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Alstiphyllanines E–H, picraline and ajmaline-type alkaloids from *Alstonia macrophylla* inhibiting sodium glucose cotransporter

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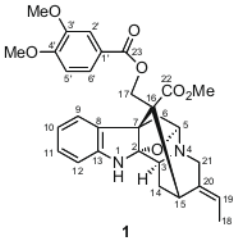
ABSTRACT

Three new picraline-type alkaloids, alstiphyllanines E–G (**1**–**3**) and a new ajmaline-type alkaloid, alstiphyllanine H (**4**) were isolated from the leaves of *Alstonia macrophylla* together with 16 related alkaloids (**5**–**20**). Structures and stereochemistry of **1**–**4** were fully elucidated and characterized by 2D NMR analysis. Alstiphyllanines E and F (**1** and **2**) showed moderate Na^+-glucose cotransporter (SGLT1 and SGLT2) inhibitory activity. A series of a hydroxy substituted derivatives **21**–**28** at C-17 of the picraline-type alkaloids have been derived as having potent SGLT inhibitory activity. 10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**6**) exhibited potent inhibitory activity, suggesting that the presence of an ester side chain at C-17 may be important to show SGLT inhibitory activity. Structure activity relationship of alstiphyllanines on inhibitory activity of SGLT was discussed.

1. Introduction

Na^+-glucose cotransporter (SGLT) is a membrane protein that plays an important role in the re-absorption of glucose in the kidneys. SGLT is known to have three isoforms (SGLT1, SGLT2, and SGLT3).[1–3] SGLT1 is expressed primarily in the brush border membrane of mature enterocytes in the small intestine, where it absorbs dietary glucose and galactose from the gut lumen.[4] SGLT2 is only expressed in the renal cortex, where it is assumed to be present in the brush border membrane of the S1 and S2 segments of the proximal tubule, and to be responsible for the re-absorption of glucose from the glomerular filtrate.[4] It is expected that the inhibition of SGLT could decrease glucose re-absorption and that this could thus result in an increase in urinary sugar excretion, and a decrease in blood glucose level. Thus, SGLT inhibitors have therapeutic potential for type 2 diabetes.[5]

Our screening study on SGLT inhibitors in traditional medicine[6] discovered that the methanol extract of *Alstonia macrophylla* shows moderate SGLT inhibitory activity. The genus *Alstonia*, which is widely distributed in tropical regions of Africa and Asia, are well-known rich sources of unique monoterpene indole alkaloids with various biological activities such as anticancer, antibacterial, anti-inflammatory, antitussive, and antimalarial properties.[7] Recently, several new indole alkaloids were isolated from extracts of *Alstonia*



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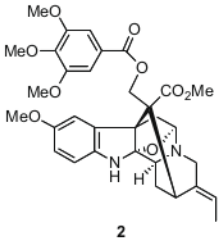

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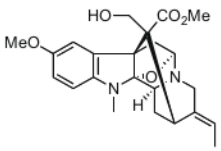

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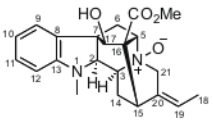

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species collected in Indonesia and Malaysia.[8,9] With an aim to isolate additional alkaloids against SGLT inhibitory activity, purification of extracts of *A. macrophylla* Wall.ex G. Don (Apocynaceae) collected in Indonesia led to four new alkaloids alstiphyllanines E–H (**1**–**4**) together with 16 known alkaloids (**5**–**20**). Herein we report the isolation and structure elucidation of four new indole alkaloids, alstiphyllanines E–H (**1**–**4**) from *A. macrophylla* as well as SGLT inhibitory activity and structure activity relationship (SAR) study of some picraline-type indole alkaloids.

2. Results and discussion

2.1. Structures of alstiphyllanines E–H (1–4)

Leaves of *A. macrophylla* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, adjusted to pH 9 with satd aq Na_2CO_3, were extracted with $CHCl_3$. The $CHCl_3$-soluble materials were subjected to an LH-20 column ($CHCl_3$/MeOH, 1:1) followed by a silica gel column ($CHCl_3$/MeOH, 1:0–0:1). The eluted fractions were further separated by ODS HPLC (MeOH/H_2O/TFA) to afford **1** (1.8 mg, 0.00050% dry weight), **2** (1.3 mg, 0.00036%), **3** (10.4 mg, 0.0029%), and **4** (3.6 mg, 0.0013%), together with 16 known alkaloids, burnamine-17-*O*-3′,4′,5′-trimethoxybenzoate[10] (**5**), 10-methoxy-*N*(1)-methylburnamine-17-*O*-veratrate[10] (**6**), alstiphyllanine D[9] (**7**), alstiphyllanine B[9] (**8**), alstiphyllanine C[9] (**9**), picralinal[11] (**10**), picrinine[11] (**11**), quaternine[12] (**12**), *O*-deacetylpicraline[13] (**13**), vincamedine[14] (**14**), vincamajine[15] (**15**), alstiphyllanine A[9] (**16**), vincamajine-17-*O*-veratrate[16] (**17**), vincamajine-17-*O*-3′,4′,5′-trimethoxybenzoate[16] (**18**), alstonal[17] (**19**), and alstonerine[14] (**20**).

Alstiphyllanine E {**1**, $[\alpha]_D^{26}$ −93 (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{30}H_{32}N_2O_7$, by HRESITOFMS [*m*/*z* 533.2272 $(M+H)^+$, Δ −1.6 mmu]. The ^{1}H NMR data (Table 1) showed the presence of seven aromatic protons, an ethylidene side chain, a methyl ester function, and two methoxy groups. The HMBC cross-peak of H_2-21 to C-19 indicated the ethylidene side chain at C-20. The position of each methoxy group was confirmed by HMBC correlations of *O*-Me to C-3′ and C-4′. HMBC correlations for H-5 to C-2, H_2-17 to C-7, and H_2-6 to C-16 indicated alstiphyllanine E possessed picraline-type skeleton. The molecular formulae of alstiphyllanine E was smaller than that of burnamin-17-*O*-3′,4′,5′-trimethoxybenzoate[9] by CH_2O unit. Compared with ^{1}H NMR data of burnamin-17-*O*-3′,4′,5′-trimethoxybenzoate,[9] alstiphyllanine E was suggested a picraline-type backbone without *O*-Me at C-5′. The relative stereochemistry of **1** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Fig. 1). The NOESY correlation of H_3-18 to H-15 indicated that the geometry of ethylidene side chain was *E*. The β-orientation of C-17 was elucidated by the NOESY correlation of H-14b/H-17a.

Alstiphyllanine F {**2**, $[\alpha]_D^{26}$ −32 (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{32}H_{36}N_2O_9$, by HRESITOFMS [*m*/*z* 593.2511 $(M+H)^+$, Δ −1.2 mmu], which was larger than that of burnamin-17-*O*-3′,4′,5′-trimethoxybenzoate by CH_2O unit. Compared with ^{1}H NMR data of burnamin-17-*O*-3′,4′,5′-trimethoxybenzoate, alstiphyllanine F was suggested a picraline-type backbone with *O*-Me. The HMBC cross-peak of H_3-*O*-Me (δ_H 3.27) to C-10 (δ_C 156.5) revealed the presence of an indole moiety with a methoxy group at C-10. HRESITOFMS data [*m*/*z* 413.2080 $(M+H)^+$, Δ −0.4 mmu] of alstiphyllanine G {**3**, $[\alpha]_D^{26}$ −42 (*c* 1.0, MeOH)} established the molecular formula, $C_{23}H_{28}N_2O_5$, which was larger than that of *O*-deacetylpicraline[13] by C_2H_4O unit. The NMR data of **3** were analogous to those of *O*-deacetylpicraline[13] except for the following observation: a methoxy signal (δ_H 3.70) and an *N*-methyl signal (δ_H 2.89) lacking in *O*-deacetylpicraline appeared for **3**. The presence of both methyl groups was verified by the HMBC correlations of the methoxy protons to C-10 and the *N*-methyl protons to C-2 and C-13.

Alstiphyllanine H {**4**, $[\alpha]_D^{26}$ −21 (*c* 1.0, MeOH)} was obtained as a brown amorphous solid and was revealed to have the molecular formula $C_{22}H_{26}N_2O_4$, by HRESITOFMS [*m*/*z* 383.1971 $(M+H)^+$, Δ −2.7 mmu], which was larger than that of vincamajine[15] by an oxygen unit. The ^{1}H NMR data (Table 1) showed the presence of four aromatic protons, an ethylidene side chain, a methyl ester function, and an *N*-methyl group. Partial structures C-9–C-12,

Table 1
^{1}H NMR data [δ_H (*J*, Hz)] of alstiphyllanines E-H (**1**–**4**)

	1[a]	**2**[a]	**3**[b]	**4**[a]
2				3.55 (d, 4.8)
3	4.07 (s)	4.00 (s)	3.73 (d, 3.6)	4.39 (m)
5	5.56 (s)	5.56 (s)	4.72 (d, 2.6)	4.42 (m)
6a	2.67 (d, 15.4)	2.66 (15.1)	2.33 (dd, 13.9, 2.6)	2.53 (d, 14.4)
6b	3.17 (d, 15.4)	3.25 (m)	3.30 (d, 13.9)	2.73 (d, 14.4)
9	7.56 (d, 7.4)	7.03 (s)	6.93 (d, 2.6)	7.20 (d, 7.2)
10	6.54 (dd, 7.4, 7.2)			6.83 (dd, 7.2, 7.2)
11	6.87 (dd, 7.5, 7.2)	6.60 (d, 8.4)	6.73 (dd, 8.5, 2.6)	7.19 (dd, 7.6, 7.2)
12	6.73 (d, 7.5)	6.33 (d, 8.4)	6.59 (d, 8.5)	6.77 (d, 7.6)
14a	2.23 (d, 14.8)	2.29 (d, 15.1)	1.97 (m)	2.10 (m)
14b	2.41 (d, 14.8)	2.37 (d, 15.1)		2.74 (m)
15	3.40 (s)	3.35 (s)	3.48 (s)	3.36 (s)
17a	4.08 (d, 11.4)	4.09 (d, 10.9)	3.47 (d, 12.3)	4.16 (s)
17b	4.57 (d, 11.4)	4.94 (d, 10.9)	3.73 (d, 12.3)	
18	1.70 (d, 6.8)	1.76 (d, 7.2)	1.56 (dd, 7.1, 2.0)	1.61 (d, 6.5)
19	5.74 (q, 6.8)	5.76 (q, 7.2)	5.35 (q, 7.1)	5.55 (q, 6.5)
21a	4.25 (d, 17.1)	4.02 (m)	3.11 (d, 15.9)	4.46 (d, 15.1)
21b	4.00 (d, 17.1)	4.16 (d, 16.1)	3.66 (d, 15.9)	4.55 (d, 15.1)
CO_2Me	3.75 (s)	3.80 (s)	3.72 (s)	3.73 (s)
10-*O*-*Me*		3.27 (s)	3.70 (s)	
3′-*O*-*Me*	3.86 (s)	3.89 (s)		
4′-*O*-*Me*	3.88 (s)	3.81 (s)		
5′-*O*-*Me*		3.89 (s)		
N(1)-*Me*			2.89 (s)	2.66 (s)
2′	7.15 (s)	6.91 (s)		
5′	6.94 (d, 8.4)			
6′	7.28 (d, 8.4)	6.91 (s)		

[a] TFA salt in CD_3OD.
[b] Free base in $CDCl_3$.

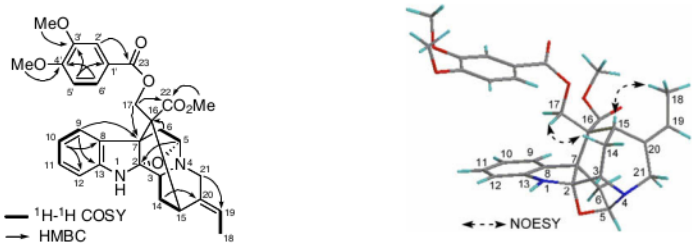


Figure 1. Selected 2D NMR correlations for alstiphyllanine E (**1**).

C-5–C-6, C-2–C-15, and C-18–C-19 were deduced from a detailed analysis of ^{1}H-^{1}H COSY spectrum of **4**. The HMBC cross-peaks of H_3-18 to C-20 and H-19 to C-15 indicated the presence of an ethylidene side chain at C-20 (Fig. 2). And the presence of an indoline ring was elucidated by HMBC correlations for H-9 to C-7 and *N*-Me to C-2 and C-13. HMBC correlations for H-2, H-5, and H-6a to C-17 and H-6a and H-14a to C-16 indicated alstiphyllanine H possessed ajmaline-type skeleton. Comparison of ^{13}C chemical shifts of C-3, C-5, and C-21 (δ_C 70.5, 77.4, and 67.3, respectively) in **4** with those (δ_C 53.2, 61.7, and 55.6, respectively) of vincamedine[14] indicated the presence of an *N*-oxide functionality at *N*-4. The relative stereochemistry of **4** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Fig. 2). NOESY correlations of H_3-18 to H-21 indicated that the geometry of the ethylidene side chain was *Z*. The NOESY correlations of H-3/H-2 and H-14a and H-14b/H-17 indicated that H-2 was α-orientated and H-17 was β-oriented. Oxidation of vincamajine with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the *N*-oxide derivative, whose spectral data and the $[\alpha]_D$ value were identical with those of natural alstiphyllanine H. Thus, the structure of asltiphyllanine H was elucidated as shown in Figure 2.

2.2. SGLT inhibitory activity

The in vitro SGLT inhibitory potential of alkaloids **1**–**20** was assessed by monitoring inhibition of uptaking of methyl-α-D-glucopyranoside in cultured cells expressing SGLT1 or SGLT2 at 50 μM (Table 3). As shown in Table 3, picraline-type alkaloids with veratrate or trimethoxybenzoate at C-17 such as compounds **1**, **2**, and **5**–**7**, showed inhibitory activity against SGLT1 and SGLT2. However, compounds **8** and **9** which have an *N*(4)-Me group were found to have no SGLT inhibitory activity. Any ajmaline and macroline type alkaloids (**4** and **14**–**20**) did not show inhibition on SGLT1 and SGLT2.

To discuss SAR of picraline-type alkaloids showing SGLT inhibitory activity, we prepared eight picraline-type derivatives **21**–**28** from **6** and **7** by use of acyl anhydride, *m*-CPBA, and boron tribromide, respectively (Table 4). As shown in Table 4, the presence of an *N*(1)-Me group promoted SGLT1 inhibitory activity when compared to those of **1**, **2** and **5**. Compound **22** which was converted a methoxy group at C-10 of **7** into a hydroxyl showed less activity against SGLT1, whereas *N*(4)-oxide derivatives **23** and **24** with a

Table 2
^{13}C NMR data (δ_C) of alstiphyllanines E–H (**1**–**4**)

	1[a]	**2**[a]	**3**[b]	**4**[a]
2	109.5	106.6	109.6	70.9
3	54.8	53.3	49.4	70.5
5	90.5	89.9	86.9	77.4
6	41.6	44.6	44.8	32.1
7	53.1	53.1	52.7	57.3
8	132.9	136.0	134.2	130.1
9	128.4	117.4	113.3	126.4
10	122.4	156.5	154.5	120.9
11	129.6	112.9	112.9	129.7
12	112.1	112.8	109.5	110.7
13	149.4	143.8	145.4	155.2
14	20.4	22.5	21.6	22.9
15	39.9	37.0	33.0	36.3
16	59.0	58.5	57.5	63.3
17	67.3	69.6	64.1	74.6
18	13.1	14.7	13.1	12.8
19	128.2	126.0	119.9	122.1
20	132.9	132.5	137.8	129.5
21	42.2	47.2	46.7	67.3
22	172.8	174.8	174.6	171.3
23	166.3	166.5		
CO_2Me	52.4	53.1	55.8	52.9
10-*O*-*Me*		56.2	51.8	
3′-*O*-*Me*	56.4	57.3		
4′-*O*-*Me*	56.4	61.8		
5′-*O*-*Me*		57.3		
N(1)-*Me*			30.1	35.0
1′	122.5	125.8		
2′	129.6	108.7		
3′	149.8	154.9		
4′	153.1	143.9		
5′	111.6	154.9		
6′	125.0	108.7		

[a] TFA salt in CD_3OD.
[b] Free base in $CDCl_3$.

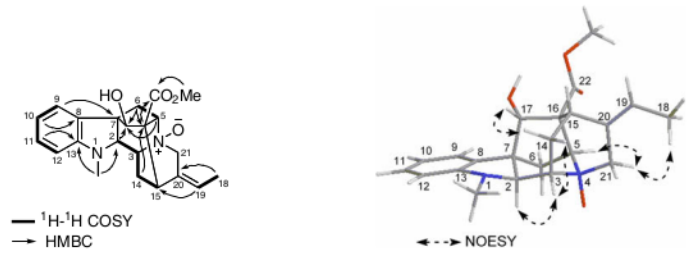
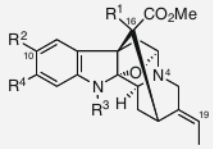


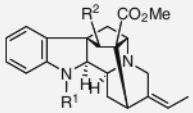
Figure 2. Selected 2D NMR correlations for alstiphyllanine H (**4**).

Table 3
Structures and SGLT inhibitory activity of alkaloids **1**–**20**

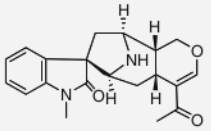
	R^1	R^2	R^3	R^4		Inhibition %[a]	
						SGLT1	SGLT2
Picraline-type alkaloids							
1	CH_2O-Bz(OMe)$_2$	H	H	H		60.3	85.9
2	CH_2O-Bz(OMe)$_3$	OMe	H	H		65.2	103.8
3	CH_2OH	OMe	Me	H		14.0	31.6
5	CH_2O-Bz(OMe)$_3$	H	H	H	19*Z*	53.0	87.3
6	CH_2O-Bz(OMe)$_2$	OMe	Me	H		95.8	102.6
7	CH_2O-Bz(OMe)$_3$	OMe	Me	H		89.9	101.4
8	CH_2O-Bz(OMe)$_2$	OMe	Me	H	*N*(4)-Me	-10.3	-0.2
9	CH_2O-Bz(OMe)$_3$	OMe	Me	H	*N*(4)-Me	-8.2	-6.1
10	CHO	H	H	H		16.5	36.3
11	H	H	H	H		9.6	27.3
12	H	OMe	H	OMe		11.7	30.0
13	CH_2OH	H	H	H		10.1	-0.2
Ajmaline-type alkaloids							
4	Me	OH			*N*(4)-oxide	4.3	23.1
14	Me	OAc				22.0	47.4
15	Me	OH				11.5	30.6
16	Me	OAc			*N*(4)-oxide	5.3	38.5
17	Me	OBz(OMe)$_2$				26.0	44.0
18	Me	OBz(OMe)$_3$				7.2	47.6
Macroline-type alkaloids							
19						15.8	26.8
20						20.7	27.7



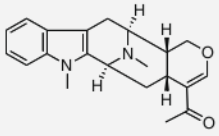
picraline type
(**1**-**3** and **5**-**13**)



ajmaline type
(**4** and **14**-**18**)



macroline type
19

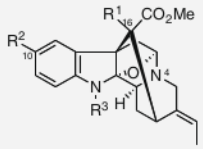


macroline type
20

[a] Inhibition (%) at 50 μM.

Table 4
Structures and SGLT inhibitory activity of picraline-type derivatives **1**, **2**, **5**–**7**, and **21**–**28**

	R^1	R^2	R^3		Inhibition %[a] (IC_{50} μM)	
					SGLT1	SGLT2
1	CH_2O-Bz(OMe)$_2$	H	H		60.3 (44)	85.9 (40)
2	CH_2O-Bz(OMe)$_3$	OMe	H		65.2 (39)	103.8 (40)
5	CH_2O-Bz(OMe)$_3$	H	H	19*Z*	53.0 (50)	87.3 (35)
6	CH_2O-Bz(OMe)$_2$	OMe	Me		95.8 (4)	102.6 (0.5)
7	CH_2O-Bz(OMe)$_3$	OMe	Me		89.9 (5)	101.4 (2)
21	CH_2O-Bz	OMe	Me		85.2 (17)	100.1 (1)
22	CH_2O-Bz(OH)$_3$	OH	Me		46.9 (50)	95.6 (7)
23	CH_2O-Bz(OMe)$_2$	OMe	Me	*N*(4)-oxide	94.6 (5)	64.9 (35)
24	CH_2O-Bz(OMe)$_3$	OMe	Me	*N*(4)-oxide	93.8 (4)	91.4 (11)
25	CH_2O-cinnamoyl	OMe	Me		96.3 (5)	102.8 (1)
26	CH_2O-Ac	OMe	Me		5.4 (>100)	39.9 (78)
27	$CH_2OCOCH_2CH_3$	OMe	Me		27.1 (97)	86.9 (12)
28	CH_2O-Bn	OMe	Me		7.6 (>100)	25.7 (>100)



picraline type (**1**, **2**, **5**-**7**, and **21**-**28**)

[a] Inhibition (%) at 50 μM.

methoxy group at C-10 showed less activity against SGLT2. Aliphatic esters at C-17 such as **26** and **27** showed less activity against both SGLT1 and SGLT2, and the presence of an aromatic long side chain at C-17 such as cinnamoyl derivative **25** potentiated the inhibitory activity against SGLT1 and SGLT2. On the other hand, the benzyl ether derivative **28** at C-17 did not show inhibitory activity.

In this work, three new picraline-type alkaloids, alstiphyllanines E–G (**1**–**3**) and a new ajmaline-type alkaloid, alstiphyllanine H (**4**) were isolated from the leaves of *A. macrophylla*, and their

structures were fully elucidated by 2D NMR analysis. SAR study of these alkaloids and synthetic analogue against STLT1 and SGLT2 suggested that the presence of picraline-type alkaloid with an ester side chain at C-17 may be important to show inhibitory activity.

3. Experimental section

3.1. General methods

^{1}H and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H–^{1}H COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. NOESY spectra in the phase sensitive mode were measured with a mixing time of 800 ms. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1 K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

3.2. Material

The leaves of *A. macrophylla* were collected at Purwodadi Botanical Garden, Indonesia in 2006. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.

3.3. Extraction and isolation

The leaves of *A. macrophylla* (363.5 g) were extracted with MeOH. The MeOH extract (43.8 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with satd aq Na_2CO_3 aq to pH 9 and extracted with $CHCl_3$ to give alkaloidal fraction (2.06 g). The alkaloidal fraction was purified by LH-20 column ($CHCl_3$/MeOH, 1:0) and SiO_2 column ($CHCl_3$/MeOH, 1:0→0:1) and the fraction eluted by MeOH was purified by ODS HPLC ($CH_3CN/H_2O/CF_3CO_2H$, 45:55:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to afford alstiphyllanines E (**1**, 1.8 mg, 0.00050% yield), F (**2**, 1.3 mg, 0.00036%), G (**3**, 10.4 mg, 0.0029%), and H (**4**, 3.6 mg, 0.0013%), together with known alkaloids, burnamine-17-*O*-3′,4′,5′-trimethoxybenzoate[10] (**5**), 10-methoxy-*N*(1)-methylburnamine-17-*O*-veratrate[10] (**6**), alstiphyllanine D[9] (**7**), alstiphyllanine B[9] (**8**), alstiphyllanine C[9] (**9**), picralina[11] (**10**), picrinine[11] (**11**), quaternine[12] (**12**), *O*-deacetylpicraline[13] (**13**), vincamedine[14] (**14**), vincamajine[15] (**15**), alstiphyllanine A[9] (**16**), vincamajine-17-*O*-veratrate[16] (**17**), vincamajine-17-*O*-3′,4′,5′-trimethoxybenzoate[16] (**18**), alstonal[17] (**19**), alstonerine[14] (**20**).

3.3.1. Alstiphyllanine E (1)

Brown amorphous solid; $[\alpha]_D^{26}$ −93 (*c* 1.0, MeOH); IR (film) ν_{max} 3390, 1740, and 1680 cm^{-1}; UV (MeOH) λ_{max} 291 (ε 4700), 264 (6200), and 204 (27,000) nm; ^{1}H and ^{13}C NMR data (Tables 1 and 2); ESIMS *m*/*z* 533 $(M+H)^+$; HRESITOFMS *m*/*z* 533.2272 [$(M+H)^+$, Δ −1.6 mmu, calcd for $C_{30}H_{33}N_2O_7$, 533.2288].

3.3.2. Alstiphyllanine F (2)

Brown amorphous solid; $[\alpha]_D^{26}$ −32 (*c* 1.0, MeOH); IR (film) ν_{max} 3420, 1740, and 1680 cm^{-1}; UV (MeOH) λ_{max} 245 (ε 6800) and 204 (28,000) nm; ^{1}H and ^{13}C NMR data (Tables 1 and 2); ESIMS *m*/*z* 593 $(M+H)^+$; HRESITOFMS *m*/*z* 593.2511 [$(M+H)^+$, Δ +1.2 mmu, calcd for $C_{32}H_{37}N_2O_9$, 593.2499].

3.3.3. Alstiphyllanine G (3)

Brown amorphous solid; $[\alpha]_D^{26}$ −42 (*c* 1.0, MeOH); IR (film) ν_{max} 3420 and 1720 cm^{-1}; UV (MeOH) λ_{max} 306 (ε 1500), 240 (3500), and 204 (12,000) nm; ^{1}H and ^{13}C NMR data (Tables 1 and 2); ESIMS *m*/*z* 413 $(M+H)^+$; HRESITOFMS *m*/*z* 413.2080 [$(M+H)^+$, Δ +0.4 mmu, calcd for $C_{23}H_{28}N_2O_5$, 413.2076].

3.3.4. Alstiphyllanine H (4)

Brown amorphous solid; $[\alpha]_D^{26}$ −21 (*c* 1.0, MeOH); IR (film) ν_{max} 3420 and 1740 cm^{-1}; UV (MeOH) λ_{max} 291 (ε 1400) and 204 (10,000) nm; ^{1}H and ^{13}C NMR data (Tables 1 and 2); ESIMS *m*/*z* 383 $(M+H)^+$; HRESITOFMS *m*/*z* 383.1944 [$(M+H)^+$, Δ −2.7 mmu, calcd for $C_{22}H_{26}N_2O_4$, 383.1971].

3.3.5. Conversion of vincamajine (15) to alstiphyllanine H (4)

m-Chloroperoxybenzoic acid (0.9 mg) was added to a stirred solution of vincamajine (**15**, 0.9 mg) in CH_2Cl_2 (0.2 mL) at room temperature. The mixture was stirred at 0 °C for 10 min, and washed with 20% Na_2SO_2 (5 mL) and H_2O (5 mL), and concentrated to give a pale yellow solid. The residue was subjected to a silica gel column ($CHCl_3$/MeOH, 10:1) to give the N-oxide derivative (1.5 mg), whose spectral data and $[\alpha]_D$ value were identical with those of alstiphyllanine H (**4**).

3.3.6. Conversion of 6 to 3

A mixture of 39.6 mg of alkaloid **6** and 20 mL of 5% NaOMe were heated for 30 min under stirring. The solution was diluted with water and extracted with $CHCl_3$. The extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 aq to pH 9 and extracted with $CHCl_3$ to give **3** (27.1 mg, 95.8%).

3.3.7. Conversion of 3 to Its benzoate derivative (21)

To a solution of **3** (3.2 mg) in CH_2Cl_2 (0.1 mL) was added benzoic anhydride (4.5 mg) and DMAP (3.2 mg), and the solution was stirred at room temperature. The mixture was diluted with $CHCl_3$ and washed with water, satd aq $NaHCO_3$, and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and then purified by an ODS HPLC (MeOH/H_2O/formic acid; flow rate, 2 mL/min; UV detection at 254 nm) to obtain **21** (2.4 mg, 60.0%): $[\alpha]_D^{27}$ −38 (*c* 0.1, MeOH); IR (film) 1740 and 1710 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.61 (dd, 7.6, 7.6, H-2′, 6′), 7.55 (dd, 7.6, 7.6, H-4′), 7.39 (d, 7.6, H-3′, 5′), 7.05 (d, 2.5, H-9), 6.57 (d, 8.6, H-12), 6.42 (dd, 2.5, 8.6, H-11), 5.66 (q, 6.9, H-19), 5.49 (br s, H-5), 4.78 (d, 10.9, H-17), 4.24 (d, 10.9, H-17) 4.12 (m, H-21), 3.70 (s, –OMe), 3.64 (br s, H-3, 15), 3.41 (s, –OMe), 3.35 (d, 15.0, H-6), 2.94 (s, –*N*Me), 2.53 (d, 15.0, H-6), 2.29 (d, 15.1, H-14), 2.19 (d, 15.1, H-14), 1.70 (d, 6.92, H-18); HRESIMS *m*/*z* 517.2323 [calcd for $C_{30}H_{33}N_2O_6$ $(M+H)^+$, 517.2339].

3.3.8. Conversion of 7 to its hydroxy derivative (22)

A solution of boron tribromide in CH_2Cl_2 (1.0 M, 8.1 μL) was added dropwise to stirred solution of **7** (1.1 mg) in CH_2Cl_2 (50 μL), stirring being continued for 15 min at 0 °C. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on an ODS HPLC (MeOH/H_2O/formic acid, 55:45:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to give compound **22** (0.3 mg, 30.3 %): $[\alpha]_D^{27}$ −78 (*c* 0.1, MeOH); IR (film) 3420, 1740, and 1710 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.00 (d, 8.4, H-9), 6.87 (s, H-2′, 6′), 6.58 (d, 2.5, H-12), 6.51 (dd, 8.4, 2.5, H-11), 5.74 (q, 7.7, H-19), 5.41 (br s, H-5), 4.53 (d, 11.4, H-17), 4.25 (d,

11.4, H-17), 4.19 (br s, H-3), 3.72 (br s, H-15), 3.99 (m, H-21), 3.70 (s, –OMe), 3.30 (m, H-6), 2.95 (s, –NMe), 2.60 (d, 15.9, H-6), 2.34 (d, 16.1, H-14), 2.28 (d, 16.1, H-14), 1.72 (d, 7.7, H-18); HRESIMS *m*/*z* 551.2052 [calcd for $C_{29}H_{31}N_2O_9(M+H)^+$, 551.2030].

3.3.9. Conversion of 6 to Its *N*(4)-oxide derivative (23)

To a solution of **6** (2.8 mg) in $CHCl_3$ (0.3 mL) was added *m*-CPBA (1.0 mg) in $CHCl_3$ (300 μL) and the mixture was kept at 4 °C for 10 min. After evaporation, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 9:1) to give **23** (1.0 mg, 34.8 %): $[\alpha]_D^{27}$ −14 (*c* 0.5, MeOH); IR (film) 1740 and 1710 cm^{-1}; ^1H NMR (CD_3OD) δ 7.24 (dd, 8.5, 2.0, H-5′), 7.11 (d, 2.0, H-2′), 7.03 (d, 2.6, H-9), 6.93 (d, 8.5, H-5′), 6.56 (d, 8.6, H-12), 6.40 (dd, 8.6, 2.6, H-11), 5.69 (q, 6.7, H-19), 5.05 (br s, H-5), 4.81 (d, 11.1, H-17), 4.34 (d, 16.4, H-21) 4.16 (d, 16.4, H-21), 4.03 (d, 3.2, H-3), 3.89 (s, –OMe), 3.88 (s, –OMe), 3.74 (s, –OMe), 3.60 (br s, H-15), 3.34 (s, –OMe), 3.30 (m, H-6), 2.95 (s, –NMe), 2.50 (m, H-6), 2.47 (m, H-14), 2.25 (d, 15.8, H-14), 1.72 (dd, 6.7, 2.3, H-18); HRESIMS *m*/*z* 593.2522 [calcd for $C_{32}H_{37}N_2O_9(M+H)^+$, 593.2499].

3.3.10. Conversion of 7 to its *N*(4)-oxide derivative (24)

To a solution of **7** (1.0 mg) in $CHCl_3$ was added *m*-CPBA (1.6 mg) in $CHCl_3$ (300 μL) and the mixture was kept at 4 °C for 10 min. After evaporation, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 9:1) to give **24** (1.0 mg, 34.8 %): $[\alpha]_D^{27}$ −24 (*c* 0.5, MeOH)); IR (film) 1730 and 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (d, 2.6, H-12), 6.89 (s, H-2′, 5′), 6.52 (d, 8.6, H-9), 6.52 (d, 8.6, H-9), 6.52 (d, 8.6, H-12), 6.36 (dd, 8.6, 2.6, H-11), 5.64 (q, 7.12, H-19), 5.21 (br s, 3.54, H-5), 4.80 (d, 10.9, H-17), 4.44 (d, 16.7, H-21) 4.32 (d, 16.7, H-21), 4.19, (d, 2.4, H-3), 4.06 (d, 10.9, H-17), 3.91 (s, –OMe), 3.88 (s, –OMe), 3.72 (s, –OMe), 3.45 (br s, H-15), 3.34 (s, –OMe), 3.30 (m, H-6), 3.00 (s, –NMe), 2.58 (dd, 15.6, 3.5, H-6), 2.54 (d, 15.7, H-14), 2.20 (d, 15.7, H-14), 1.69 (dd, 7.0, 2.0, H-18); HRESIMS *m*/*z* 623.2624 [calcd for $C_{33}H_{39}N_2O_{10}(M+H)^+$, 623.2605].

3.3.11. Conversion of 3 to its cinnamoyl derivative (25)

Compound **3** (13.9 mg), hydrocinnamic acid (5.8 mg), and DMAP (5.7 mg), were combined with CH_2Cl_2 (100 μL). 1,3-Dicyclohexylcarbodiimide (DCC) (23.5 mg) in CH_2Cl_2 (50 μL) was added dropwise over 10 min at 0 °C. The solution was warmed to room temperature and stirred overnight. The reaction mixture was partitioned with $CHCl_3$ and 1 N aq HCl, 10 % aq $NaHCO_3$, and water. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo and then purified by an ODS HPLC (MeOH/H_2O/formic acid, 60:40:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to obtain compound **25** (0.7 mg, 3.8%): $[\alpha]_D^{27}$ −49 (*c* 0.5, MeOH); IR (film) 1740 and 1710 cm^{-1}; ^1H NMR (CD_3OD) δ 7.52 (m, H-4′, 8′), 7.41 (m, H-5′, 6′, 7′), 7.24 (d, 16.1, H-2′), 7.08 (s, H-9), 6.58 (s, H-11, 12), 5.97 (d, 16.1, H-1′), 5.52 (q, 7.4, H-19), 4.98 (m, H-5), 4.65 (d, 10.9, H-17), 4.08 (d, 10.9, H-17), 3.83 (m, H-21), 3.79 (m, H-3), 3.71 (s, –OMe), 3.68 (m, H-21), 3.48 (s, –OMe), 3.48 (m, H-15), 3.30 (m, H-6), 2.90 (s, –NMe), 2.39 (d, 14.6, H-6), 2.12 (d, 14.3, H-14), 2.04 (d, 14.3, H-14), 1.65 (d, 7.4, H-18); HRESIMS *m*/*z* 543.2490 [calcd for $C_{32}H_{35}N_2O_6(M+H)^+$, 543.2495].

3.3.12. Conversion of 3 to its acetylate derivative (26)

Compound **3** (1.0 mg), acetic anhydride (7.5 μL), triethylamine (2.5 μL), and DMAP (0.5 mg) in CH_2Cl_2 (50 μL) was stirred at room temperature for 1.5 h. The reaction mixture was partitioned with $CHCl_3$ and 10 % aq $NaHCO_3$. The combined organic extract was concentrated in vacuo and then purified by a silica gel column ($CHCl_3$/MeOH, 1:0–0:1) to obtain compound **26** (0.8 mg, 73.4%). $[\alpha]_D^{27}$ −32 (*c* 0.5, MeOH); IR (film) 1740 cm^{-1}; ^1H NMR (CD_3OD) δ 7.02 (d, 2.6, H-12), 6.73 (dd, 8.6, 2.6, H-11), 6.61 (d, 8.6, H-9), 5.51 (q, 7.3, H-19), 4.94 (m, H-5) 4.53 (d, 11.0, H-17), 3.86, (d, 11.0, H-17), 3.78 (d, 14.6, H-21), 3.72 (s, –OMe), 3.70 (s, –OMe), 3.44 (br s, H-3), 3.36 (m, H-21), 3.35 (m, H-15), 3.30 (m, H-6), 2.89 (s, –NMe), 2.36 (dd, 14.4, 2.8, H-6), 2.09 (d, 15.4, H-14), 2.00 (d, 15.4, H-14), 1.64 (d, 7.3, H-18), 1.54 (s, $-COCH_3$); HRESIMS *m*/*z* 455.2161 [calcd for $C_{25}H_{31}N_2O_6(M+H)^+$, 455.2182].

3.3.13. Conversion of 3 to its propionate derivative (27)

To a solution of **3** (1.6 mg) in CH_2Cl_2 (0.05 mL) was added propionic anhydride (3 μL), and DMAP (1.2 mg) in CH_2Cl_2 (50 μL) and the solution was stirred at room temperature. The mixture was diluted with $CHCl_3$ and washed with water, satd aq $NaHCO_3$, and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo and then purified by an ODS HPLC (MeOH/H_2O/formic acid; flow rate, 2 mL/min; UV detection at 254 nm) to obtain **27** (0.2 mg, 60.0%). $[\alpha]_D^{27}$ −143 (*c* 0.1, MeOH); IR (film) 1740 cm^{-1}; ^1H NMR (CD_3OD) δ 7.02 (d, 2.6, H-2), 6.80 (dd, 8.6, 2.6, H-11), 6.70 (d, 8.6, H-12), 5.74 (q, 6.5, H-19), 5.55 (br s, H-5) 4.52 (d, 11.2, H-17), 4.21 (m, H-21), 3.98 (m, H-21), 3.93, (d, 11.2, H-17), 3.75 (m, H-3), 3.74 (s, –OMe), 3.73 (s, –OMe), 3.64 (br s, H-15), 3.23 (d, 15.5, H-6), 2.95 (s, –NMe), 2.61 (d, 15.5, H-6), 2.32 (d, 14.6, H-14), 2.21 (d, 14.6, H-14), 1.84 (m, H-1′), 1.72 (d, 6.5, H-18), 0.85 (t, 7.5, H-2′); HRESIMS *m*/*z* 469.2352 [calcd for $C_{26}H_{33}N_2O_6(M+H)^+$, 469.2339].

3.3.14. Conversion of 3 to its benzyl ether derivative (28)

To a solution of **3** (2.7 mg) in dry CH_2Cl_2 (53 μL) were added triethylamine (1.27 μL), benzyl bromide (0.93 μL), and DMAP (0.4 mg). The reaction mixture was heated for 3 h, then cooled to room temperature and diluted with $CHCl_3$. The organic phase was washed twice with an aqueous solution of $NaHCO_3$ and once with water. The organic phase was dried Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on an ODS HPLC (MeOH/H_2O/formic acid, 61:39:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to give **28** (0.6 mg, 18.2%): $[\alpha]_D^{27}$ −4.6 (*c* 0.5, MeOH); IR (film) 1730 cm^{-1}; ^1H NMR (CD_3OD) δ 7.64 (d, 7.8, H-3′, 7′), 7.57 (m, H-4′, 5′, 6′), 6.85 (m, H-9, 12), 6.78 (d, 9.5, H-11), 5.65 (m, H-5), 5.62 (m, H-19), 4.61 (s, H-1′), 4.45 (d, 16.1, H-21), 4.41 (s, H-3), 3.97 (d, 16.1, H-21), 3.77, (m, H-15), 3.74 (s, –OMe), 3.72 (s, –OMe), 3.66 (d, 17.5, H-17), 3.61 (d, 17.5, H-17), 3.30 (m, H-6), 3.03 (s, –NMe), 2.54 (dd, 16.6, 3.7, H-6), 2.38 (m, H-14), 1.65 (d, 5.5, H-18); HRESIMS 503.2535 [calcd for $C_{30}H_{35}N_2O_5(M+H)^+$, 503.2546].

3.3.15. Uptake of Methyl-α-D-glucopyranoside in cultured cells expressing SGLT1 or SGLT2[18]

COS-1 cells were cultured at 37 °C in Dulbecco's modified Eagle's/Ham's F-12 medium (1:1) supplemented with 10% fetal calf serum. For the uptake assay, the cells were plated at 1×10^5 cells/24-well plate (Asahi Techno Glass, Tokyo, Japan), and 1 μg of each transporter plasmid was transfected into subconfluent cultures of COS-1 cells using Lipofectamine 2000 (Invitrogen). The cells were used 2–3 days after transfection. They were incubated in a pretreatment buffer [140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM Hepes/Tris (pH 7.5)] with a test sample at 37 °C for 30 min. An uptake solution containing 80 mM methyl-α-D-glucopyranoside and 4 μCi/mL methyl α-D-[U-^{14}C]glucopyranoside was then added into each well and the mixture was incubated at 37 °C for 30 min. Following incubation, the plates were washed three times with cold stop buffer [140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM Hepes/Tris (pH 7.5)] containing 300 μM phlorizin. The cells were then solubilized with 0.1 M NaOH, and their radioactivity was measured with a liquid scintillation counter (3100TR, Perkin–Elmer). Phlorizine was used as a standard drug for this bioassay and its IC_{50} values were 0.2 and 0.1 mM against SGLT1 and SGLT2, respectively.

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Alstiphyllanines E–H, picraline and ajmaline-type alkaloids from Alstonia macrophylla inhibiting sodium glucose cotransporter

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