Chemical Constituents of *Glycosmis arborea*: Three New Carbazole Alkaloids and Their Biological Activity[1]

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As part of the phytochemical studies of the plant genus *Glycosmis*, the constituents of the plant *Glycosmis arborea* were investigated. Three new carbazole alkaloids named glybomines A (**1**), B (**2**), and C (**3**), along with known monomeric alkaloids belonging to the carbazole, quinazoline, furoquinoline, quinolone, and acridone classes, were isolated from stems of the plant collected at Mymensing in Dhaka, Bangladesh. Glybomine A (**1**) is the first example of a 2,5-oxygenated carbazole alkaloid from natural sources. As a primary screening test for anti-tumor promoters, nine alkaloids isolated from this plant have been tested for their inhibitory effects on Epstein−Barr virus early antigen (EBV-EA) induction by the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA). All alkaloids tested showed inhibitory activity.

In previous phytochemical studies of plants in the genus *Glycosmis*, we investigated *G. citrifolia*,[2] *G. pentaphylla*,[3] and *G. cochinchinensis*[4] and characterized numerous alkaloids. Here we report on the alkaloidal components of *G. arborea* (Roxb.) DC. (Rutaceae) collected from Mymensing in Dhaka, Bangladesh. Three new carbazole alkaloids named glybomines A (**1**), B (**2**), and C (**3**) along with known monomeric alkaloids belonging to the carbazole, quinazoline, furoquinoline, quinolone, and acridone classes were identified. In our previous papers we reported studies of several alkaloids, including carbazoles,[5] quinolones,[6] froquinolines,[6] isoquinolines,[7] and acridones,[8,9] and their inhibitory effects on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein−Barr virus early antigen (EBV-EA) activation as potential anti-tumor-promoting agents. In the course of our continuing screening of various plants for anti-tumor-promoting agents, the acetone extract of *Glycosmis* stems exhibited significant anti-tumor-promoting activity on EBV-EA activation. In this paper, we also report the results of an assay on inhibitory effects of nine alkaloids isolated from this plant on EBV-EA activation.

Results and Discussion

The acetone extract of stems was fractionated by a combination of silica gel column chromatography and preparative TLC to give three new carbazole alkaloids along with 18 known alkaloids.

Glybomine A (**1**) was obtained as a colorless oil. The molecular formula was determined as $C_{15}H_{15}NO_2$ by HRE-IMS. The UV spectrum showed a strong absorption at λ_{max} 239 nm accompanied by two medium (λ_{max} 294 and 330 nm) and one low (316 nm) intensity peak. The IR spectrum showed an NH absorption at ν_{max} 3475 cm^{-1}. These spectroscopic data together with the analysis of the ^1H NMR data suggested that glybomine A had a carbazole nucleus.[10−12] The ^1H NMR spectrum (Table 1) in acetone-d_6 indicated the presence of two *O*-methyl (δ_H 3.87 and 4.03), an arylmethyl (δ_H 2.29), and an NH group (δ_H 10.09). Furthermore, in the aromatic proton region, two 1H singlets at δ_H 6.99 and 7.94 and three contiguous 1H proton signals at δ_H 6.65, 7.02, and 7.18 were observed. The results of NOE experiments (Figure 2) suggested arrangements of the substituents on the carbazole nucleus as follow. (a) Observation of a 3% NOE enhancement of both signals of the higher field singlet at δ_H 6.99 and a doublet at δ_H 7.02 on irradiation of the NH proton at δ_H 10.09 showed that these protons were assignable to H-1 and H-8, respectively. (b) Appearance of a 13% NOE between the 1H singlet at δ_H 6.99 (H-1) and an *O*-methyl signal at δ_H 3.87 suggested the methoxy group was located at C-2. (c) Location of another methoxy group (δ_H 4.03) at C-5 was confirmed by appearances of an 11% and 1% NOE, respectively, at the doublet (δ_H 6.55, H-6) and the lower field singlet (δ_H 7.94, H-4) on irradiation of this methoxy signal. (d) The deshielded 1H singlet at δ_H 7.94 (H-4) also showed a 6% NOE on irradiation of the arylmethyl signal (δ_H 2.29). On the basis of the above analyses, the structure of **1** was inferred to be glybomine A. This is the first isolation of a 2,5-oxygenated carbazole alkaloid from natural sources.

Glybomine B (**2**) was isolated as a colorless oil, and the molecular formula, $C_{19}H_{21}NO_2$, was established by HRE-IMS. UV bands were observed at λ_{max} 217, 239, and 307 nm as two strong and one medium intensity peak, respectively, accompanied by two shoulders at λ_{max} 263 and 336 nm. This absorption spectrum was similar to that of 2,6-dimethoxy-3-methylcarbazole, called glycozolidine (**5**), from *G. arborea*.[13] In the ^1H NMR spectrum (Table 1), *ortho*-coupled AB-type doublets at δ_H 6.99 and 7.13 (J = 8.4 Hz) and two singlets at δ_H 6.77 and 7.82 appeared as aromatic protons, and as remaining signals, an arylmethyl (δ_H 2.39), a methoxy (δ_H 3.87), a prenyl (δ_H 5.32, 3.92, 1.93, 1.70), and two D_2O-exchangeable signals (OH: δ_H 4.85, NH: δ_H 7.68) were observed. Locations of these moieties on the carbazole nucleus were revealed by the NOE experiments (Figure 2). On irradiation of the NH protons at δ_H 7.68, 3% NOE enhancement of the doublet (δ_H 7.13, H-8) and singlet (δ_H 6.77, H-1) were observed, respectively. The presence of a 2% NOE increment at the singlet (δ_H 6.77, H-1) on irradiation of a hydroxy proton (δ_H 4.85) indicated

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Table 1. ^{1}H and ^{13}C NMR Data of Glybomines (**1**, **2**, and **3**)[a]

	glybomine A (**1**)	glybomine B (**2**)			glybomine C (**3**)		
	δ_H[b]	δ_C	δ_H	HMBC	δ_C	δ_H	HMBC
1	6.99 (s)	96.2 (d)	6.77 (s)		96.7 (d)	6.88 (s)	2-OH
2		152.7 (s)		H-1, H-4, 3-CH_3	154.9 (s)		H-1, H-4, 2-OH, 3-CH_3
2-OH			4.85 (br s)			8.15 (br s)	
2-OCH_3	3.87 (3H, s)						
3		115.6 (s)		H-4, 3-CH_3	116.6 (s)		H-1, 2-OH, 3-CH_3
3-CH_3	2.29 (3H, s)	16.3 (q)	2.39 (3H, s)	H-4	16.9 (q)	2.31 (3H, s)	H-4
4	7.94 (s)	124.5 (d)	7.82 (s)	3-CH_3	124.7 (d)	7.77 (s)	3-CH_3
4a		117.6 (s)		H-1, H-4, NH	117.4 (s)		NH
4b		122.8 (s)		H-4, H-8, NH	123.6 (s)		H-4, H-8, NH
5		124.3 (s)		H-7, H-1′	121.1 (s)		H-7, H-1′, 6-OH
5-OCH_3	4.03 (3H, s)						
6	6.65 (d, 8.1)	151.0 (s)		H-7, H-8, H-1′, 6-OCH_3	148.2 (s)		H-7, H-8, H-1′, 6-OH
6-OH						7.54 (br s)	
6-OCH_3		57.9 (q)	3.87 (3H, s)				
7	7.18 (t, 8.1)	110.9 (d)	6.99 (d, 8.4)		113.6 (d)	6.84 (d, 8.4)	6-OH
8	7.02 (d, 8.1)	107.7 (d)	7.13 (d, 8.4)		108.6 (d)	7.03 (d, 8.4)	
8a		135.1 (s)		H-7, NH	135.5 (s)		H-7, NH
9a		140.6 (s)		H-1, H-4, NH	141.9 (s)		H-1, H-4, NH
NH	10.09 (br s)		7.68 (br s)			9.64 (br s)	
1′		25.7 (t)	3.92 (2H, d, 7.0)		26.2 (t)	3.90 (2H, d, 7.0)	
2′		122.5 (d)	5.32 (m)	H-1′, H-4′, H-5′	124.3 (d)	5.31 (m)	H-1′, H-4′, H-5′
3′		132.2 (s)		H-1′, H-4′, H-5′	131.6 (s)		H-1′, H-4′, H-5′
4′		18.2 (q)	1.93 (3H, s)	H-2′, H-5′	18.3 (q)	1.91 (3H, s)	H-2′, H-5′
5′		25.6 (q)	1.70 (3H, s)	H-2′, H-4′	25.8 (q)	1.66 (3H, s)	H-2′, H-4′

[a] Values in (δ_H and δ_C) ppm. All signals correspond to 1H, unless otherwise stated. Numbers in parentheses are coupling constants (J) in Hz. [b]Spectra were taken in acetone-d_6.

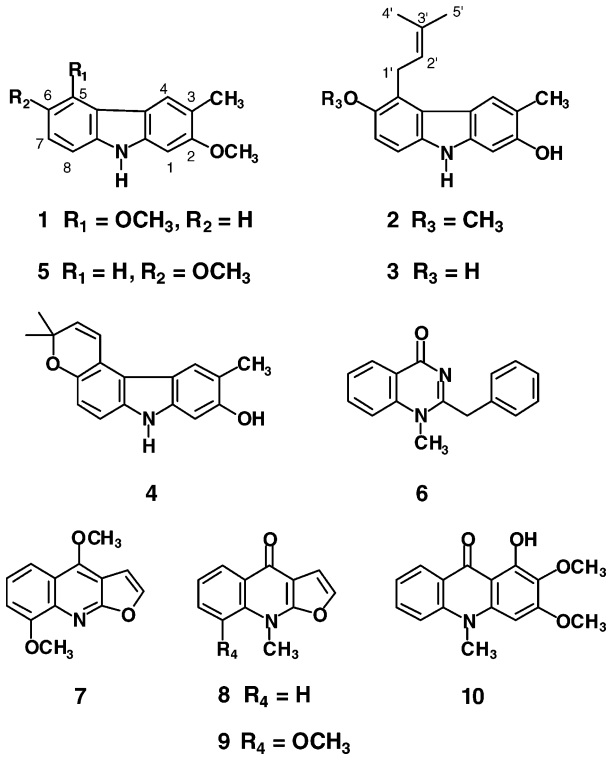

Figure 1. Structures of alkaloids from *Glycosmis arborea*.

the location of the hydroxy group at C-2. The location of an arylmethyl group at C-3 was confirmed on the basis of reciprocal NOE enhancements between the deshielded singlet at δ_H 7.82 (H-4) and this methyl signal. Furthermore, appearances of NOE increments between the H-4 signal and both a vinyl and methylene proton on the prenyl group suggested the location of the prenyl moiety at C-5. The methoxy group was placed at C-6 on the basis of an 8% NOE enhancement between one of the AB-type doublets (δ_H 6.99) and this methoxy signal (δ_H 3.87). On the basis of these spectroscopic analyses and the results of HMBC correlations shown in Table 1, structure **2** was assigned to glybomine B.

Glybomine C (**3**) was isolated as a colorless oil. The HREIMS analysis indicated the molecular formula to be $C_{18}H_{19}NO_2$, a difference of CH_2 compared with **2**. The UV spectrum was similar to that of **2**. The spin patterns in the ^{1}H NMR spectrum (Table 1) showed a good similarity to that of **2**, except for a lack of a methoxy signal at δ_H 3.87 in the spectrum of **2**. On the basis of these spectroscopic data coupled with results of NOE and HMBC experiments (Figure 2 and Table 1), we proposed the structure **3** for glybomine C.

Five types of other alkaloids including carbazole, furoquinoline, quinolone, acridone, and quinazoline alkaloids were isolated from *G. arborea*. The carbazole alkaloids include: 3-methylcarbazole,[14] methyl carbazole-3-carboxylate,[15] glycozolinine,[16] glycoborinine (**4**),[13] glycozoline,[15] 5-methoxy-3-methylcarbazole,[17] glycozolidine (**5**),[13] and glycomaurrol.[18] Furoquinoline alkaloids include skimianine[13] and 4,8-dimethoxyfuro[2,3-*b*]quinoline (**7**).[19] 2-Quinolone alkaloids include glycocitlone C,[2] acutifolin,[20] and 4,8-dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone.[21] 4-Quinolone alkaloids include isodictamnine (**8**)[22] and iso-γ-fagarine (**9**).[23] Acridone alkaloids comprise 1-hydroxy-3-methoxy-10-methylacridan-9-one[24] and arborinine (**10**).[25] Quinazoline alkaloids comprise arborine (**6**).[25]

The major alkaloid was arborine (**6**), belonging to the quinazoline alkaloid group. Although these alkaloids are known to be derived biogenetically from anthranilic acid,[4] *G. arborea* is one of the rare examples of plants containing various types of alkaloids as secondary metabolites.

Inhibitory Effects on EBV-EA Activation. The antitumor-promoting activity of the nine alkaloids isolated from this plant was tested in a short-term in vitro assay of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein–Barr virus early antigen (EBV-EA) activation in Raji cells. Their inhibitory effects on the activation of the virus-genome and the viabilities of Raji cells are shown in Table 2. All alkaloids showed potent dose-dependent inhibitory

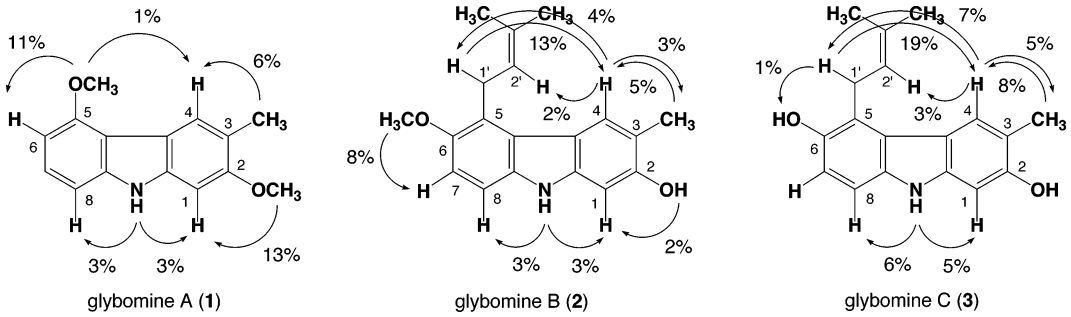

Figure 2. NOE spectra of glybomines A (**1**), B (**2**), and C (**3**).

Table 2. Inhibitory Effects of Alkaloids from *G. arborea* on TPA-Induced EBV-EA Activation[a]

	EBV-EA-positive cells (% viability)			
	compound concentration (mol ratio/32 pmol TPA)			
compound	1000	500	100	10
glybomine B (**2**)	15.3 ± 0.6 (60)	46.7 ± 1.8 (>80)	68.7 ± 2.2 (>80)	96.4 ± 1.1 (>80)
glybomine C (**3**)	13.4 ± 1.0 (60)	45.6 ± 2.0 (>80)	68.9 ± 2.0 (>80)	94.6 ± 0.8 (>80)
glycoborinine (**4**)	17.4 ± 1.1 (60)	49.1 ± 1.6 (>80)	73.7 ± 2.2 (>80)	100.0 ± 0.9 (>80)
glycozolidine (**5**)	24.3 ± 0.5 (60)	51.3 ± 1.9 (>80)	76.0 ± 2.1 (>80)	100.0 ± 0.7 (>80)
arborine (**6**)	12.7 ± 1.1 (60)	40.4 ± 1.1 (>80)	75.6 ± 1.9 (>80)	100.0 ± 0.4 (>80)
4,8-dimethoxyfuro[2,3-*b*]quinoline (**7**)	15.4 ± 0.5 (60)	38.2 ± 1.7 (>80)	77.7 ± 1.8 (>80)	100.0 ± 0.2 (>80)
isodictamnine (**8**)	18.4 ± 0.6 (60)	40.3 ± 1.4 (>80)	72.2 ± 1.5 (>80)	100.0 ± 0.7 (>80)
iso-γ-fagarine (**9**)	19.9 ± 0.1 (60)	40.5 ± 1.2 (>80)	79.5 ± 2.0 (>80)	100.0 ± 0.1 (>80)
arborinine (**10**)	2.7 ± 0.5 (60)	39.6 ± 2.2 (>80)	74.3 ± 2.0 (>80)	95.6 ± 0.8 (>80)
β-carotene[b]	9.1 ± 0.5 (60)	34.3 ± 1.1 (>80)	82.7 ± 1.8 (>80)	100.0 ± 0.2 (>80)

[a] Mol ratio/TPA (32 pmol = 20 ng/mL), 1000 mol ratio = 32 nmol, 500 mol ratio = 16 nmol, 100 mol ratio = 3.2 nmol, and 10 mol ratio = 0.32 nmol. Values are EBV-EA activation (%) ± SD in the presence of the test compound relative to the positive control (100%). Values in parentheses represent the surviving Raji cells measured by Trypan Blue staining. A minimum 60% survival rate of Raji cells 2 days after treatment with the compounds is required for an accurate result. [b] Reference compound.

effects on EBV-EA induction by TPA. The inhibitory effects of all alkaloids tested exhibited significant activity of 75.7−97.3% inhibition at 1×10^3 mol ratio/TPA but only weak cytotoxicity against Raji cells even at 1×10^3 mol ratio/TPA. In four carbazole alkaloids (**2**−**5**), glybomine B (**2**) and glybomine C (**3**) with a prenyl moiety at C-5 showed weak inhibitory activity even at 1×10 mol ratio/TPA (3.6−5.4%) and were more effective than glycoborinine (**4**) and glycozolidine (**5**) at all concentrations. In a previous paper, we reported that 4-prenylated carbazole alkaloids display a significant inhibitory effect.[5] The present study also gives a consistent result and suggests that the presence of a prenyl moiety in the carbazole alkaloids plays an important role in terms of anti-tumor-promoting activity. Quinazoline (**6**) and three furanoquinoline alkaloids (**7**−**9**) also showed about the same inhibitory activity as glycoborinine (**4**) and glycozolidine (**5**). Arborinine (**10**), the major acridone alkaloid in this plant, showed weak inhibitory activity even at 1×10 mol ratio/TPA (4.4%), the same as carbazole alkaloids (**2** and **3**).

These results suggest that some alkaloids isolated from *G. arborea* are nearly equivalent to β-carotene, a vitamin A precursor commonly used in cancer prevention studies as a standard reference,[26] and might be valuable as anti-tumor promoters and as chemopreventive agents in chemical carcinogenesis. An investigation into the structure−activity relationship and the inhibitory mechanisms of these alkaloids on the tumor-promoting stage is now in progress.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR, COSY, HMQC, HMBC (J = 8 Hz), and NOE were measured on either a JNM A-400, A-600 or a ECP-500 (JEOL) spectrometer. Chemical shifts are in δ (ppm) with tetramethylsilane (TMS) as an internal reference. Mass spectra were taken under EI conditions, unless otherwise stated, using an HX-110 (JEOL) and/or JMS-700 (JEOL) spectrometers with a direct inlet system. UV spectra were recorded on a UVIDEC-610C double-beam spectrophotometer (JASCO) in MeOH; IR spectra on an IR-230 (JASCO) in $CHCl_3$. Preparative TLC was done on Kieselgel 60 F_{254} (Merck).

Plant Materials. Stems of *G. arborea* [Roxb.] DC. (Rutaceae) were collected from Mymensing, Bangladesh, in April, 1997. A voucher specimen was deposited in the herbarium of the Department of Botany, University of Dhaka. The plant was identified by Md. Shajahan of the Department of Pharmacy, University of Dhaka.

Isolation of Glybomines A (1), B (2), and C (3) from *G. arborea*. The dried stems (350 g) of *G. arborea* were extracted with acetone. The acetone extract (1.77 g) was subjected to silica gel column chromatography, eluted successively with hexane−acetone (20:1, 19:1, 9:1, 6:1, 7:3, and 1:1), acetone, CH_2Cl_2−MeOH (3:1), and MeOH to give 11 fractions. Each fraction was further subjected to silica gel column and preparative thin-layer chromatography to give three new carbazole alkaloids along with 18 known compounds. From the hexane−acetone (20:1) eluate 3-methylcarbazole (1.6 mg) was isolated. From the hexane−acetone (19:1) eluate glycozoline (15.9 mg), 5-methoxy-3-methylcarbazole (1.2 mg), 4,8-dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone (24.7 mg), actifolin (2.2 mg), and glycocitlone C (15.4 mg) were isolated. From the hexane−acetone (9:1) eluate glybomine A (**1**, 0.8 mg), methyl carbazole-3-carboxylate (12.7 mg), glycozolidine (**5**, 34.0 mg), and isodictamnine (**8**, 10.8 mg) were isolated. From the hexane−acetone (6:1) eluate 1-hydroxy-3-methoxy-10-methylacridan-9-one (2.3 mg) and glycomurrol (0.6 mg) were isolated. From the hexane−acetone (7:3) eluate 4,8-dimethoxyfuro[2,3-*b*]quinoline (**7**, 8.5 mg), arborinine (**10**, 52.9 mg), glycozolinine (0.5 mg), skimmianine (9.4 mg), glycoborinine (**4**, 43.4 mg), and glybomine B (**2**, 4.2 mg) were isolated. From the hexane−acetone (1:1) eluate glybomine C (**3**, 3.2 mg) was isolated. From the acetone eluate iso-γ-fagarine (**9**, 4.8 mg) was isolated. From the $CHCl_3$−acetone (85:15) eluate arborine (**6**, 61.8 mg) was isolated.

Known components were fully characterized by comparison of ^{1}H NMR and IR spectra with reported data.

Glybomine A (1): colorless oil; UV (MeOH) λ_{max} 209, 239, 264sh, 294, 316, 330 nm; IR ($CHCl_3$) ν_{max} 3475 cm^{-1}; ^{1}H NMR, see Table 1; NOE, see Figure 2; EIMS *m*/*z* 241 $[M]^+$ (100), 226 (66), 211 (13), 198 (19), 183 (18), 154 (11); HREIMS *m*/*z* 241.1091 (calcd for $C_{15}H_{15}NO_2$, 241.1103).

Glybomine B (2): colorless oil; UV (MeOH) λ_{max} 217, 239, 263sh, 307, 336 nm; IR ($CHCl_3$) ν_{max} 3473, 3342 (br) cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; NOE, see Figure 2; EIMS *m*/*z* 295 $[M]^+$ (100), 280 (21), 264 (26), 238 (24), 227 (12), 210 (12), 197 (12); HREIMS *m*/*z* 295.1558 (calcd for $C_{19}H_{21}NO_2$, 295.1573).

Glybomine C (3): colorless oil; UV (MeOH) λ_{max} 218, 237, 266, 309, 338 nm; IR ($CHCl_3$) ν_{max} 3465, 3325 (br) cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; NOE, see Figure 2; EIMS *m*/*z* 281 $[M]^+$ (84), 264 (27), 225 (100), 197 (18); HREIMS *m*/*z* 281.1409 (calcd for $C_{18}H_{19}NO_2$, 281.1415).

In Vitro EBV-EA Activation Experiments. The inhibition of EBV-EA activation was assayed using the method previously described.[5−9] In brief, Raji cells were grown to a density of 10^6 cells/mL, harvested by centrifugation, and resuspended in RPMI 1640 medium (Nakalai Tesque, Kyoto, Japan) with 10% FCS containing 4 mM *n*-butyric acid as inducer, 32 pmol of TPA (20 ng/mL in DMSO), and 32, 3.2, or 0.32 nmol of the test compound (DMSO solutions). The cells were incubated at 37 °C for 48 h. Cell number and viability were determined after 48 h by means of a hemocytometer (Trypan Blue staining method). Untreated cultures served as the controls, and EBV-EA inhibitory activity of the test compounds was estimated on the basis of the percentage of the number of positive cells compared to that observed in the case of a control without the test product. In each assay, at least 500 cells were counted and the results were read blind.

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