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FLAVONOIDS, AMIDOSULFOXIDES AND AN ALKALOID FROM THE LEAVES OF *GLYCOSMIS CITRIFOLIA*

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Key Word Index—*Glycosmis citrifolia*; Rutaceae; flavonoid; amidosulphoxide; 2-quinolone alkaloid; glychalcone-A; glychalcone-B; glyflavanone-A; glyflavanone-B; glycothiomin-A; glycothiomin-B; glycocitridine.

Abstract—Four flavonoids: glychalcone-A, glychalcone-B, glyflavanone-A and glyflavanone-B; two amidosulphoxides: glycothiomin-A and glycothiomin-B; a 2-quinolone alkaloid: glycocitridine and nine known compounds were isolated from the leaves of *Glycosmis citrifolia*. Their structures were elucidated on the basis of spectroscopic analyses.

INTRODUCTION

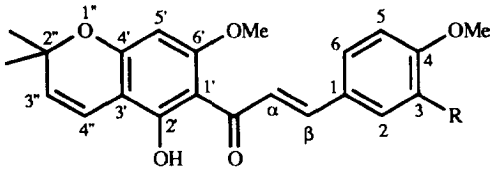
Glycosmis citrifolia (Willd.) Lindl. [1] is a wild shrub which is used in folk medicine for the treatment of skin itch, scabies, boils and ulcers [2]. Several acridone alkaloids, isolated from the root and stem barks of this plant, showed cell growth inhibition of human promyelocytic leukaemic cells (HL-60) and also inhibited macromolecular synthesis [3]. In our continuing investigation on the leaf constituents of the same plant, 16 compounds, including seven new compounds made up of four flavonoids, glychalcone-A (**1**), glychalcone-B (**2**), glyflavanone-A (**3**) and glyflavanone-B (**4**), two amidosulphoxides, glycothiomin-A (**5**) and glycothiomin-B (**6**), and one 2-quinolone alkaloid, glycocitridine (**7**), were isolated. Here we report on the structural elucidation of these new compounds.

RESULTS AND DISCUSSION

The methanolic extract from the leaves of *G. citrifolia* was partitioned between H_2O and $CHCl_3$. The H_2O layer was extracted with EtOAc and *n*-BuOH. The $CHCl_3$ layer was basified and extracted with $CHCl_3$. Each organic layer was repeatedly chromatographed. Seven new compounds as well as nine known compounds were isolated and characterized.

Glychalcone-A (**1**), a new chalcone derivative, was isolated as a pale yellow oil. Its molecular formula was determined as $C_{22}H_{22}O_5$ by high-resolution mass spectrometry. The UV absorption at 230.8, 277.0sh, 286.6, 303.2, 328.2sh and 365.8 nm was similar to that of chalcones [4]. The low energy carbonyl band at 1617 cm^{-1} in the IR spectrum and a D_2O-exchangeable hydroxyl singlet at δ14.73 in the ^1H NMR (acetone-d_6) spectrum revealed the presence of strong intramolecular hydrogen bonding by a phenolic hydroxyl group chelated with an acyl substituent. In the downfield region of the ^1H NMR spectrum, two pairs of mutually coupled protons at δ7.00 (2H, *d*, J = 8.8 Hz, H-3 and H-5) and 7.69 (2H, *d*, J = 8.8 Hz, H-2 and H-6); 7.77 (1H, *d*, J = 15.6 Hz, H-α) and 7.89 (1H, *d*, J = 15.6 Hz, H-β), as well as a methoxyl singlet at δ3.86 indicated a side-chain as a *trans-p*-methoxyphenylpropenoyl group. This was confirmed by the NOEs between H-α and H-2, 6; H-β and H-2, 6; H-2 and H-3; H-3 and 4-OMe; 4-OMe and H-5; H-5 and H-6 (Fig. 1). A 2,2-dimethylpyran ring fused to a chalcone nucleus was identified by a six-proton singlet at δ1.43 (6H, *s*, 2 × Me) and two *cis* vinyl protons at δ5.56 (1H, *d*, J = 10.0 Hz, H-3″) and 6.61 (1H, *dd*, J = 10.0, 0.8 Hz, H-4″). The last signal at δ4.00 (3H, *s*) was assigned to a methoxyl substituent at C-6′ on the basis of a *Z*-type long-range coupling (0.8 Hz) between H-4″ (δ6.61) and H-5′ (δ6.03, *br s*) together with a cross-peak between H-5′ and 6′-OMe in a NOESY experiment (Fig. 1). Thus, the substantial upfield shift of the aromatic signal H-5 could be explained clearly by two alkoxyl and one hydroxyl substituents *ortho* or *para* to this proton. Consequently, the structure of glychalcone-A was established as (**1**).

Glychalcone-B (**2**) was obtained as a yellow oil. High-resolution mass spectrometry indicated the molecular formula as $C_{23}H_{24}O_6$. The UV and IR data as well as ^1H NMR signals at δ1.42, 1.44 (each 3H, *s*, 2 × 2″-Me), 4.00 (3H, *s*, 6′-OMe), 5.56 (1H, *d*, J = 10.0 Hz, H-3″), 6.03 (1H, *br s*, H-5′), 6.61 (1H, *dd*, J = 10.0, 0.8 Hz, H-4″), 7.74 (1H, *d*, J = 15.6 Hz, H-α), 7.89 (1H, *d*, J = 15.6 Hz, H-β) and 13.62 (1H, *s*, 2′-O H, D_2O exchangeable) closely resembled those of **1** with a pyran ring linearly fused on a chalcone skeleton. The major difference was the presence of an ABD signal pattern in the aromatic region at δ7.02 (1H, *d*, J = 8.4 Hz, H-5), 7.29 (1H, *dd*, J = 8.4,



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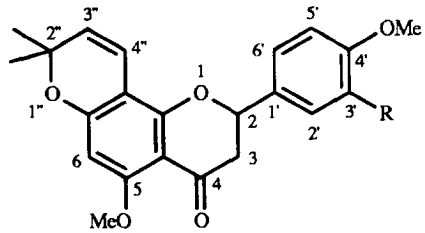

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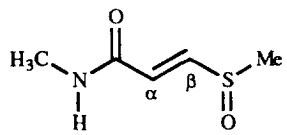

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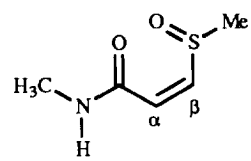

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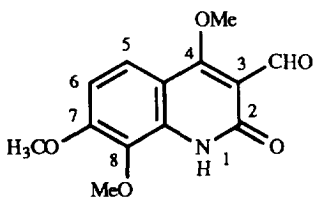

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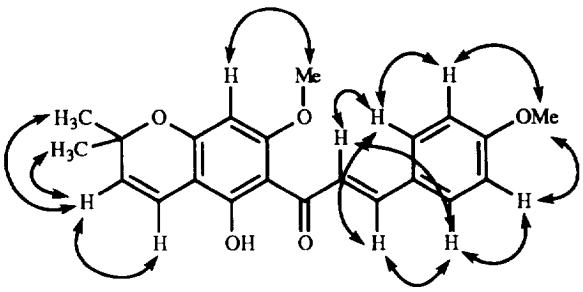
2.0 Hz, H-6) and 7.32 (1H, *d*, *J* = 2.0 Hz, H-2) which indicated a 1,3,4-trisubstituted benzene system. In addition, two remaining methoxyl substituents at δ3.87 and 3.90 had to be placed on C-4 and C-3 of this benzene ring, respectively. According to the NOESY spectrum of compound **2** (Fig. 1), the NOEs between H-2 (δ7.32) and 3-OMe (δ3.90); H-5 (δ7.02) and 4-OMe (δ3.87); H-5′ (δ6.03) and 6′-OMe (δ4.00); H-3″ (δ5.56) and 2″-Me (δ1.42, 1.44) further confirmed the assignment of substituents. On the basis of these results, glychalcone-B may be represented by structure **2**.

Glyflavanone-A (**3**) was obtained as an optically active yellow oil, $[\alpha]_D = +13.5°$, with molecular formula $C_{22}H_{22}O_5$. The IR carbonyl band at 1640 cm^{-1} and UV absorption at 227.6, 271.0, 289.2sh and 321.6sh nm suggested that compound **3** was a flavanone derivative [5]. The ^1H NMR spectrum was close to that of **1** with signals for a 2,2-dimethyl pyran ring at δ1.44, 1.46 (each 3H, *s*), 5.45 (1H, *d*, *J* = 10.2 Hz, H-3″) and 6.58 (1H, *d*, *J* = 10.2 Hz, H-4″), a lone aromatic proton at δ6.05 (1H, *br s*, H-6), a methoxyl group at δ3.89 (3H, *s*, 5-OMe), and *p*-disubstituted benzene moiety at δ6.94 (2H, *d*, *J* = 6.8 Hz, H-3′ and H-5′) and 7.38 (2H, *d*, *J* = 6.8 Hz, H-2′ and H-6′). However, it lacked the signals for a phenolic proton and two vinyl protons. Instead, three characteristic ABX signals at δ2.78 (1H, *dd*, *J* = 16.4, 3.1 Hz), 3.01 (1H, *dd*, *J* = 16.4, 12.5 Hz) and 5.36 (1H, *dd*, *J* = 12.5, 3.1 Hz) were easily assigned to methylene protons on C-3 adjacent to a carbonyl group and one methine proton on C-2 bearing a heteroatom, O, phenyl substituents in the flavanone nucleus. In a NOESY experiment (Fig. 1), the correlation between 5-OMe (δ3.89) and H-6 (δ6.05) suggested an angular orientation of the pyran ring to the flavanone skeleton. Therefore, the structure of **3** was established as glyflavanone-A.

An optically active glyflavanone-B (**4**), $[\alpha]_D = +18.3°$, was isolated as a yellow syrup with molecular formula $C_{23}H_{24}O_6$. Compound **4** was easily identified by comparison of its spectral data with those of **3** and **2**. A flavanone derivative containing a 2,2-dimethyl pyran group was supported by the close similarity of the UV, IR and ^1H NMR spectra with those of **3**. A 3′,4′-dimethoxybenzene ring in this structure was deduced from the remaining ^1H NMR signals which were in accord with **2**. A NOE difference experiment confirmed the angular orientation of the pyran ring, i.e. enhancement of the signal at δ6.05 (H-6) by 4.87% on irradiation of the signal at δ3.90 (5-OMe). Thus, glyflavanone-B has the structure **4**.

A rare sulphur-containing compound, glycothiomin-A (**5**), was isolated as needles, mp 160–161° ($CHCl_3$). The



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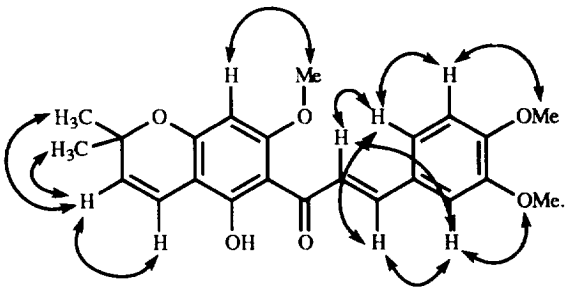

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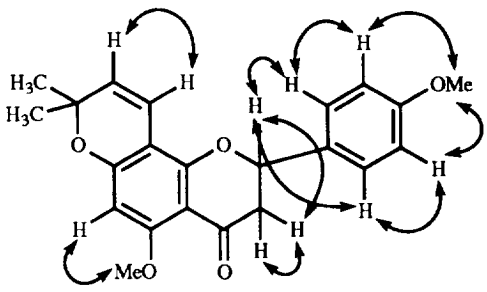

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Fig. 1. The NOESY correlations of compounds **1**, **2** and **3**.

high-resolution mass spectrum suggested the molecular formula as $C_5H_9NO_2S$. The ^1H NMR signals at δ2.91 (3H, *d*, J = 4.9 Hz) and 6.52 (1H, *br s*, D_2O exchangeable) and the IR absorptions at 3306 and 1649 cm^{-1} indicated that **5** was an *N*-methylamide derivative. The nature of the chemical shifts and the magnitude of the coupling constants in two downfield vinyl protons at δ6.71 (1H, *d*, J = 14.5 Hz, H-α) and 7.56 (1H, *d*, J = 14.5 Hz, H-β) indicated a *trans* double bond configuration bearing a strong electron-withdrawing substituent. A single methyl signal at δ2.69 as well as a strong IR band at 1050 cm^{-1} together with a fragment ion at *m/z* 84 $[M - MeS = O]^+$ in the mass spectrum showed the presence of sulphoxide functionality. The ^{13}C NMR spectrum of **5** was also in agreement with this structure: one amidic carbon at δ163.2, two vinyl carbons conjugated with a carbonyl group at δ128.6 (C-α) and 145.6 (C-β) and two methyl carbons at δ26.4 and 39.8 adjacent to S and N heteroatoms, respectively. Therefore, the structure of glycothiomin-A was established as **5**.

A stereoisomeric glycothiomin-B (**6**) was subsequently isolated as a yellow oil with the same molecular formula, $C_5H_9NO_2S$, as **5**. Both **5** and **6** showed comparable ^1H NMR spectra. The expected *cis*-amidosulphoxide structure for **6** was evident from the smaller coupling constant between the two vinyl protons at δ6.79 (H-β) and 6.19 (H-α). This allowed us to deduce the structure of glycothiomin-B as **6**.

Glycocitridine (**7**), $C_{13}H_{13}NO_5$, was purified as needles with mp 174–175°. The presence of a 2-quinolone skeleton [6] was suggested by the UV absorption at 216.8, 229.8sh, 251.2sh and 323.6 nm and the following observations: (i) a positive response to Dragendorff's test, (ii) an IR carbonyl band at 1619 cm^{-1}, (iii) a broad IR NH band at 3386 cm^{-1} together with a deuterium-exchangeable proton signal at δ8.95. The ^1H NMR spectrum revealed the presence of an aldehydic proton, two mutually coupled aromatic protons and three methoxyl groups. On inspection of the chemical shifts of these protons, the downfield shifted methoxyl signal at δ4.16 was assigned as 4-OMe. This could be rationalized as due to the anisotropic effect of the 3-formyl group (δ10.43, *s*). As the AX-type aromatic protons at δ6.87 (1H, *d*, J = 9.2 Hz) and 7.75 (1H, *d*, J = 9.2 Hz) were assigned as H-6 and H-5, respectively, the remaining two singlet methoxyl signals at δ3.96 and 4.00 had to be located at C-7 and C-8 in order to account for the shielding of H-6 and the deshielding of H-5. H-5 was also deshielded by the *peri*-OMe at C-4. All these findings established that the alkaloid glycocitridine had structure **7**.

The known quinoline alkaloids γ-fagarine (**8**) [7, 8], skimmianine (**9**) [9], 1,2-dimethyl-4(1H)-quinolone (**10**) [10] and evomeliaefolin (**11**) [11]; furopyridine alkaloids (*Z*)-rhoifolic acid methyl ester (**12**) [12] and (*E*)-rhoifolic acid methyl ester (**13**) [12], chlorophylls methyl-21-hydroxy-(21*R*)-pheophorbide-a (**14**) [13] and methyl-21-hydroxy-(21*R*)-pheophorbide-b (**15**) [13] and amidosulphide penangin (**16**) [14] were characterized by comparison of their spectroscopic data (UV, IR, NMR and mass spectrum) with literature values.

From a biogenetic point of view, the co-occurrence of glychalcone-A (**1**) and -B (**2**) and glyflavanone-A (**3**) and -B (**4**) indicated chalcone–flavanone interconversion [15]. The formation of glycothiomin-A (**5**) and -B (**6**) could take place as a result of the further oxidation of penangin (**16**) in which the sulphur-containing acid moiety is claimed to be derived by the desamination and *S*-methylation of cysteine [14]. Finally, glycocitridine (**7**) would be the cleavage product following oxidation of the furan ring in a furoquinoline alkaloid. The isolation of glycocitridine (**7**), (*Z*)-rhoifolic acid methyl ester (**12**) and (*E*)-rhoifolic acid methyl ester (**13**) from *G. citrifolia* is the first time that the ring C opened products of a furoquinoline alkaloid have been reported from the same plant.

EXPERIMENTAL

Mps: uncorr.; UV: MeOH; IR: KBr unless otherwise stated; ^{1}H NMR and ^{13}C NMR: $CDCl_3$ or acetone-d_6, TMS as int. standard except where noted; MS: direct inlet system.

Plant material. Glycosmis citrifolia (Willd.) Lindl. used in this investigation was collected from Pen Lin, Tainan, Taiwan. A specimen of the plant has been deposited at the herbarium of the National Cheng Kung University, Tainan, Taiwan.

Extraction and separation. The dried leaves (1.87 kg) of *G. citrifolia* were extracted with hot MeOH (×5). The combined MeOH extracts were concd under red. pres. to give a dark green syrup (306 g). This was partitioned between H_2O and $CHCl_3$. The H_2O layer was extracted with EtOAc and *n*-BuOH successively. Compounds **5** (3 mg) and **6** (1 mg) were obtained from the EtOAc extract by chromatography over silica gel with $CHCl_3$–MeOH (5:1) as eluent. The *n*-BuOH extract gave **5** (1 mg) and **16** (3 mg) after chromatography over silica gel eluting with a gradient of $CHCl_3$ and MeOH. The $CHCl_3$ layer was concd and then extracted several times with 5% aq. HCl until it gave a negative response with Mayer's reagent. On chromatography over silica gel eluting with a gradient of $CHCl_3$ and MeOH it gave **8** (8 mg), **14** (8 mg), **15** (12 mg), **1** (3 mg), **2** (4 mg), **3** (2 mg), **4** (1 mg) and **11** (1 mg). The combined acidic soln was adjusted to pH > 9 with aq. NH_4OH and extracted with $CHCl_3$ again. This $CHCl_3$ extract was directly chromatographed on silica gel eluting with a gradient of $CHCl_3$ and Me_2CO to afford **9** (213 mg), **10** (2 mg), **12** (3 mg), **13** (1 mg) and **7** (1 mg), successively.

Glychalcone-A (**1**). HRMS: calcd for $C_{22}H_{22}O_5$, *m/z* 366.1467 $[M]^+$; found 366.1469; IR ν_{max} cm^{-1}: 3400, 1617, 1574, 1557, 1509; EIMS *m/z* (rel. int.): 366 $[M]^+$ (45), 351 (33), 232 (9), 218 (12), 217 (100); ^{1}H NMR (acetone-d_6): δ1.43 (6H, *s*, 2×2″-Me), 3.86 (3H, *s*, 4-OMe), 4.00 (3H, *s*, 6′-OMe), 5.56 (1H, *d*, *J* = 10.0 Hz, H-3″), 6.03 (1H, *br s*, H-5′), 6.61 (1H, *dd*, *J* = 10.0, 0.8 Hz, H-4″), 7.00 (2H, *d*, *J* = 8.8 Hz, H-3 and H-5), 7.69 (2H, *d*, *J* = 8.8 Hz, H-2 and H-6), 7.77 (1H, *d*, *J* = 15.6 Hz, H-α), 7.89 (1H, *d*, *J* = 15.6 Hz, H-β), 14.73 (1H, *s*, OH, D_2O exchangeable).

Glychalcone-B (**2**). HRMS: calcd for $C_{23}H_{24}O_6$, *m/z* 396.1573 $[M]^+$; found 396.1570; UV λ_{max} nm: 234.8, 266.6, 286.8, 299.0, 374.6; IR ν_{max} cm^{-1}: 2922, 2850, 1618, 1577, 1501; EIMS *m/z* (rel. int.): 396 $[M]^+$ (47), 381 (35), 232 (10), 217 (100); ^{1}H NMR (acetone-d_6): δ1.42 and 1.44 (each 3H, *s*, 2×2″-Me), 3.87 (3H, *s*, 4-OMe), 3.90 (3H, *s*, 3-OMe), 4.00 (3H, *s*, 6′-OMe), 5.56 (1H, *d*, *J* = 10.0 Hz, H-3″), 6.03 (1H, *br s*, H-5′), 6.61 (1H, *dd*, *J* = 10.0, 0.8 Hz, H-4″), 7.02 (1H, *d*, *J* = 8.4 Hz, H-5), 7.29 (1H, *dd*, *J* = 8.4, 2.0 Hz, H-6), 7.32 (1H, *d*, *J* = 2.0 Hz, H-2), 7.74 (1H, *d*, *J* = 15.6 Hz, H-α), 7.89 (1H, *d*, *J* = 15.6 Hz, H-β), 13.62 (1H, *s*, OH, D_2O exchangeable).

Glyflavanone-A (**3**). $[\alpha]_D$ = +13.5° ($CHCl_3$; *c* 0.065). HRMS: calcd for $C_{22}H_{22}O_5$, *m/z* 366.1467 $[M^+]$; found 366.1464; IR ν_{max} cm^{-1}; 2920, 1680, 1641, 1584, 1516; EIMS *m/z* (rel. int.): 366 $[M]^+$ (33), 351 (21), 232 (26), 217 (100), 203 (32), 149 (47), 134 (30), 125 (60); ^{1}H NMR ($CDCl_3$): δ1.44 and 1.46 (each 3H, *s*, 2×2″-Me), 2.78 (1H, *dd*, *J* = 16.4, 3.1 Hz, H-3), 3.01 (1H, *dd*, *J* = 16.4, 12.5 Hz, H-3), 3.84 (3H, *s*, 4′-OMe), 3.89 (3H, *s*, 5-OMe), 5.36 (1H, *dd*, *J* = 12.5, 3.1 Hz, H-2), 5.45 (1H, *d*, *J* = 10.2 Hz, H-3″), 6.05 (1H, *br s*, H-6), 6.58 (1H, *d*, *J* = 10.2 Hz, H-4″), 6.94 (2H, *d*, *J* = 6.8 Hz, H-3′ and H-5′), 7.38 (2H, *d*, *J* = 6.8 Hz, H-2′ and H-6′).

Glyflavanone-B (**4**). $[\alpha]_D$ = +18.3° ($CHCl_3$; *c* 0.05). HRMS: calcd for $C_{23}H_{24}O_6$, *m/z* 396.1573 $[M]^+$; found 396.1573; UV λ_{max} nm: 226.2, 269.8, 295.8sh, 335.8sh; IR ν_{max} cm^{-1}: 2940, 1680, 1605, 1585, 1520; EIMS *m/z* (rel. int.): 396 $[M]^+$ (11), 381 (9), 347 (38), 234 (15), 232 (14), 217 (63), 164 (20), 120 (100); ^{1}H NMR ($CDCl_3$): δ1.44 and 1.46 (each 3H, *s*, 2×2″-Me), 2.77 (1H, *dd*, *J* = 16.3, 4.0 Hz, H-3), 3.04 (1H, *dd*, *J* = 16.3, 11.9 Hz, H-3), 3.90 (3H, *s*, 5-OMe), 3.91, 3.92 (each 3H, *s*, 3′-OMe and 4′-OMe), 5.36 (1H, *dd*, *J* = 11.9, 4.0 Hz, H-2), 5.48 (1H, *d*, *J* = 9.7 Hz, H-3″), 6.05 (1H, *br s*, H-6), 6.59 (1H, *d*, *J* = 9.7 Hz, H-4″), 6.95 (3H, *m*, 3×arom. H).

Glycothiomin-A (**5**). HRMS: calcd for $C_5H_9NO_2S$, *m/z* 147.0354 $[M]^+$; found 147.0357; UV λ_{max} nm: 205.0, 260.0; IR ν_{max} cm^{-1}: 3306, 3050, 1649, 1616, 1563, 1050; EIMS *m/z* (rel. int.): 147 $[M]^+$ (38), 132 (3), 117 (10), 101 (36), 90 (12), 84 (37), 58 (100); ^{1}H NMR ($CDCl_3$): δ2.69 (3H, *s*, S-Me), 2.91 (3H, *d*, *J* = 4.9 Hz, N-Me), 6.52 (1H, *br s*, NH, D_2O exchangeable), 6.71 (1H, *d*, *J* = 14.5 Hz, H-α), 7.56 (1H, *d*, *J* = 14.5 Hz, H-β). ^{13}C NMR ($CDCl_3$): δ26.4 (Me-S), 39.8 (Me-N), 128.6 (C-α), 145.6 (C-β), 163.2 (C=O).

Glycothiomin-B (**6**). HRMS: calcd for $C_5H_9NO_2S$, *m/z* 147. 0354 $[M]^+$; found 147.0352; UV λ_{max} nm: 210.8, 251.4sh, 293.4sh; IR ν_{max} cm^{-1}: 3226, 2922, 1658, 1556, 1060; EIMS *m/z* (rel. int.): 147 $[M]^+$ (11), 132 (100), 117 (7), 84 (23), 71 (18). ^{1}H NMR ($CDCl_3$): δ2.88 (3H, *s*, S-Me), 2.89 (3H, *d*, *J* = 4.9 Hz, N-Me), 6.19 (1H, *d*, *J* = 10.1 Hz, H-α), 6.79 (1H, *d*, *J* = 10.1 Hz, H-β).

Glycocitridine (**7**). IR ν_{max} cm^{-1}: 3386, 2928, 2854, 1666, 1619, 1502; EIMS *m/z* (rel. int.): 263 $[M]^+$ (7), 253 (24), 220 (16), 205 (21), 149 (74), 109 (17), 95 (21), 83 (29), 71 (40), 69 (53), 57 (100); ^{1}H NMR ($CDCl_3$): δ3.96 and 4.00 (each 3H, *s*, 7-OMe and 8-OMe), 4.16 (3H, *s*, 4-OMe), 6.87 (1H, *d*, *J* = 9.2 Hz, H-6), 7.75 (1H, *d*, *J* = 9.2 Hz, H-5), 8.95 (1H, *br s*, NH, D_2O exchangeable), 10.43 (1H, *s*, CHO).

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