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Graphical Abstract

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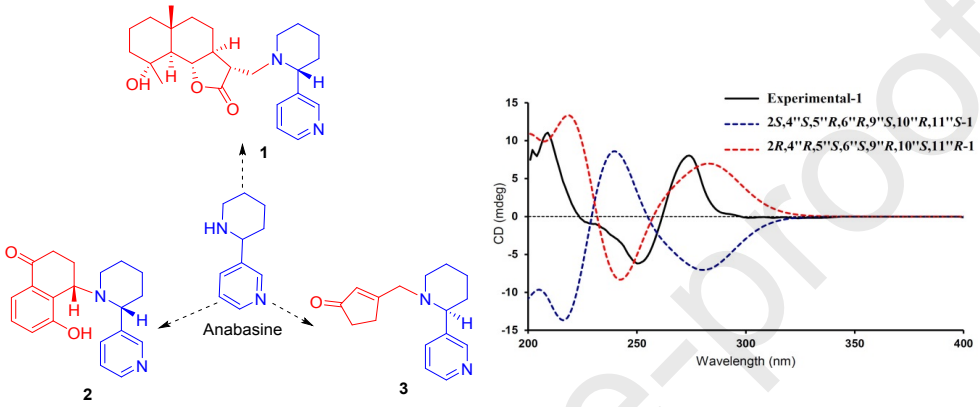

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Antitumor Pyridine Alkaloids Hybrid with Diverse Units from *Alangium chinense*

Xin Wei[a,c,#], Jing Yang[a,#], Zhi Dai [b,#], Hao-Fei Yu[a], Cai-Feng Ding[a], Afsar Khan[d], Yun-Li Zhao[a], Ya-Ping Liu[a], and Xiao-Dong Luo[a,b,*]

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ABSTRACT

Alangiumines A-C (**1-3**), three novel additive pyridine alkaloids representing the unprecedented santanolide-anabasine, benzcyclohexanone-anabasine, and cyclopentenone-anabasine skeletons, were isolated from *Alangium chinense*. Their structures with absolute configurations were elucidated by spectroscopic techniques and electronic circular dichroism (ECD). Moreover, compound **1** exhibited selective antitumor *in vitro* activity against glioma stem cells (GSCs). This finding might provide new type of lead for the selective killing of human glioma stem cells.

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Alkaloids are the heterocyclic organic derivatives with complex frameworks and intriguing biological properties, containing basic nitrogen ring and occurring in many folk medicinal plants.[1] Over the past decades, the alkaloids research for promising drug leads from natural sources has culminated in considerable important discoveries.[2-7] In particular, since a number of revolutionary alkaloids were extensively used in clinical practice, such as antitumor vincristine,[8] antihypertensive reserpine,[11] and stimulant yohimbine,[10] the search for structurally novel alkaloids with potent bioactivities has been a valuable topic in the fields of natural products chemistry, biosynthesis, and organic synthesis.

Cancer stem cells are considered to be the special population cells of important for cancer initiation, maintenance and metastasis, and glioma stem cells (GSCs) were the first verified stem cell isolated from solid tumor in 2003.[3] It is noteworthy that cancer stem cells are more resistant than other cancer cells to current cancer therapies and its unlimited proliferation and self-renewal features may make them capable of recapturing the tumor sphere and contributing to cancer recurrence after initial regression.[11] Thus, the discovery of leading compounds targeting cancer stem cells may have more important value and better therapeutic effect.

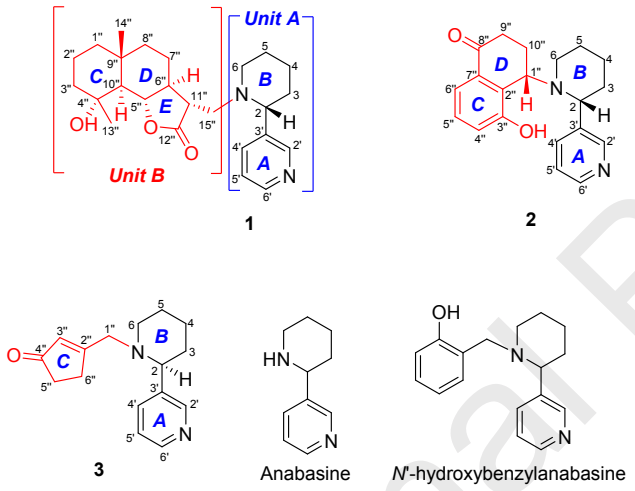


Fig. 1. Structures of compounds **1-3**

The fibrous roots of *Alangium chinense* named "Bai Long Xu" or "Ba Jiao Feng" in Traditional Chinese Medicine(TCM), historically have been applied as a treatment for rheumatoid, arthritis, and traumatic injury by the Miao people of Guizhou province, China.[12] Previous studies on *Alangium* plants showed alkaloids as their main component with immunosuppressive, antioxidant, antiviral, and recently reported antitumor activity.[12-13] Among them, pyridine alkaloids from *A. chinense* have caused widespread attention of pharmaceutical chemists due to their pyridine-piperidine structural characteristics and the clinical muscular relaxant anabasine.[14] In our study, alangiumines A-C (**1-3**), three novel additive pyridine alkaloids respectively possessing the unique santanolide-anabasine, benzcyclohexanone-anabasine, and cyclopentenone-anabasine skeletons, were isolated from *A. chinense*. Furthermore, cytotoxic evaluation of the new compounds indicated the selective antitumor activity of compound **1** against glioma stem cells (GSC-3# and GSC-18#) with IC_{50} values in the range of 12.8 and 23.0 μM, which were comparable with those of positive control, the well-known antitumor drug taxol (13.6 and 15.7μM). The isolation, structural elucidation, plausible biogenetic pathway and their bioactivity are herein described.

Alangiumine A (**1**)[15], colorless oil, displayed a positive reaction to Dragendorff's reagent. Its molecular formula was assigned as $C_{25}H_{36}N_2O_3$ by a quasi-molecular ion peak in HRESIMS at *m/z* 413.2795 $[M + H]^+$ (calcd for $C_{25}H_{37}N_2O_3^+$, 413.2799). The ^{13}C and ^1H NMR spectroscopic data of **1** (Table 1) displayed 10 carbon resonances of the basic framework for pyridine-piperidine alkaloids, including four methylenes (δ_C 37.0, 24.8, 25.8, and 52.7), five methines (δ_C 67.2, 123.9, 136.4, 148.9, and 149.4), and one aromatic quaternary carbon (δ_C 140.6), which were similar to those of anabasine [16] (Unit A, Fig. 1). The remaining 15 carbons were typically assignable to colartin[17-19] (Unit B, Fig.1), a santanolide type eudesmane sesquiterpene, except for the methyl-C_{15} of the colartin which was substituted by a methylene [δ_C 55.6 (t), δ_H 2.42 (2H, m)] in **1**.

The linkage between the santanolide and anabasine moieties was indicated by the correlations of δ_H 2.42 (H_2-15″) with δ_C 67.2 (C-2) and 52.7 (C-6) in the HMBC spectrum of **1** (Fig. 2). Thus, the planar structure of compound **1** was established as an unprecedented pyridine alkaloid with novel santanolide-anabasine framework.

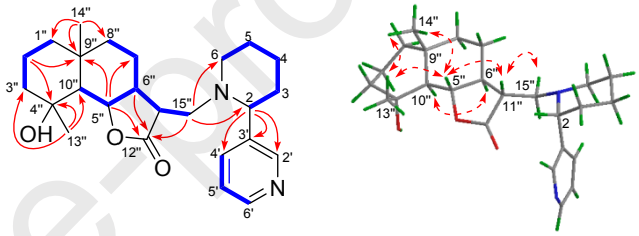


Fig. 2. Selective HMBC ( ), ^1H-^1H COSY ( ) and ROESY ( ) correlations of **1**

In Unit B, the NOE correlations of δ_H 2.42 (H_2-15″)/ 2.58 (H-11″)/ 4.00 (H-5″)/ 0.98 (H_3-14″)/ 1.29 (H_3-13″) in its ROESY spectrum, suggested those protons were co-facial (Fig. 2). Meanwhile, due to the fact that H-11″ and H-6″ were located on different sides of the six-membered ring-D, the NOE correlation of δ_H 2.58 (H-11″)/ 4.00 (H-5″) placed H-6″ at the reverse side of H-5″. Similarly, the NOE correlation of δ_H 4.00 (H-5″)/ 1.29 (H_3-13″) positioned H-10″ on the other side of H-5″, which were identical to colartin.[17-19] Based on the above evidences, the relative configuration of Unit B was established and its absolute configurations was deduced to be either 4″*S*,5″*R*,6″*R*,9″*S*,10″*R*,11″*S* or 4″*R*,5″*S*,6″*S*,9″*R*,10″*S*,11″*R*. Then, considering the only undetermined chiral C-2 in Unit A, the possible absolute configurations of **1** might be assigned as 2*R*,4″*S*,5″*R*,6″*R*,9″*S*,10″*R*,11″*S* or 2*R*,4″*R*,5″*S*,6″*S*,9″*R*,10″*S*,11″*R* or 2*S*,4″*S*,5″*R*,6″*R*,9″*S*,10″*R*,11″*S* or 2*S*,4″*R*,5″*S*,6″*S*,9″*R*,10″*S*,11″*R*. Finally, the electronic circular dichroism (ECD) calculation provided indubitable evidences for the assignment of chiral carbons as 2*R*,4″*R*,5″*S*,6″*S*,9″*R*,10″*S*,11″*R* following the means described previously.[20] As shown in Fig. 3, the calculated ECD spectrum for 2*R*,4″*R*,5″*S*,6″*S*,9″*R*,10″*S*,11″*R*-**1** was only one well matched with the experimental curves in all the possible configurations.

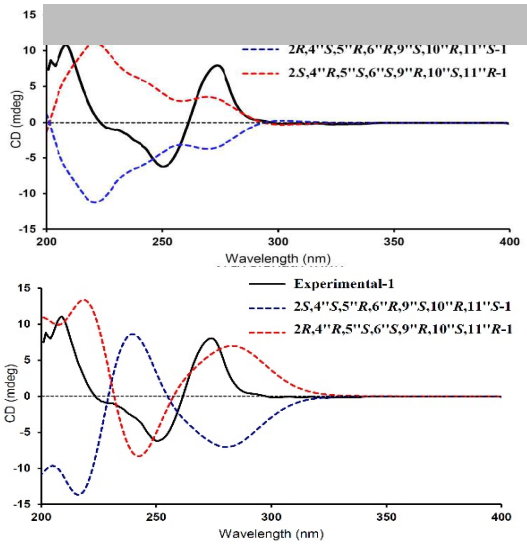


Fig. 3. Experimental and calculated ECDs for **1.**

Compound **2**[15] was assigned the molecular formula $C_{20}H_{22}N_2O_2$ on the basis of its HRESIMS ($[M + H]^+$ (*m/z* 323.1754) and ^{13}C NMR spectra, indicating 11 degrees of unsaturation. The ^1H and ^{13}C NMR spectroscopic data of **2** (Table 1) were comparable to those of *N*′-hydroxybenzylanabasine (Fig. 1),[13] suggesting a similar basic skeleton between **2** and *N*′-hydroxybenzylanabasine, except for the presence of an extra ketone carbonyl signal [δ_C 196.9 (s)], two methylene signals [δ_C 37.5 (t) and 20.4 (t)], and one more methine [δ_C 58.4 (d), δ_H 4.22] in **2**. Meanwhile, considering an unassigned unsaturation degree, compound **2** might have an additional ring-D. In its HMBC spectrum (Fig. 4), correlations of δ_H 4.22 (H-1″) with δ_C 37.5 (t) and 20.4 (t), and of δ_H 7.44 (H-6″) with δ_C 196.9 (s) suggested the presence of a new cyclohexanone unit (ring-D).

Since the chiral centers (C-1" and C-2) of **2** were in different rings, and there was no conjugation or steric hindrance in the structure to fix the rotation of $C_{1''}$-N_1 single bond, the relative configuration of these chiral centers could not be determined only by ROESY experiment. Thus, the ECD calculation was carried out for all possible configurations. The results showed that the calculated curve of 2*R*,1"*S*-**2** was in good agreement with the experiment ECD data of **2** (Fig. 5). Thus, the compound **2** was identified as shown in Fig. 1, and named alangiumine B.

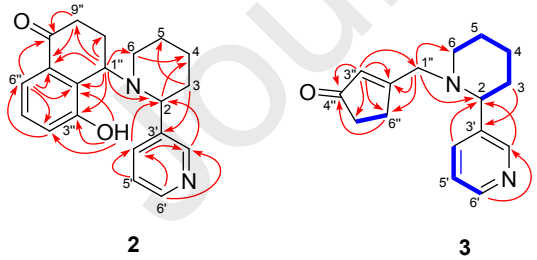


Fig. 4. Selective HMBC ( ) correlations for **2** and **3**, and key ^1H-^1H COSY ( ) correlations of **3**.

Table1.^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data for 1-3 (δ in ppm, J in Hz)

	1[c]		**2**[c]		**3**[c]	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	3.03 (dd, 2.7, 11.2)	67.2	3.73 (dd, 2.4, 11.2)	62.6	3.18 (dd, 2.8, 11.1)	66.5
3	1.53[a] 1.75 (m)	37.0	1.79 (m) 1.91 (m)	36.6	1.55 (m) 1.77 (m)	37.0
4	1.37 (m) 1.80 (d, 12.9)	24.8	1.45 (m) 1.89 (m)	25.0	1.40 (m) 1.82 (d, 12.8)	25.0
5	1.58[a] 1.76 (m)	25.8	1.75 (m) 1.81 (m)	25.8	1.63 (m) 1.69 (m)	26.0
6	2.01 (td, 2.3, 11.4) 3.16 (d, 11.4)	52.7	2.48 (td, 2.8, 11.8) 2.92 (d, 11.8)	47.2	2.04 (td, 2.8, 11.8, 11.8) 3.00 (d, 11.8)	54.6
2′	8.54 (br. s)	149.4	8.61 (br. s)	150.0	8.56 (br. s)	149.4
3′		140.6		137.2		140.5
4′	7.56 (d, 7.8)	136.4	7.83 (d, 7.7)	135.5	7.70 (d, 7.8)	135.0
5′	7.25[b]	123.9	7.36 (dd, 4.7, 7.7)	124.7	7.25[b]	124.0
6′	8.52 (d, 4.0)	148.9	8.57 (d, 4.7)	149.5	8.50 (d, 3.9)	149.1
1″	1.23 (dd, 3.8, 13.0) 1.42[a]	40.9	4.22 (m)	58.4	2.84 (d, 16.5) 3.27 (d, 16.5)	57.6
2″	1.53[a] 1.60 (m)	19.3		126.0		180.9
3″	1.42[a] 1.74 (m)	40.3		158.4	6.13 (s)	130.8
4″		71.8	6.96 (d, 8.0)	121.9		210.1
5″	4.00 (m)	81.6	7.20 (t, 8.0)	129.0	2.37 (2H, m)	35.3
6″	1.58[a]	53.0	7.44 (d, 8.0)	118.6	2.58 (m) 2.38 (m)	30.0
7″	1.58[a] 2.28 (m)	24.9		134.3		
8″	1.36 (dd, 3.2 13.3) 1.50 (m)	43.5		196.9		
9″		37.4	2.19 (m) 2.65 (dd, 4.6, 8.0)	37.5		
10″	1.66 (d, 11.5)	57.5	2.17 (2H, m)	20.4		
11″	2.58 (td, 4.7, 11.4)	43.1				
12″		177.6				
13″	1.29 (s)	24.3				
14″	0.98 (s)	20.1				
15″	2.42 (2H, m)	55.6				
-OH			13.07 (s)			

[a]Overlapped by other signals; [b]Overlapped by solvent; [c]Recorded in $CDCl_3$.

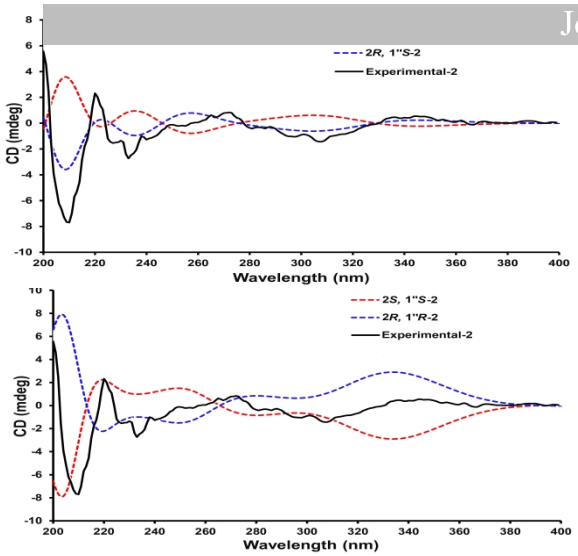


Fig. 5. Experimental and calculated ECDs for **2.**

The molecular formula of alangiumine C (**3**)[15] was established as $C_{16}H_{20}N_2O$ from its HRESIMS at *m/z* 279.1465 $[M+Na]^+$ and ^{13}C NMR spectrum, which had 3 degrees of unsaturation less than that of compound **2**. The ^1H and ^{13}C NMR spectroscopic data of **3** (Table 1) were similar to those of *N*′-hydroxybenzylanabasine (Fig. 1).[13] The visible differences were that the signals of the benzene ring (ring-C) in *N*′-hydroxybenzylanabasine were replaced by a typical *α,β*-unsaturated ketone [δ_C 180.9 (s), 130.8 (d) and 210.1 (s); and two methylene carbons δ_C 30.0 (t) and 35.3 (t)] in **3**. In its HMBC spectrum, the correlations of δ_H 3.27 (H-1″) with δ_C 180.9 (s, C-2″) and 30.0 (t, C-6″), and of δ_H 2.38 (H-6″) with δ_C 210.1 (s, C-4″) (Fig. 4) established the additional *α,β*-unsaturated cyclopentanone moiety (ring-C) in **3**. The configuration of a single chiral center (C-2) was determined as *S* because the specific rotation of **3** was with the same sign to that of (2*S*)-*N*′-hydroxybenzylanabasine, but opposite to that of the (2*R*)-*N*′-hydroxybenzylanabasine.[13]

to anabasine (Scheme 1), which is a major component of *A. chinense*.[16-17] Structurally, the residual lone pair electrons of anabasine are beneficial for nucleophilic addition. Then, compound **1** could be formed by the nucleophilic addition reaction between arbusculin A and 2*R*-anabasine.[18] Similarly, compound **2** could be derived from juglone,[21] a well-known naphthoquinone naturally occurring in plants, which then may undergo a nucleophilic addition reaction at *N*-1 of the 2*R*-anabasine and subsequent reduction. Likewise, the intermolecular nucleophilic addition reaction between *a*-hydroxybenzaldehyde and *N*-1 of 2*S*-anabasine should be a key step to form 2*S*-*N*′-hydroxybenzylanabasine, and then it might undergo cleavage of six-membered ring and reconstruction of five-membered ring by the removal of CO to afford compound **3**.

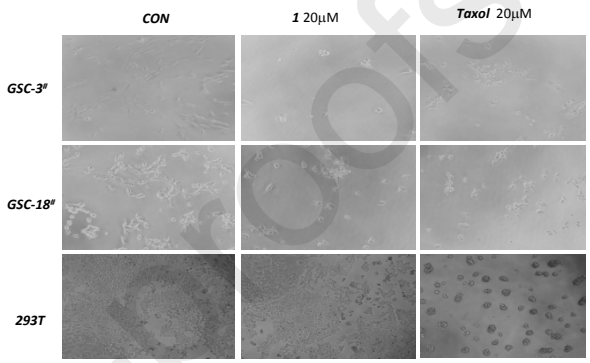
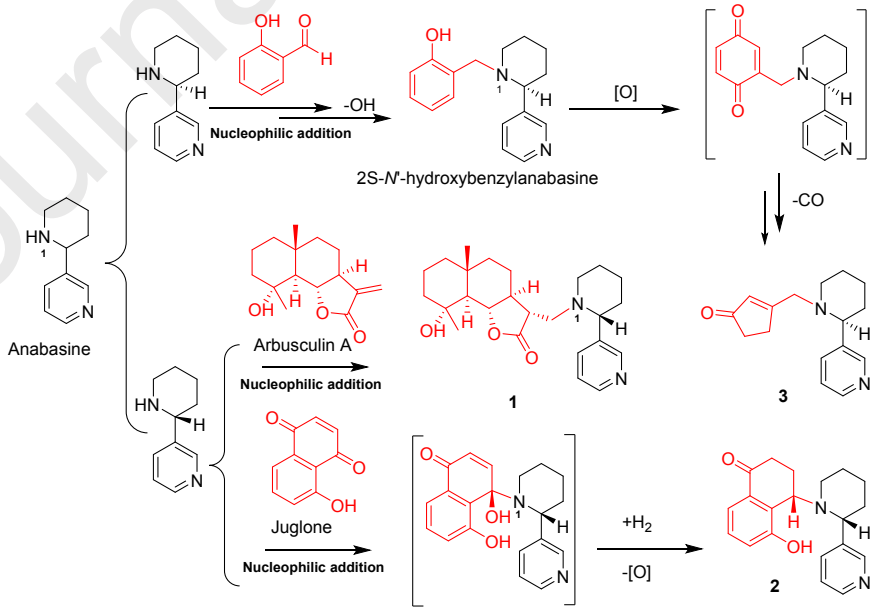


Fig. 6. Cytotoxicity tests of **1** and taxol against GSCs (GSC-3# and GSC-18#) and human normal cell lines (293T) at 20 *μ*M concentration by phenotypic screening *in vitro*.

Alangiumines A-C (**1-3**) were evaluated for their anti-cancer activity against glioma stem cell lines (GSC-3# and GSC-18#) and the cytotoxicity for human normal embryonic kidney cell lines (293T) following the protocols described previously.[22-23] The initial results exhibited that compound **1** was able to inhibit the growth of GSCs (GSC-3# and GSC-18#) significantly, but without effect on human normal embryonic kidney cells at 20 *μ*M concentration (Fig. 6). Further cell viability assay by the



Scheme 1. Possible biosynthetic pathway for gelselegandines A-C (**1-3**).

MTS method showed that the IC_{50} of **1** against GSCs-3# was 12.8 *μ*M, 23.0 *μ*M against GSCs-18# (Fig. 7a), while 13.6 and 15.7

μM respectively (Fig. 7b). However, the IC_{50} of **1** and taxol against human normal cell lines (293T) were more than 50.0 μM and 14.3 nM (Fig. 7a-b), which indicating the selective antitumor activities of **1** against GSCs. Compounds **2** and **3** were inactive at 20 μM concentration.

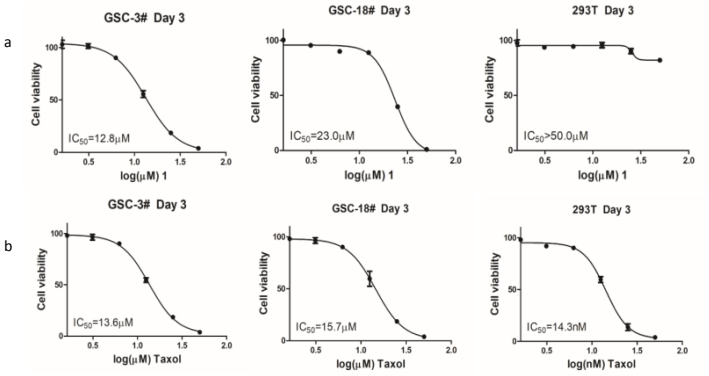


Fig. 7. (a) The IC_{50} values of **1** against GSCs (GSC-3$^{\#}$ and GSC-18$^{\#}$) and human normal cells (293T); (b) The IC_{50} values of taxol against GSCs (GSC-3$^{\#}$ and GSC-18$^{\#}$) and human normal cells (293T).

The present investigation reported alangiumines A-C (**1-3**), unique hybrid pyridine alkaloids with unprecedented santanolide-anabasine, benzcyclohexanone-anabasine, and cyclopentenone-anabasine skeletons from *A. chinense*. Besides, compound **1** exhibited the selective antitumor activity against glioma stem cells, which may provide new type of lead for the selective inhibition of human glioma cells.

Acknowledgments

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Supplementary Material

Detailed description of the experimental procedures, 1D and 2D NMR spectra, HRESIMS, and UV and ECD spectra of compounds **1-3** are available as Supporting Information.

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15. *Alangiumine A (1)*: colorless oil; $[\alpha]^{24}_{D}$ +30.0 (*c* 0.07, MeOH); UV (MeOH) λ_{max} (log ε): 204 (3.99), 261 (3.51) nm; IR (KBr) ν_{max} 3425, 2930, 1776, 1457, 1275, and 1097 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 413.2795 [M + H]$^{+}$ (calcd for $C_{25}H_{37}N_2O_3^{+}$, 413.2799).
Alangiumine B (2): colorless oil; $[\alpha]^{21}_{D}$ -34.0 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε): 205 (4.23), 223 (4.20), 259 (3.88), 319 (3.42) nm; IR (KBr) ν_{max} 3429, 2931, 1628, 1459, 1290, and 1088 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 323.1754 [M + H]$^{+}$ (calcd for $C_{20}H_{23}N_2O_2^{+}$, 323.1754).
Alangiumine C (3): colorless oil; $[\alpha]^{24}_{D}$ -30.0 (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ε): 206 (4.14), 224 (4.18), 257 (3.61) nm; IR (KBr) ν_{max} 3428, 2932, 1671, 1384, 1272, and 1025 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 279.1465 [M + Na]$^{+}$ (calcd for $C_{16}H_{20}N_2ONa^{+}$, 279.1468).
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Highlights

Antitumor Pyridine Alkaloids Hybrid with Diverse Units from *Alangium chinense*

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Three novel additive pyridine alkaloids.

Unprecedented santanolide-anabasine, benzcyclohexanone-anabasine, and cyclopentenone-anabasine skeletons.

ECD calculations.

Selective antitumor activity against glioma stem cells.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: