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Phleghenrines A–D and Neophleghenrine A, Bioactive and Structurally Rigid *Lycopodium* Alkaloids from *Phlegmariurus henryi*

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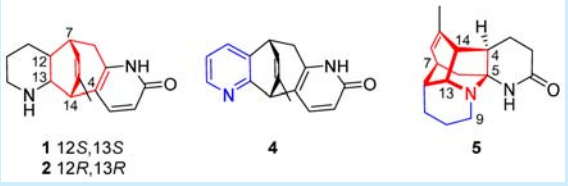
Supporting Information

ABSTRACT: Five new *Lycopodium* alkaloids, phleghenrines A–D (**1**–**4**) and neophleghenrine A (**5**), were isolated from *Phlegmariurus henryi* (Baker) Ching. The structures and absolute configurations of **1**–**5** were determined using extensive spectroscopic data coupled with computational calculations and revealed **1**–**4** possess a bicyclo[3.2.2]-nonane core, whereas **5** possesses an unprecedented 9-azaproto-adamantane core. Compounds **1** and **4** showed potent acetyl-cholinesterase (AChE) inhibitory activities, and **4** is a good lead natural product for the treatment of Alzheimer's disease.



Alzheimer's disease (AD) is a common age-related, chronic degenerative brain disease and recognized as the most common form of dementia, accounting for an estimated 60–80% of all cases. According to the Alzheimer's Association in 2015, one in nine Americans age 65 and older (11%), and an estimated 5.3 million Americans of all ages, have AD.[1] Acetylcholinesterase (AChE) increases levels of the neuro-transmitter acetylcholine in the brain and remains the most valuable therapeutic target for symptomatic improvement in AD.[2] Among the six drugs approved (as of December 2015) by the U.S. Food and Drug Administration (FDA), four are AChE inhibitors: galantamine, rivastigmine, donepezil, and tacrine.[1,3] However, each of these drugs only temporarily improves, rather than cures, symptoms of AD and has common gastrointestinal side effects such as nausea and vomiting.[1,4] Therefore, it is imperative to develop new pharmacologic treatments to slow or stop the progress of AD.

Lycopodium alkaloids are a family of structurally diverse natural products from the genus *Lycopodium* (Lycopodiaceae) with a wide range of biological activities including AChE inhibitory activity.[3,5] This family was separated into four structural classes: the lycopodines, the lycodines, the fawcettimines, and the miscellaneous.[3,5] Huperzines A (HupA, **6**) and B (HupB, **7**) (Figure 1), first isolated from *Huperzia serrata* (Thunb) Trev. in 1986, are two representatives of the lycodine class of *Lycopodium alkaloids* and exhibit potent inhibitory activity against AChE.[6] HupA (**6**) has already been marketed as a new drug in the treatment of AD in China and as a dietary supplement in the USA.[7] A second phase clinical trial for the effects of HupA (**6**) in the treatment of Traumatic Brain Injury (TBI) is also in progress (Clinical-Trials.gov identifier: NCT01676311).

Phlegmariurus henryi (Baker) Ching belongs to the family Huperziaceae and is distributed in the Guangxi and Yunan provinces in China, and in northern Vietnam.[8] This plant was

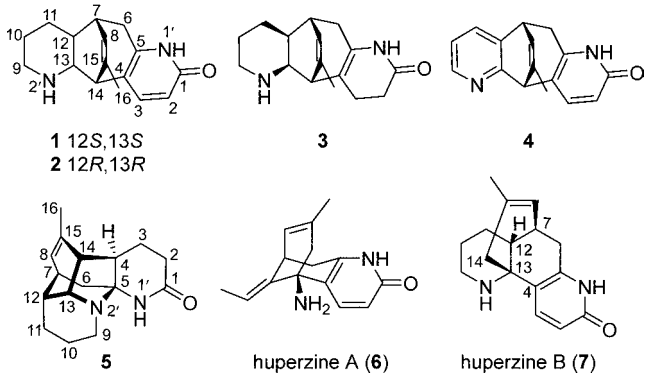


Figure 1. Chemical structures of phleghenrines A–D (**1**–**4**), neophleghenrine A (**5**), and huperzines A and B.

reported to produce large amounts of HupA (**6**), but no detailed chemical constituent investigation has been performed.[8] Herein, we report the isolation of five new *Lycopodium* alkaloids belonging to the lycodine class, phleghenrines A–D (**1**–**4**) and neophleghenrine A (**5**), together with HupA (**6**) and HupB (**7**) from *P. henryi*. A combination of extensive spectroscopic data and Boltzmann-weighted density functional theory (DFT) GIAO NMR and time-dependent DFT (TD-DFT) electronic circular dichroism (ECD) spectra calculations revealed **1**–**4** possess a bicyclo[3.2.2]nonane core, while **5** possesses an unprecedented 9-azaprotoadamantane core, the first natural product found to contain this moiety. We also proposed a possible biosynthetic pathway for the formations of the C-4–C-14 and N-2′–C-5 bonds from HupB (**7**) via an aza-semipinacol rearrangement (Scheme S1). The AChE and butyrylcholinesterase (BuChE) inhibitory activities were

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determined for **1**−**4** revealing that all congeners possessed AChE inhibitory activities, but only **1** showed moderate inhibitory activity against BuChE.

Phleghenrine A (**1**) was obtained as a colorless gum. High-resolution EIMS (HREIMS) analysis showed an $[M]^+$ ion at m/z 256.1562, consistent with a molecular formula of $C_{16}H_{20}N_2O$ (calculated $[M]^+$ ion at m/z 256.1576) and indicative of eight degrees of unsaturation. The UV absorptions (λ_{max}) at 236 and 315 nm revealed the presence of an α-pyridone ring.[9] In the ^{1}H NMR spectrum (Table 1), a methyl

Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data for 1 and 2 in CD_3OD (δ in ppm, J in Hz)

	1		2	
no.	δ_H	δ_C	δ_H	δ_C
1		165.8		165.8
2	6.32, d (9.0)	117.6	6.28, d (9.0)	116.8
3	7.41, d (9.0)	145.7	7.31, d (9.0)	146.8
4		117.1		118.9
5		146.0		145.9
6a	2.83, dd (18.6, 3.6)	36.5	2.92, dd (18.6, 3.6)	31.8
6b	2.76, dd (18.6, 3.6)		2.65, dd (18.6, 3.6)	
7	2.50, m	36.2	2.53, m	35.7
8	6.00, br d (6.6)	125.8	5.87, dt (6.0, 1.2)	126.1
9a	3.23, m	41.4	2.96, ddd (13.2, 10.2, 4.8)	41.9
9b	3.16, m		2.71, ddd (13.2, 9.6, 4.8)	
10a	1.89, overlapped	18.5	1.80, m	22.3
10b	1.75, m		1.43, m	
11a	1.89, overlapped	25.1	1.43, m	22.3
11b	1.37, m		1.34, m	
12	2.43, m	37.5	1.87, m	37.6
13	3.87, d (8.4)	59.7	3.08, dd (10.8, 4.8)	58.6
14	3.15, br s	47.1	2.98, d (4.8)	49.1
15		142.2		145.1
16	1.87, s	22.4	1.81, d (1.2)	21.7

at δ_H 1.87 (s, H_3-16) and three olefinic protons at δ_H 6.00 (br d, J = 6.6 Hz, H-8), 6.32 (d, J = 9.0 Hz, H-2), and 7.41 (d, J = 9.0 Hz, H-3) were clearly observed. The ^{13}C and DEPT NMR spectra (Table 1) exhibited 16 carbon signals attributable to a methyl (δ_C 22.4), an α-pyridone moiety (δ_C 165.8, 146.0, 145.7, 117.6, and 117.1), a trisubstituted double bond (δ_C 142.2 and 125.8), an aminomethine (δ_C 59.7), three methines, and four methylenes. The α-pyridone ring and one double bond accounted for five degrees of unsaturation; the remaining three degrees of unsaturation indicated the presence of an additional tricyclic system in the structure of **1**.

Interpretation of the 2D NMR (^{1}H−^{1}H COSY, HSQC, and HMBC) spectra of **1** allowed the construction of the planar structure. The connection of C-9 and C-13 through a nitrogen atom was established by a combination of their chemical shifts (δ_C 41.4 and 59.7, respectively), together with the HMBC correlations from H_2-9 to C-13. In addition, a proton spin system of H_2-9/H_2-10/H_2-11/H-12/H-13 was also observed in the ^{1}H−^{1}H COSY spectrum. Taken together, the presence of a piperidine ring (B ring) was confirmed (Figure 2). A cycloheptane ring was established as a linkage between α-pyridone and B rings. This assignment was supported by HMBC correlations of H_2-6 and H-14 with C-4 and C-5, as well as a proton spin system of H_2-6/H-7/H-12/H-13/H-14 found in ^{1}H−^{1}H COSY spectrum. Furthermore, the HMBC correlations from H-14 and H-7 to the double bond of C-8−C-15 in combination with the proton spin system of H-7/H-8 deduced from the ^{1}H−^{1}H COSY spectrum suggested the presence of a trisubstituted double bond bridge between C-7 and C-14 and led to the establishment of the bicyclo[3.2.2]-nonane core. Finally, the planar structure of **1** was completed by the attachment of the methyl group of C-16 to C-15 as evidenced by the HMBC correlations from H_3-16 to C-8, C-14, and C-15.

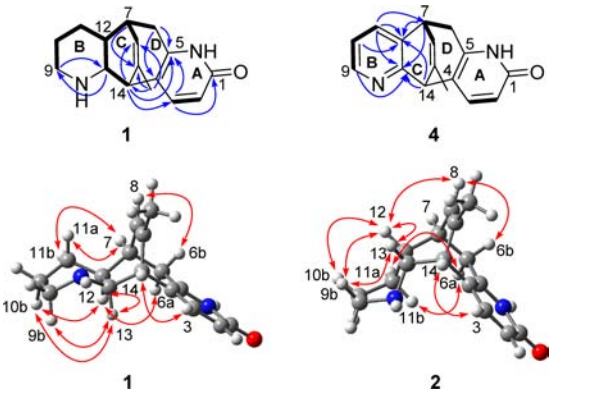

Figure 2. ^{1}H−^{1}H COSY (bold) and selected HMBC (arrows) correlations of **1** and **4**; and selected ROESY (double arrows) correlations of **1** and **2**.

Phleghenrine B (**2**) has the same molecular formula of $C_{16}H_{20}N_2O$ as **1**, as deduced by HREIMS analysis (m/z 256.1570 $[M]^+$). In addition, the ^{1}H and ^{13}C NMR data of **2** were remarkably similar to those of **1** (Table 1). Detailed analysis of the 2D NMR (^{1}H−^{1}H COSY, HSQC, and HMBC) spectra confirmed **2** and **1** were diastereomers (Figure 1).

The relative configurations of **1** and **2** were determined by interpretation of ROESY spectra. Compared with the structures of HupB (**7**) and other members of the lycodine class of *Lycopodium* alkaloids, compounds **1** and **2** possess a new seven-membered D ring through a C-4−C-14 bond, but keep the A, B, and C rings.[3,5] Thus, biosynthetically, the double bond bridge of C-8−C-15 was likely on top of the cycloheptane ring. In the ROESY spectrum of **1** (Figure 2), the correlation of H-8 with H-6b was observed, suggestive of the same β-orientation. Meanwhile, the correlations of H-12 with H-6a and H-10b, as well as H-13 with H-10b, were observed, suggestive of an α-orientation of these four protons. In the case of **2**, however, the H-8 showed correlation with not only H-6b but also H-12. The strong correlation of H-13 with H-9b together with the weak correlation of H-12 with H-9b was also observed (Figure 2). Taken together, these data supported the opposite orientation (β) of H-12 and H-13 in **2**. Interestingly, in contrast to the chair conformation of B ring in HupB (**7**), compounds **1** and **2** possess a rare boat conformation, which was supported by the correlations of H-13 with H-9b, and H-12 with H-10b in both cases (Figure 2).[3]

The absolute configurations of **1** and **2** were established by comparison of their experimental and Boltzmann-weighted TD-DFT calculated ECD spectra. The Boltzmann-weighted TD-DFT calculated ECD spectra for (7*R*,12*S*,13*S*,14*R*)-**1** and (7*R*,12*R*,13*R*,14*R*)-**2** at the B3LYP/6-31+G(d,p) level of theory in methanol using the COSMO solvent continuum model were carried out.[10] Comparisons of the observed and calculated ECD spectra are shown in Figure 3. There is an overall agreement between the experimental and TD-DFT calculated ECD

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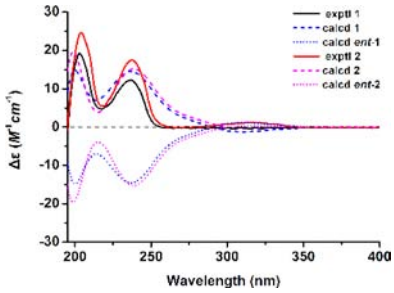

Figure 3. Experimental and calculated ECD spectra for **1** and **2**, as well as their enantiomers (***ent*-1** and ***ent*-2**) in methanol.

spectra of (7*R*,12*S*,13*S*,14*R*)-**1** and (7*R*,12*R*,13*R*,14*R*)-**2**. Therefore, the absolute configurations of **1** and **2** were established.

Phleghenrine C (**3**) showed a molecular ion at *m*/*z* 258.1723 $[M]^+$ in its HREIMS spectrum, corresponding to molecular formula $C_{16}H_{22}N_2O$ (calculated $[M]^+$ ion at *m*/*z* 258.1732) with two mass units higher than **1**. The ^1H and ^{13}C NMR data of **3** and **1** were comparable with a marked difference in the A ring (Table S1). Signals for the C-2−C-3 double bond were absent in **3** and replaced by two saturated carbons at δ_C 31.5 and 29.1. This conjugated double bond disappearance in the A ring was further supported by the downfield chemical shift of C-1 (δ_C 173.3) as well as the HMBC correlations from H_2-2 and H_2-3 to C-1. The stereochemistry of **3** was elucidated as 7*R*, 12*S*, 13*S*, 14*R*, the same as that in **1**, through the combination of the ROESY correlations of H-12 with H_2-6 (overlapped signals), and H-12 and H-13 with H-10b, as well as the comparable experimental ECD spectrum of **3** with the calculated ECD spectrum of (7*R*,12*S*,13*S*,14*R*)-**3** (Figure S25).

Phleghenrine D (**4**) gave the HREIMS ion at *m*/*z* 250.1113, suggestive of a molecular formula of $C_{16}H_{14}N_2O$ (calculated $[M]^+$ ion at *m*/*z* 250.1106). This molecular formula showed that **4** had 11 degrees of unsaturation, which is more than any other reported *Lycopodium* alkaloid monomer in the literature.[3,5] By comparing the ^1H and ^{13}C NMR spectra of **4** with those of **1** (Table S1), along with the signals of the α-pyridone group and a trisubstituted double bond ascribed to C-8−C-15, three additional downfield hydrogen signals were observed at δ_H 8.22 (dd, *J* = 4.8, 1.5 Hz, H-9), 7.49 (dd, *J* = 7.8, 1.5 Hz, H-11), and 7.06 (dd, *J* = 7.8, 4.8 Hz, H-10), and five carbon signals observed at δ_C 163.6 (s, C-12), 145.9 (d, C-9), 134.4 (s, C-12), 132.8 (d, C-11), and 121.5 (d, C-9). These signals implied that the piperidine ring (B ring) of **1** is replaced by a pyridine ring in **4**. This inference was supported by the observation of the $^1H-^1H$ COSY correlations of H-9/H-10/H-11 and HMBC correlations from H-11, H-7, and H-14 to C-12 and C-13, and H-9 to C-13 (Figure 2). The stereochemistry at C-7 and C-14 was assigned as *R* and *S*, respectively, using computational calculation as described above (Figure S34). Accordingly, compound **4** with a pyridine ring (B ring) was elucidated as shown in Figure 1.

Neophleghenrine A (**5**) had a molecular formula of $C_{16}H_{22}N_2O$ based on HREIMS analysis ($[M]^+$ ion at *m*/*z* 258.1732; calculated $[M]^+$ ion for $C_{16}H_{22}N_2O$ at *m*/*z* 258.1732). It has an identical molecular formula with **3**, i.e., seven degrees of unsaturation. The ^{13}C and DEPT NMR spectra of **3** and **5** were also similar, except for two marked differences that revealed the structure of **5** (Table S2). Compared with the ^{13}C NMR spectrum of **3**, only three downfield signals were observed. The signal of δ_C 175.1 was ascribable to C-1, whereas the other two signals were ascribable to the double bond of C-8−C-15, which was supported by their HMBC correlations with H_3-16 (Figure 4), suggesting the loss

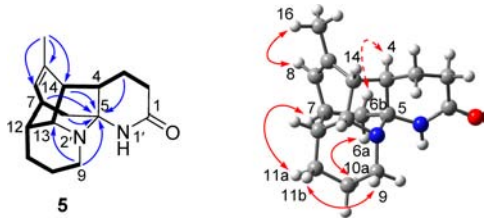

Figure 4. $^1H-^1H$ COSY (bold) and selected HMBC (arrows) and ROESY (double arrows) correlations of **5**.

of the C-4−C-5 double bond in **5**. Consistently, two new signals of δ_C 51.6 (d, C-4) and 78.7 (s, C-5) were detected using a combination of ^{13}C and DEPT NMR, and HMBC spectra. Due to the identical degrees of unsaturation in **3** and **5**, the loss of a double bond indicated that a new ring was formed in **5**. We suspected that the new ring was likely formed between N-2′ and C-5. The relative downfield chemical shift of C-5 (δ_C 78.7) was similar to that of C-9 (δ_C 77.1) in lycopalhine A.[10a] Additionally, an HMBC correlation between H-9b and C-5, together with a ROESY correlation of H-6a with H-10a, was observed (Figure 4), supporting the linkage of N-2′ and C-5. Thus, the planar structure of **5** was established as a *Lycopodium* alkaloid containing a 9-azaprotoadamantane moiety.

The stereochemistry of **5** was determined by ROESY analysis together with the biosynthetic point of view. Biosynthetically, compounds **1**−**3** were produced prior to **5**, suggesting the stereochemistry at C-7 and C-14 were *R* and *S*, respectively (Scheme S1). Due to the strained bridge of C-8−C-15 in the bicyclo[3.2.2]nonane core, the attack from N-2′ to C-5 was only possible from the bottom of the bridge, indicating the precursor of **5** was **2**, rather than **1** or **3**. Thus, the stereochemistry at C-12, C-13, and C-5 were assigned as *R*, *R*, and *S*, respectively. The above prediction was further supported by the ROESY correlations of H-7 with H-11a and H-6a with H-10a. Furthermore, a ROESY correlation of H-6b with H-4 supported the *R* configurarion at C-4. Due to the very close chemical shifts of H-4 and H-3b, however, we were unable to fully exclude the possibility of **5** possessing a 4*S* configuration.

In order to provide further evidence for the assignment of the stereochemistry at C-4, we set out an *ab initio* DFT calculation of NMR chemical shifts for (**4*R*)-5** and (**4*S*)-5**.[11] Previously, this method has already been proven as a powerful tool for the assignments of gross structure and stereochemistry of *Lycopodium* alkaloids in the case of only having one set of experimental data in our group.[10a,12] Briefly, a conformational search for (**4*R*)-5** and (**4*S*)-5** was performed in Discovery Studio 3.1 Client using molecular mechanics calculations.[13] The corresponding minimum geometries were optimized at the B3LYP/6-31G(d) level and then followed at the B3LYP/6-31+G(d, p) level in the gas phase to obtain more accurate conformers. In this study, we utilized the DFT GIAO technique at the mPW1PW91-SCRF/6-311+G(2d,p) level of theory in the PCM solvent continuum model with methanol as a solvent to calculate their ^{13}C NMR chemical shifts.[10a,12] As shown in Table S2, both the largest deviation (4.34 ppm) and corrected mean absolute deviation (1.16 ppm) of (**4*R*)-5** were smaller than those (5.63 and 2.15 ppm, respectively) of (**4*S*)-5**.

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Furthermore, when the parameter of DP4 probability was used, the configuration of (4*R*)-**5** was more likely than (4*S*)-**5** (99.98% vs 0.02%).[12,14] These data, in combination with the biosynthetic relationship to **2**, supported the absolute stereochemistry of (4*R*,5*S*,7*R*,12*R*,13*R*,14*S*)-**5**.

Compounds **1**−**4** were tested for AChE and BuChE inhibitory activities using the Ellman method with tacrine used as a positive control (Table 2).[15] While **2** and **3** showed

Table 2. IC_{50} (μM) Values of 1−4 against AChE and BuChE[a]

	Tacrine[b]	HupA	HupB	1	2	3	4
AChE	0.30	0.24	0.51	4.91	20.5	25.6	4.32
BuChE	0.02	>100	65.1	39.3	>100	>100	>100

[a]The Ellman method was used.[15] [b]Positive control.

good AChE inhibitory activities, **1** and **4** showed potent AChE inhibitory activities with IC_{50} values of 4.91 and 4.32 μM, respectively. In addition, **1** also showed moderate BuChE inhibitory activity (IC_{50} 39.3 μM). Interestingly, compound **4** had the best bioactivity against AChE, albeit still ∼15-fold lower than that of tacrine; **4** showed no inhibition against BuChE in comparison with tacrine. This finding is quite inspiring because the significant BuChE inhibitory activity of tacrine was suggested to contribute to its severe side effects (hepatotoxicity); thus its use was discontinued in the USA in 2013.[3] In addition, compound **4** is a promising medicinal chemistry target due to its simple structure, which only possesses two configurations (i.e., **4** and its enantiomer), as well as the presence of the pyridine ring (B ring) that conveniently allows chemical modification. Therefore, compound **4** is a good lead natural product for the further development of novel AChE inhibitors for the treatment of AD.

In summary, we have identified five new *Lycopodium* alkaloids (**1**−**5**) from *P. henryi*, again demonstrating *Lycopodium* alkaloids continue to reveal new and unexpected phenomena.[16] Each of these new natural products has structurally intriguing elements including a bicyclo[3.2.2]-nonane moiety in **1**−**4**, boat conformations of the B rings in **1**−**3**, a pyridine B ring in **4**, and an unprecedented 9-azaprotoadamantane moiety in **5**. Compounds **1** and **4** showed significant AChE inhibitory activities, with **4** showing potential due to its lack of BuChE inhibition as well as its simple chemical skeleton with a modifiable pyridine ring. Continued investigation of the production, total synthesis, structure−activity relationships, and biological mechanisms of this new family of *Lycopodium* alkaloids toward AD promises to be extremely rewarding.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02065.

A proposed biogenetic pathway for **1**−**5** from HupB (**7**), 1D and 2D NMR spectra of **1**−**5**, experimental and calculated ECD spectra for **3** and **4**, and detailed experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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