 1.5 M sulfuric acid in aq. MeOH produced two compounds (**1** and its epimer): each one (11 : 9) was isolated using preparative HPLC. The configuration of OMe-16 in **1** was determined by a nuclear Overhauser effects (NOEs) experiment. Irradiation at the OMe-16 proton at δ 3.30 induced 7% NOE enhancement in H-7, indicating a β-orientation of the OMe-16 group. On the basis of the above spectral and chemical evidence, the structure of javanicin E was proposed to be formula **1**.

Javanicin F (**2**) was obtained as colorless prisms, mp 133 °C, $[\alpha]_D$ +67.2° (c=1.2, $CHCl_3$) and its molecular formula was determined to be $C_{21}H_{26}O_6$ by HRMS. The IR and UV spectra of **2** indicated the presence of δ-lactone (ν_{max} 1735 cm^{-1}) and α,β-unsaturated carbonyl (ν_{max} 1700, 1685 cm^{-1} and λ_{max} 254 nm) groups. The ^{1}H-NMR spectrum of **2** showed signals due to three tertiary methyls at δ 1.20 (s, Me-8), 1.52 (Me-10) and 1.88 (Me-13), two methoxyls at δ 3.59 (s, OMe-2) and 3.67 (s, OMe-12) and an olefinic proton at δ 5.52 (dd, J=6 and 2 Hz). From a comparison of ^{1}H- and ^{13}C-NMR spectra of **2** with those of quassin (**5**), these data suggested that the main difference between **2** and **5** was the lack of the methyl signal at C-4 in **2**. The relative stereochemistry of **2** was determined by NOE measurements as follows. Irradiation of Me-8 protons at δ 1.20 produced NOEs on Me-10 (11%), H-7 (7%) and H-14 (7%). Irradiation of Me-10 protons at δ 1.52 produced 11% NOE at Me-8. On the basis of the above data, the structure of javanicin F was proposed to be des-4-methylquassin (**2**).

Javanicin G (**3**) was obtained as colorless prisms, mp 243 °C, $[\alpha]_D$ −38.2° (c=1.2, $CHCl_3$) and its molecular

TABLE I. ^{1}H-NMR Spectral Data for Compounds **1**—**7**

Proton	**1**[a]	**6**[b]	**2**[a]	**5**[a]	**3**[a]	**7**[b]	**4**[a]
H-2					4.12 dd (11, 7)	5.49 dd (12, 7)	
H-3	5.62 dd (6, 2)	5.45 dd (5, 2)	5.52 dd (6, 2)	5.31 d (3)	1.49 m 2.26 m	1.70 m 2.19 m	5.39 d (2)
H-4	2.12 ddd (18, 4, 2) 2.30 ddd (18, 11, 2)	1.79 ddd (20, 5, 4) 2.09 ddd (20, 11, 2)	2.18 m 2.30 m	2.49 m	1.44 m 1.78 m	1.34 m 1.75 m	2.45 m
H-5	2.42 m	2.53 m	2.25 m	1.83 m	1.80 m	2.19 m	1.97 m 2.07 m[c]
H-6	1.42 ddd (14, 3, 3) 1.97 ddd (14, 13, 3)	1.48 ddd (14, 4, 3) 1.85 ddd (14, 10, 2)	1.77 ddd (15, 3, 3) 2.01 ddd (15, 12, 3)	1.86 ddd (14, 3, 3) 2.09 ddd (14, 12, 3)	1.73 ddd (14, 3, 3) 1.92 ddd (14, 13, 3)	1.44 ddd (14, 3, 3) 1.96 ddd (14, 11, 3)	1.74 m 1.76 m[c] 1.81 m 1.85 m[c]
H-7	3.53 t (3)	3.10 t (3)	4.27 t (3)	4.29 t (3)	4.17 t (3)	3.70 t (3)	3.29 t (3) 3.84 t[c] (3)
H-9	2.52 d (12)	2.75 d (11)	2.99 s	2.99 s	2.92 d (12)	3.62 d (12)	2.52 d (11) 2.54 d[c] (11)
H-11	3.70 ddd (12, 11, 10)	3.88 dd (11, 8)			5.50 dd (12, 9)	6.48 dd (12, 10)	3.69 m
H-12	2.84 dd (11, 9)	2.86 t (8)			3.26 dd (11, 9)	5.67 d (10)	2.85 m
H-13	2.05 m	2.05 m			2.24 m		2.08 m[c]
H-14	1.69 m	1.17 ddd (13, 4, 4)	2.41 dd (12, 7)	2.40 dd (12, 7)	1.82 m	2.28 m	1.39 m 1.82 m[c]
H-15	1.67 ddd (21, 14, 3) 1.73 ddd (21, 11, 4)	1.56 ddd (14, 13, 9) 1.70 ddd (14, 4, 2)	2.62 dd (19, 12) 3.01 dd (19, 7)	2.61 dd (19, 12) 3.00 dd (19.7)	2.62 dd (20, 12) 2.68 dd (20, 8)	1.69 m 1.79 m	1.45 m 1.80 m 1.68 m[c] 1.75 m[c]
H-16	4.74 d (3)	5.15 dd (9, 2)				4.76 d (2)	4.70 dd (9, 3) 5.34 br s[c]
Me-4				1.12 d (7)			1.10 d (6) 1.11 d[c] (6)
Me-8	1.11 s	0.94 s	1.20 s	1.21 s	1.34 s	1.72 s	1.09 s 1.13 s[c]
Me-10	1.38 s	1.34 s	1.52 s	1.56 s	1.27 s	1.50 s	1.42 s
Me-13	0.96 d (7)	0.88 d (8)	1.88 s	1.86 s	1.05 d (7)	1.29 s	0.98 d (7) 1.00 d[c] (7)
OH-11	3.95 d (10)						
OMe-2	3.58 s	3.48 s	3.59 s	3.58 s	2.84 s	2.00 s (OAc-2)	3.58 s
OMe-12	3.61 s	3.68 s	3.67 s	3.67 s	3.30 s	1.61 s (OAc-12)	3.61 s
OMe-16	3.30 s	5.53 d (8) (glc-H-1)				3.31 s	
H-2′		4.05 dd (9, 8) (glc-H-2)			7.53 d (2)	7.85 d (2)	
H-5′		4.20 m (glc-H-3)			6.82 d (8)	6.93 d (8)	
H-6′		4.20 m (glc-H-4)			7.72 dd (8, 2)	7.99 dd (8, 2)	
H-2″		3.97 m (glc-H-5)			6.01 d (1)	5.92 d (1)	
		4.43 dd (12, 6) 4.55 dd (12, 2) (glc-H-6)			6.02 d (1)	6.01 d (1)	

Coupling constants (J in Hz) are given in parentheses. *a*) In $CDCl_3$. *b*) In C_5D_5N. *c*) Signals due to another isomer at C-16.

formula was determined to be $C_{29}H_{36}O_9$ by HRMS. The IR spectrum of **3** indicated the presence of δ-lactone (ν_{max} 1730 cm^{-1}), aromatic (ν_{max} 1610 and 1490 and 760 cm^{-1}) and ester (ν_{max} 1715 and 1285 cm^{-1}) groups. Its UV spectrum (λ_{max} 220, 264 and 298 nm) was similar to that of javanicin D (**7**)[6] which indicates that **3** has an aromatic ring in the molecule. The ^{1}H-NMR spectrum of **3** showed signals due to one secondary methyl at δ 1.05 (d, J=7 Hz, Me-13), two tertiary methyls at δ 1.27 (s, Me-10) and 1.34 (s, Me-8) and two methoxyls at δ 2.84 (s, OMe-2) and 3.30 (s, OMe-12), nonequivalent methylene protons at δ 6.01 and 6.02 (each 1H, d, J=1 Hz) and ABX-type phenyl protons at [δ 6.82 (1H, d, J=8 Hz), 7.53 (1H, d, J=2 Hz) and 7.72 (1H, dd, J=8 and 2 Hz)]. The results of ^{1}H–^{1}H shift-correlated spectroscopy (COSY) revealed the presence of two isolated structural units, CH–$(CH_2)_2$–CH–CH_2–CH and CH–$(CH)_4$–CH_2 groups along with a 3,4-methylenedioxybenzoyloxyl group in the formula. The spectral features were very similar to those of **7** except for the presence of a corresponding proton signal due to H-13 at δ 2.24 (1H, m) in **3**. Also, the hemiacetal function at C-16 in **7** was replaced by δ-lactone carbonyl in **3**. Long-range ^{1}H–^{13}C COSY experiments with **3** clearly showed correlations from H-11 to C-1″ and from OMe-2 protons to C-2 and from OMe-12 protons to C-12. Therefore, the location of the 3,4-methylenedioxybenzoyloxyl group and two methoxyl groups were determined to be at C-11, C-2 and C-12, respectively. The relative stereochemistry of **3** was examined through an extensive series of NOE experiments, the significant results of which are shown in Fig. 1. Irradiation of the Me-8 at δ 1.34 induced NOEs at H-7 (7%), H-11 (10%) and H-13 (6%). Irradiation of Me-10 at δ 1.27 induced NOEs at H-2 (12%) and H-11 (8%). Irradiation of H-11 at 5.50 induced NOEs at Me-8 (11%), Me-10 (6%) and H-13 (6%). Irradiation of OMe-12 at δ 3.30 induced NOEs at Me-8 (4%), H-11 (8%) and H-13 (5%). Irradiation of H-7 at δ 4.17 induced 4% NOE at H-14. Irradiation of Me-13 at δ 1.05 induced 8% NOE at H-12. These NOE experiments and J_{HH} coupling constants led us to establish the following: (i) all the angular chiral centers (C-5, C-7, C-8, C-9, C-10 and C-14) together with C-13 were concluded to be compatible with those of javanicin D (**7**); (ii) the proton on the C-2 at δ 4.12 was assigned as β-axial from the coupling constants (J=11 and 7 Hz) and the presence of an NOE with C-10 β-axial methyl proton signal; (iii) from the coupling constants between H-9 and H-11, H-11 and H-12, and H-12 and H-13 (J=12, 9 and 11 Hz, respectively), the H-11, H-12 and H-13 protons were deduced to be β-axial, α-axial and β-axial, respectively. On the basis of the above data, the structure of javanicin G was proposed to be formula **3**.

Javanicin M (**4**) was obtained as colorless needles, mp 273°C, $[\alpha]_D$ +37.0° (c=0.8, $CHCl_3$) and its molecular formula was determined to be $C_{22}H_{34}O_6$ by HRMS. The IR and UV spectra of **4** indicated the presence of hydroxyl (ν_{max} 3400 cm^{-1}) and α,β-unsaturated carbonyl (ν_{max} 1675, 1640 cm^{-1} and λ_{max} 268 nm) groups. The ^{1}H-NMR spectrum of **4** showed a hemiacetal proton at C-16 [δ 4.70 (1H, dd, J=9 and 3 Hz) and/or 5.34 (1H, br s)], an olefinic proton at C-3 [δ 5.39 (2H, d, J=2 Hz)], four sets of methyls at Me-4 [δ 1.10 (3H, d, J=6 Hz) and/or 1.11 (3H, d, J=6 Hz)], Me-8 [δ 1.09 (3H, s) and/or 1.13 (3H, s)], Me-10 [δ 1.42 (6H, s)] and Me-13 [δ 0.98 (3H, d, J=7 Hz) and/or 1.00 (3H, d, J=7 Hz)] and bridge head protons at H-7 [δ 3.29 (1H, t, J=3 Hz) and/or 3.84 (1H, t, J=3 Hz)] and H-9 [δ 2.52 (1H, d, J=11 Hz) and/or 2.54 (1H, d, J=11 Hz)]. These phenomena showed that they are tautomers of hemiacetal protons at C-16.[4,8] Enzymatic hydrolysis of picrasinoside F (**8**)[4,8] with β-glucosidase afforded javanicin M (**4**). On the basis of the above data, the structure of javanicin M was proposed to be formula **4**.

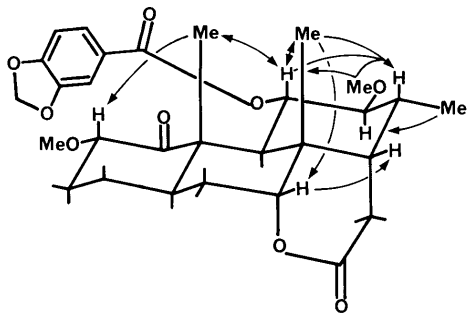

Fig. 1. NOEs Observed in NOE Difference Spectra of Javanicin G (**3**)

TABLE II. ^{13}C-NMR Spectral Data for Compounds **1**, **2**, **3**, **5**, **6** and **7**

Carbon	**1**[a]	**6**[b]	**2**[a]	**5**[a]	**3**[a]	**7**[b]
C-1	205.81	205.86	197.21	197.75	211.01	208.75
C-2	149.57	149.65	148.39	148.05	79.99	73.05
C-3	111.80	112.38	109.67	116.33	35.32	34.17
C-4	28.36	28.28	26.96	31.19	25.26	25.52
C-5	37.28	37.78	36.09	43.24	42.04	43.35
C-6	29.56	29.71	29.07	25.87	29.19	29.28
C-7	70.00	78.26	82.10	82.10	82.61	69.85
C-8	38.02	38.15	37.47	37.10	34.92	38.57
C-9	36.91	38.59	46.68	46.29	35.80	37.73
C-10	48.15	48.64	46.31	45.87	50.70	52.00
C-11	74.07	74.36	191.01	190.95	73.57	71.03
C-12	89.32	89.65	149.25	148.37	85.74	79.24
C-13	34.60	34.95	137.59	137.38	35.58	75.82
C-14	41.98	47.75	46.76	46.67	45.49	48.94
C-15	26.14	27.74	31.66	31.68	27.93	29.17
C-16	98.44	99.64	169.00	169.04	169.91	98.11
C-18				19.45		
C-19	11.15	11.30	11.34	12.72	12.64	12.55
C-20	21.78	21.50	22.33	22.37	22.24	25.41
C-21	15.00	15.22	15.37	15.37	14.42	25.99
OMe-2	55.27	54.96	55.05	54.99	57.44	
OMe-12	61.26	60.86	59.36	59.31	61.00	
OMe-16	54.44					54.31
OCOMe-2		100.56				20.37
OCOMe-2		(glc-C-1)				169.24
OCOMe-12		75.02				20.37
OCOMe-12		(glc-C-2)				170.32
C-1′		78.29			123.75	125.06
C-2′		(glc-C-3)			110.01	110.86
C-3′		71.65			147.73	147.99
C-4′		(glc-C-4)			151.83	151.98
C-5′		78.64			107.96	107.96
C-6′		(glc-C-5)			126.16	126.63
C-1″		62.87			165.26	165.99
C-2″		(glc-C-6)			101.80	102.24

a) In $CDCl_3$. *b*) In C_5D_5N.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The UV and IR spectra were recorded on Hitachi 340 and Hitachi 260-30 spectrophotometers, respectively. The

^{1}H- amd ^{13}C-NMR spectra were recorded with a JEOL JNM GX-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Chemical shifts are given on the δ-scale (with ppm downfield from tetramethylsilane as an internal standard) and coupling constants (J) in hertz (Hz). Electron-impact (EI) MS and HRMS were run on JEOL JMS D-300 and JEOL JMS DX-303 mass spectrometers, respectively. Optical rotations were determined on a JASCO DIP-4 digital polarimeter. Column chromatography was carried out on silica gel (BW-820MH, Fuji Davison). Low-pressure LC and HPLC were carried out on silica gel (CQ-3, 24 mm i.d. × 360 mm, Fuji Gel, detector: 254 nm) and silica gel (Senshu Pak SSC-Silica 3251-N, 8 mm i.d. × 250 mm, detector: 254 nm), respectively.

Isolation The fractionation of the MeOH extract from *Picrasma javanica* was described in a previous paper.[4] The $CHCl_3$-soluble fraction (60 g) was applied to a column of silica gel (900 g). Elution was performed with $CHCl_3$, 1, 5, 10, 20 and 50% MeOH in $CHCl_3$ and MeOH. The 10% MeOH in the $CHCl_3$ fraction was subjected to preparative low-pressure LC on CQ-3 with CH_2Cl_2–MeOH (50 : 1, v/v) and then further purified by preparative HPLC on silica gel with CH_2Cl_2–MeOH (100 : 1, v/v) to afford javanicins E (**1**, 80 mg), F (**2**, 37 mg), G (**3**, 12 mg), M (**4**, 8 mg) and quassin (**5**, 10 mg).

Javanicin E (1) Colorless needles (acetone), mp 105 °C, $[\alpha]_D^{22}$ +78.0° (c=0.9, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 270 (3.74). IR ν_{max}^{KBr} cm^{-1}: 3450, 2940, 1675, 1635, 1605, 1440, 1125, 1050. ^{1}H- and ^{13}C-NMR data are given in Tables I and II, respectively. MS m/z: 394 (M^+, 25%), 362 (63), 347 (53), 331 (32), 314 (24), 296 (100), 252 (38), 237 (26). HRMS m/z: 394.2390 [M^+] (Calcd for $C_{22}H_{34}O_6$: 394.2355).

Acid Hydrolysis of Javanicinoside A (6) A solution of javanicinoside A (**6**, 5 mg) in 1.5 M H_2SO_4 (2 ml) and MeOH (4 ml) was stirred at 80°C for 5 h. After cooling the reaction mixture, water (5 ml) was added and the product was extracted with $CHCl_3$ (5 ml × 3 times). The $CHCl_3$ extract was subjected to preparative HPLC (Senshu Pak, silica gel, CH_2Cl_2–MeOH, 50 : 1, v/v) and produced two compounds: Javanicin E (**1**, 1 mg); IR ν_{max}^{KBr} cm^{-1}: 3450, 1675, 1635, 1125. MS m/z: 394 (M^+). 16-Epijavanicin E (0.9 mg): IR ν_{max}^{KBr} cm^{-1}: 3450, 1675, 1635, 1125. MS m/z: 394 (M^+).

Javanicin F (2) Colorless prisms (MeOH–H_2O), mp 133 °C, $[\alpha]_D^{22}$ +67.2° (c=1.2, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 254 (3.96). IR ν_{max}^{KBr} cm^{-1}: 2930, 1735, 1700, 1685, 1638, 1240, 1145, 1040. ^{1}H- and ^{13}C-NMR data are given in Tables I and II, respectively. MS m/z: 374 (M^+, 100%), 359 (23), 341 (7), 315 (15), 299 (7), 271 (6). HRMS m/z: 374.1730 [M^+] (Calcd for $C_{21}H_{26}O_6$: 374.1729).

Javanicin G (3) Colorless prisms (MeOH–H_2O), mp 243 °C, $[\alpha]_D^{22}$ −38.2° (c=1.2, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 220 (4.71), 264 (4.29), 298 (4.26). IR ν_{max}^{KBr} cm^{-1}: 2930, 1730, 1710, 1630, 1600, 1505, 1490, 1445, 1285, 1260, 1235, 1160, 1120, 1110, 1080, 760. ^{1}H- and ^{13}C-NMR data are given in Tables I and II, respectively. MS m/z: 528 (M^+, 14%), 379 (53), 362 (15), 334 (25), 302 (13), 276 (30), 259 (12), 166 (12), 149 (100), 121 (15). HRMS m/z: 528.2342 [M^+] (Calcd for $C_{29}H_{36}O_9$: 528.2359).

Javanicin M (4) Colorless needles (acetone), mp 273 °C, $[\alpha]_D^{22}$ +37.0° (c=0.8, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 268 (3.64). IR ν_{max}^{KBr} cm^{-1}: 3400, 2930, 1675, 1640, 1450, 1240, 1115, 1095, 1080, 1050. ^{1}H- and ^{13}C-NMR data are given in Tables I and II, respectively. MS m/z: 394 (M^+, 10%), 362 (35), 344 (20), 328 (100), 313 (45), 285 (12), 251 (14). HRMS m/z: 394.2342 [M^+] (Calcd for $C_{22}H_{34}O_6$: 394.2355).

Enzyme Hydrolysis of Picrasinoside F (7) Picrasinoside F (**7**, 3 mg)[4,8] and β-glucosidase (60 mg, from almond, Sigma) were dissolved in water (3 ml) and incubated 37 °C for 14 d. After cooling, the aglycone was extracted with $CHCl_3$ and afforded javanicin M (**4**).

Quassin (5) Colorless prisms (acetone), mp 223 °C, $[\alpha]_D^{22}$ +11.8° (c=0.8, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 2960, 1735, 1700, 1685, 1640, 1260, 1095, 1035. ^{1}H- and ^{13}C-NMR data are given in Tables I and II, respectively. MS m/z: 388 (M^+). Compound **5** was found to be identical with quassin by direct comparison (TLC, IR, ^{1}H-NMR and mixed melting point determination) with an authentic sample.[7]

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