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Flueggeacosines A−C, Dimeric Securinine-Type Alkaloid Analogues with Neuronal Differentiation Activity from *Flueggea suffruticosa*

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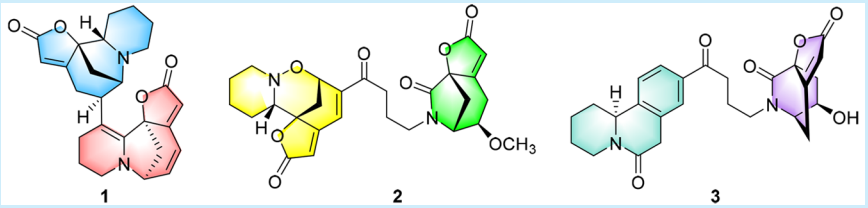
Supporting Information



ABSTRACT: Flueggeacosines A−C (**1**−**3**), three dimeric securinine-type alkaloid analogues with unprecedented skeletons, were isolated from *Flueggea suffruticosa*. Compounds **1** and **2** are the first examples of C-3−C-15′ connected dimeric securinine-type alkaloids. Compound **3** is an unprecedented heterodimer of securinine-type and benzoquinolizidine alkaloids. Biosynthetic pathways for **1**−**3** were proposed on the basis of the coexisting alkaloid monomers as the precursors. Compound **2** exhibited significant activity in promoting neuronal differentiation of Neuro-2a cells.

The *Securinega* alkaloids are an emerging group of plant-derived indolizidine alkaloids with promising bioactivities for central nervous system (CNS), antitumor, and antibacterium.[1−3] Commonly, these alkaloids feature a unique bridged tetracyclic core, including a piperidine (or pyrrole) ring (ring A), a fused azabicyclo[3.2.1] or azabicyclo[2.2.2] octane ring (rings B and C), and a butenolide moiety (ring D). According to the size of ring A, the *Securinega* alkaloids are usually classified into two main subgroups: securinine-type (ring A is a piperidine, Figure 1) and norsecurinine-type (ring A is a pyrrole).[1] In the recent years, more than 30 oligomeric *Securinega* alkaloids spanning from dimers to pentamers had been characterized.[4,5] Interestingly, almost all of these oligomers were derived from norsecurinine-type alkaloids via C-12, C-14, or C-15 positions. However, oligomers derived from securinine-type alkaloids are rarely reported so far.

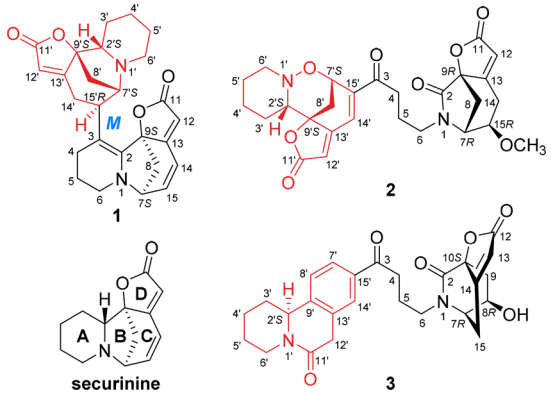


Figure 1. Chemical structures of **1**−**3** and securinine.

Our previous studies on the genus *Flueggea* had led to the isolation of flueggenine, the sole case of dimeric securinine-type alkaloid, which is presumably biosynthesized via a [2 + 2] cycloaddition reaction between two molecules of virosecurinine.[6] In our continuing research, three novel dimeric securinine-type alkaloid analogues, flueggeacosines A−C (**1**−**3**), along with their putative biosynthetic precursors [securinine (**4**), allosecurinine (**5**), and 15*β*-methoxy-14,15-dihydroviroallosecurinine (**6**)] were isolated from the roots of *Flueggea suffruticosa* (Figure 1). Structurally, compounds **1** and **2** represent the first members of two new classes of dimeric securinine-type alkaloids with an unprecedented C-3−C-15′ linkage. Notably, the unusual dimerization pattern in **1** resulted in the presence of a rare configurationally stable alkenyl-Csp[3] chiral axis, while compound **2** possesses a unique ring A opened securinine-type alkaloid motif. Compound **3** is an unprecedented heterodimer of securinine-type (ring A opened) and benzoquinolizidine alkaloids. Herein, we report the isolation, structural elucidation, and the hypothetical pathways of these novel alkaloids. Additionally, their activities

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for regulating the morphology of Neuro-2a cells were also evaluated.

Flueggeacosine A (**1**) was isolated as orange needles. The molecular formula of **1** was established as $C_{26}H_{28}N_2O_4$ based on its HR-ESI-MS data (*m*/*z* 433.2133 [M + H]$^+$, calcd for $C_{26}H_{29}N_2O_4$: 433.2122). The ^{1}H and ^{13}C NMR data of **1** revealed the presence of signals for two monomeric securinine-type alkaloids, including two typical *α*,*β*-unsaturated *γ*-lactone rings, a disubstituted double bond, and a tetrasubstituted double bond. The above spectral data combined with the molecular formula information suggested that **1** was a dimeric securinine-type alkaloid. Based on comprehensive analysis of ^{1}H−^{1}H COSY, HSQC, and HMBC spectra, the ^{1}H and ^{13}C NMR data of **1** were assigned and shown in Table S1 (see the Supporting Information).

The ^{1}H−^{1}H COSY spectrum of **1** displayed the presence of four spin-coupling systems (H_2-4 to H_2-6, H_2-8 to H-14, H-2′ to H_2-6′, and H_2-8′ to H_2-14′). In the HMBC spectrum, the correlations between H-7 and C-2/C-6/C-9, between H_2-8 and C-2/C-13, between H-12 and C-9/C-14, between H-15 and C-13, between H-2′ and C-6′/C-7′/C-8′/C-13′, between H-7′ and C-6′/C-9′, as well as between H-12′ and C-9′/C-14′ were observed. The above data suggested that **1** possessed two monomeric securinine-type alkaloid units. Furthermore, the HMBC correlations between H-15′ and C-2/C-4 indicated that the two units were connected through C-3 and C-15′. Thus, the plannar structure of **1** was established as shown in Figure 2.

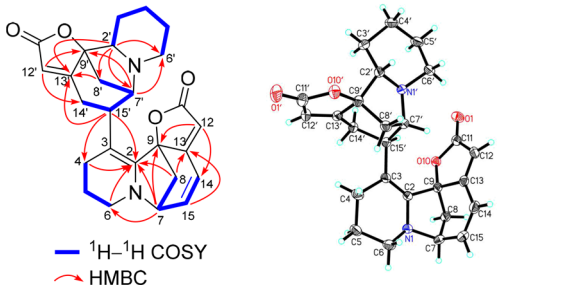

Figure 2. Key 2D NMR correlations and X-ray ORTEP drawing of **1**.

Crystals of **1** for single-crystal X-ray diffraction were acquired from MeOH−$CHCl_3$ (1:1). In the X-ray structure of **1** [Cu K*α*, Flack parameter = 0.04(13)], the two bulky monomeric *Securinega* alkaloid units adopt a fairly fixed and somewhat "*anti*" relationship, resulting in the formation of a rare alkenyl−Csp^3 chiral axis along the C-3−C-15′ bond. Interestingly, the obvious NOE correlations between H_2-4 and H-8′b/H-14′b suggested that this alkenyl−Csp^3 chiral axis could stably exist in solution at room temperature and was determined to be *M*-configured.[7] Moreover, the result of conformational distribution analysis of **1** indicated that only the 3*M*-configuration could actually occur at room temperature because of its predominantly thermodynamic stability (with a population of 100% for 3*M*-configuration, Table S2). Employing the noncovalent interaction (NCI) analysis,[8] the significant hydrogen-bond and van der Waals interactions between the two fragments further confirmed the stability of 3*M*-configuration for **1** (Figures S1 and S2). Hence, the absolute configuration of **1** was determined to be 3*M*,7*S*,9*S*,2′*S*,7′*S*,9′*S*,15′*R*.

The molecular formula of flueggeacosine B (**2**) was deduced to be $C_{27}H_{30}N_2O_8$ on the basis of its HR-ESI-MS at *m*/*z* 511.2078 [M + H]$^+$ (calcd for $C_{27}H_{31}N_2O_8$: 511.2080). Analysis of the ^{1}H and ^{13}C NMR spectra of **2** revealed the presence of a ketone carbonyl, an amide carbonyl, two *α*,*β*-unsaturated *γ*-lactones, and a methoxy group. The above data indicated that **2** was also a dimeric securinine-type alkaloid. With the aid of 1D and 2D NMR experiments, the ^{1}H and ^{13}C NMR data of **2** were assigned and listed in Table S3.

The ^{1}H−^{1}H COSY correlations led to the establishment of four spin-coupling systems in **2**. In the HMBC spectrum, key correlations between H_2-5 and C-3, between H_2-6 and C-2, between H-7 and C-2/C-6/C-9, between H_2-8 and C-2/C-13, between H-12 and C-9/C-14, between H-15 and C-13, as well as between 15-OCH_3 and C-15 suggested the existence of an unprecedented ring A opened 15-methoxy-14,15-dihydrosecurinine unit (**2a**). In addition, the HMBC correlations between H-2′ and C-6′/C-8′/C-13′, between H_2-3′ and C-9′, between H-7′ and C-9′, between H_2-8′ and C-13′/C-15′, between H-12′ and C-9′, as well as between H-14′ and C-7′/C-9′/C-12′ established a phyllanthidine motif with a tetrahydro-1,2-oxazine ring (**2b**).[9] Furthermore, the HMBC correlations between H-7′/H-14′ and C-3 implied that two substructures **2a** and **2b** were also connected through the C-3−C-15′ bond. Hence, the gross structure of **2** was established and shown in Figure 3.

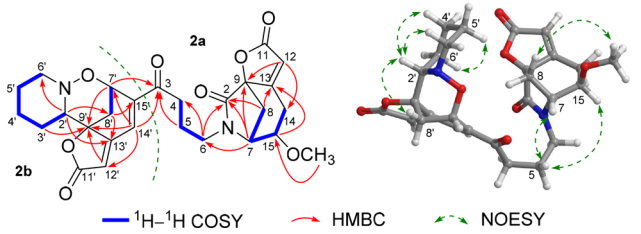

Figure 3. Key 2D NMR correlations of **2**.

The relative configuration of **2** could be determined by NOESY experiment as well as comparison of the NMR spectral data of **2** with those of the known compound. The NOE correlation between H-2′ and H-8′a in the NOESY spectrum of **2**, as well as the significant similarities between the NMR data assigned to unit **2b** and those of phyllanthidine suggested that **2b** possessed consistent relative stereochemistry with phyllanthidine.[9] Besides, as depicted in the optimized molecular model of **2** (Figure 3), the NOE interactions between H_2-5 and H-7/H-15 as well as between 15-OCH_3 and H-8b indicated that 15-OCH_3 and the C-7−C-8−C-9 carbon bridge were of the same orientation. To determine the absolute configuration of **2**, the theoretical ECD spectra of four possible stereoisomers of **2** were predicted by TDDFT calculation. Among the overall of predicted ECD spectra of four possible isomers of **2**, the calculated ECD curve of isomer 7*R*,9*R*,15*R*,2′*S*,7′*S*,9′*S*-**2** revealed a good agreement with the measured one (Figure S3A). Hence, the absolute configuration of **2** was assigned as 7*R*,9*R*,15*R*,2′*S*,7′*S*,9′*S*.

The molecular formula of flueggeacosine C (**3**) was determined to be $C_{26}H_{28}N_2O_6$ on the basis of a quasi-molecular ion at *m*/*z* 465.2020 [M + H]$^+$ (calcd for $C_{26}H_{29}N_2O_6$: 465.2026) in its HR-ESI-MS. The UV absorption maxima at 208 and 242 nm as well as IR bands at 3445, 1748, 1627, and 1436 cm^{-1} implied the presence of a

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hydroxyl group, a benzene ring, and an α,β-unsaturated γ-lactone ring. The NMR spectra revealed that **3** possessed twenty-six carbons including a ketone carbonyl, two amide carbonyls, an α,β-unsaturated γ-lactone ring, and a trisubstituted benzene ring.

The ^{1}H–^{1}H COSY spectrum of **3** revealed the existence of four spin-coupling systems as drawn in blue bold lines shown in Figure 4. In the HMBC spectrum, key correlations between

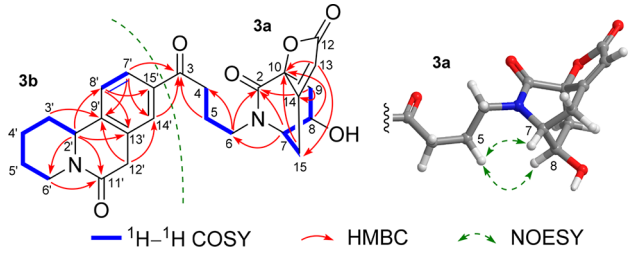


Figure 4. Key 2D NMR correlations of **3**.

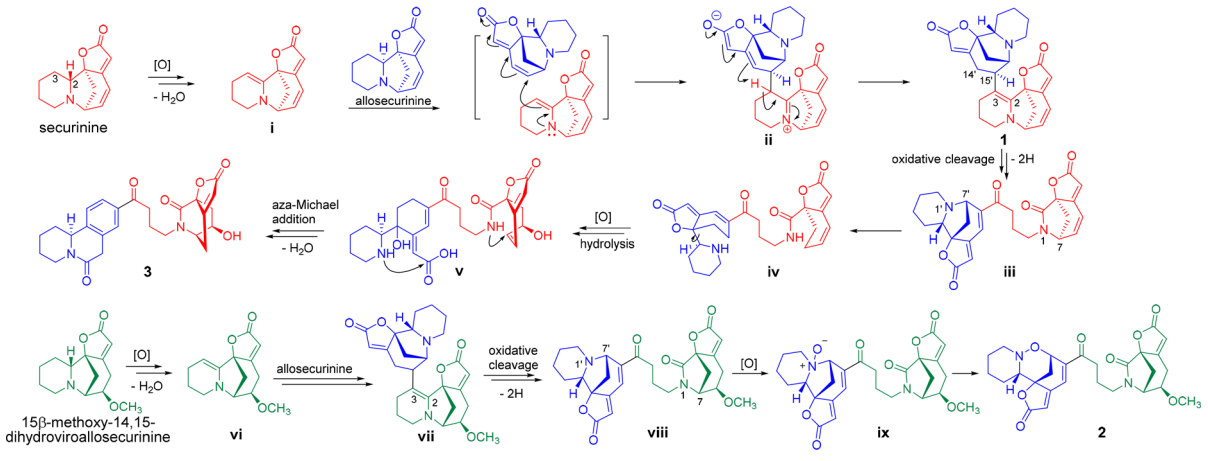
H_2-5 and C-3, between H-7 and C-2/C-6/C-14, between H_2-9 and C-2/C-14, between H-13 and C-10/C-15, and between H_2-15 and C-10 established a ring A opened neosecurinine motif (**3a**). Additionally, the HMBC correlations between H-2′ and C-6′/C-8′/C-11′/C-13′, between H_2-3′ and C-9′, between H_2-6′ and C-11′, between H-7′ and C-9′/C-14′, between H-8′ and C-13′/C-15′, as well as between H_2-12′ and C-9′/C-14′ revealed the existence of a benzoquinolizidine unit (**3b**). Moreover, the HMBC correlations between H-7′/H-14′ and C-3 indicated that two substructures **3a** and **3b** were connected through C-3–C-15′ bond.

In the NOESY spectrum of **3**, the cross-peaks between H_2-5 and H-7/H-8 were observed, suggesting that those protons were of the same orientation. This assignment was supported by the predominant conformer obtained at the B3LYP/6-311++G(2d,p) level (Figure 4). Furthermore, the modified Mosher's method was applied to determine the absolute configuration of **3a**. Comparison of the ^{1}H NMR chemical shift differences [$\Delta\delta^{SR}$ ($\delta S - \delta R$)] between (*S*)- and (*R*)-MTPA esters of **3** led to the assignment of absolute configurations for 7*R*,8*R*,10*S* in **3** (Figure S4).[10] To further determine the stereochemistry of C-2′, the theoretical optical rotation (OR) values of two possible absolute configurations of **3**, 7*R*,8*R*,10*S*,2′*S* (**3A**) and 7*R*,8*R*,10*S*,2′*R* (**3B**), were calculated at B3LYP/6-311++G(2d,p), B3LYP/cc-pVDZ, and PBE0/def2-TZVP levels, respectively.[6,11] Using the corresponding lower energy conformations, the calculated OR magnitudes of **3A** (−72.6°, −78.3°, and −71.5°, respectively) were much closer to the recorded one (−74.1°) than those of **3B** (−48.4°, −17.2°, and −25.8°, respectively). Therefore, the absolute configuration of **3** was established as 7*R*,8*R*,10*S*,2′*S*. This assignment was subsequently confirmed by comparison of the calculated ECD spectrum with the experimental one of **3** (Figure S3B).

Compounds **1**–**3** represent three new classes of dimeric securinine-type alkaloid analogues. Based on the coexisting alkaloid monomers securinine (**4**), allosecurinine (**5**), and 15β-methoxy-14,15-dihydroviroallosecurinine (**6**, see the Supporting Information) in the same plant material, the hypothetical biogenetic pathways for **1**–**3** are proposed as shown in Scheme 1. Starting from the oxidation and dehydration of ring A of securinine, the key intermediate **i** could be yielded.[3e,12] Subsequently, allosecurinine could incorporate with enamine **i** through an electrophilic addition to produce **1**.[5] Oxidative cleavage of the C-2–C-3 double bond and dehydrogenation of C-14′–C-15′ bond of **1** could lead to the generation of the ring A opened intermediate **iii**.[13] After the cleavage of the N-1–C-7 and N-1′–C-7′ bonds,[14] intermediate **iv** could be formed. Further allylic oxidation of **iv** and subsequent hydrolysis could generate intermediate **v**, which could produce **3** through aza-Michael addition and lactam formation reactions. The formation of **2** might employ 15β-methoxy-14,15-dihydroviroallosecurinine and allosecurinine as the biosynthetic precursors. Through the similar procedures to **3**, intermediate **vii** could be obtained from the coupling of the two aforementioned putative precursors. Then, the oxidative cleavage of the C-2–C-3 double bond of **vii** and subsequent dehydrogenation could yield the ring A opened intermediate **viii**. Finally, intermediate **viii** could undergo an oxidation to form *N*-oxide **ix**, which could afford **2** through a rearrangement reaction.[15]

Neurite outgrowth is a crucial process during neuronal development and regeneration. Failure of this step normally leads to synapse dysfunction which contributes to a major pathogenesis cause of a wide variety of neurological diseases.[16] To explore the potential bioactivities of compounds **1**–**3** on neuronal differentiation, we took advantage of a mouse neuroblastoma cell model (Neuro-2a cells).[17,18] As a result,

Scheme 1. Hypothetical Biogenetic Pathways for 1–3



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compounds **1**−**3** exhibited activities to promote the cells to differentiate into a neuron-like morphology, such as elongation of cell bodies and extension of neurites (Figure 5A). Relative

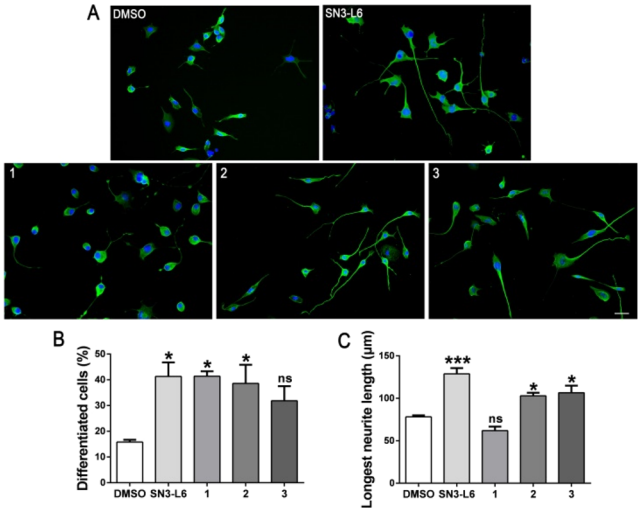

Figure 5. Compounds **1**−**3** promoted differentiation of Neuro-2a cells. (A) Neuro-2a cells were treated with **1**−**3** (25 μM) or SN3-L6 (25 μM) for 2 days. DMSO was a solvent control. Cells were immunostained using β-tubulin III antibody for visualization of neurites. Scale bar, 50 μm. (B) Cell differentiation rate (% of cells that bear neurites). (C) Average length of the longest neurites. *p < 0.05, **p < 0.01, ***p < 0.001, one way analysis of variance (ANOVA) with a Dunnett's multiple comparisons test, at least 400 cells/group were analyzed in each experiment, n = 4. Error bars indicate ± SEM.

to **1** and **3**, statistical analysis showed that **2** has better neuronal differentiation activity, as **2** not only induced more cells to differentiate, but also promoted the extension of neurites (Figures 5B and 5C). The activity of **2** was comparable to SN3-L6, a synthetic compound regarding as a potent neuritogenesis,[18] which suggested that **2** might provide a potentially new structure for future drug design of diseases involving disrupted neuronal differentiation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03432.

Detailed descriptions of the experimental procedure; UV, IR, MS, and NMR spectra for compounds **1**−**6**; DFT calculations for **2** and **3** (PDF)

Accession Codes

CCDC 1819362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on the *Securinega* alkaloids, see: (a) Weinreb, S. M. *Nat. Prod. Rep.* **2009**, *26*, 758−775. (b) Chirkin, E.; Atkatlian, W.; Porée, F. H. *Alkaloids. Chemistry and Biology* **2015**, *74*, 1−120. (c) Wehlauch, R.; Gademann, K. *Asian J. Org. Chem.* **2017**, *6*, 1146−1159.

(2) (a) Neganova, M. E.; Sercova, T. P.; Shevtsova, E. F.; Klochkov, S. G.; Bachurin, S. *J. Neurochem.* **2009**, *110*, 10−18. (b) Gupta, K.; Chakrabarti, A.; Rana, S.; Ramdeo, R.; Roth, B. L.; Agarwal, M. L.; Tse, W.; Agarwal, M. K.; Wald, D. N. *PLoS One* **2011**, *6*, No. e21203. (c) Vu, H.; Roullier, C.; Campitelli, M.; Trenholme, K. R.; Gardiner, D. L.; Andrews, K. T.; Skinner-Adams, T.; Crowther, G. J.; Van Voorhis, W. C.; Quinn, R. J. *ACS Chem. Biol.* **2013**, *8*, 2654−2659.

(3) (a) Ohsaki, A.; Kobayashi, Y.; Yoneda, K.; Kishida, A.; Ishiyama, H. *J. Nat. Prod.* **2007**, *70*, 2003−2005. (b) Zhao, B. X.; Wang, Y.; Zhang, D. M.; Huang, X. J.; Bai, L. L.; Yan, Y.; Chen, J. M.; Lu, T. B.; Wang, Y. T.; Zhang, Q. W.; Ye, W. C. *Org. Lett.* **2012**, *14*, 3096−3099. (c) Wu, Z. L.; Zhao, B. X.; Huang, X. J.; Tang, G. Y.; Shi, L.; Jiang, R. W.; Liu, X.; Wang, Y.; Ye, W. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5796−5799. (d) Zhang, H.; Zhu, K. K.; Han, Y. S.; Luo, C.; Wainberg, M. A.; Yue, J. M. *Org. Lett.* **2015**, *17*, 6274−6277. (e) Luo, X. K.; Cai, J.; Yin, Z. Y.; Luo, P.; Li, C. J.; Ma, H.; Seeram, N. P.; Gu, Q.; Xu, J. *Org. Lett.* **2018**, *20*, 991−994.

(4) For selected examples, see: (a) Gan, L. S.; Fan, C. Q.; Yang, S. P.; Wu, Y.; Lin, L. P.; Ding, J.; Yue, J. M. *Org. Lett.* **2006**, *8*, 2285−2288. (b) Zhao, B. X.; Wang, Y.; Zhang, D. M.; Jiang, R. W.; Wang, G. C.; Shi, J. M.; Huang, X. J.; Chen, W. M.; Che, C. T.; Ye, W. C. *Org. Lett.* **2011**, *13*, 3888−3891. (c) Zhang, H.; Zhang, C. R.; Zhu, K. K.; Gao, A. H.; Luo, C.; Li, J.; Yue, J. M. *Org. Lett.* **2013**, *15*, 120−123. (d) Zhang, H.; Han, Y. S.; Wainberg, M. A.; Yue, J. M. *Tetrahedron* **2015**, *71*, 3671−3679.

(5) Jeon, S. B.; Han, S. K. *J. Am. Chem. Soc.* **2017**, *139*, 6302−6305.

(6) Zhao, B. X.; Wang, Y.; Li, C.; Wang, G. C.; Huang, X. J.; Fan, C. L.; Li, Q. M.; Zhu, H. J.; Chen, W. M.; Ye, W. C. *Tetrahedron Lett.* **2013**, *54*, 4708−4711.

(7) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. *Chem. Rev.* **2015**, *115*, 11239−11300.

(8) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498−6506.

(9) Chirkin, E.; Atkatlian, W.; Do, Q.; Gaslonde, T.; Dufat, T.; Michel, S.; Lemoine, P.; Genta-Jouve, G.; Poree, F.-H. *Nat. Prod. Res.* **2015**, *29*, 1235−1242.

(10) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451−2458.

(11) (a) Dong, L. B.; Gao, X.; Liu, F.; He, J.; Wu, X. D.; Li, Y.; Zhao, Q. S. *Org. Lett.* **2013**, *15*, 3570−3573. (b) Hashmi, M. A.; Andreassend, S. K.; Keyzers, R. A.; Lein, M. *Phys. Chem. Chem. Phys.* **2016**, *18*, 24506−24510.

DOI: 10.1021/acs.orglett.8b03432
Org. Lett. 2018, 20, 7703−7707

(12) Arata, Y.; Yoshifuji, S.; Yasuda, Y. *Chem. Pharm. Bull.* **1969**, *17*, 1363−1368.
(13) (a) Lara, M.; Mutti, F. G.; Glueck, S. M.; Kroutil, W. *J. Am. Chem. Soc.* **2009**, *131*, 5368−5369. (b) Bugg, T. D. H. *Tetrahedron* **2003**, *59*, 7075−7101.
(14) Arbain, D.; Girkbeck, A. A.; Byrne, L. T.; Sargent, M. V.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1863−1869.
(15) Li, J. Y.; Zhao, B. X.; Zhang, W.; Li, C.; Huang, X. J.; Wang, Y.; Sun, P. H.; Ye, W. C.; Chen, W. M. *Tetrahedron* **2012**, *68*, 3972−3979.
(16) Krstic, D.; Knuesel, I. *Nat. Rev. Neurol.* **2013**, *9*, 25−34.
(17) Xiao, Y. G.; Peng, Y. H.; Wan, J.; Tang, G. Y.; Chen, Y. W.; Tang, J.; Ye, W. C.; Ip, N. Y.; Shi, L. *J. Biol. Chem.* **2013**, *288*, 20034−20045.
(18) (a) Tang, G. Y.; Liu, X.; Ma, N.; Huang, X. J.; Wu, Z. L.; Zhang, W.; Wang, Y.; Zhao, B. X.; Wang, Z. Y.; Ip, F. C.F.; Ip, N. Y.; Ye, W. C.; Shi, L.; Chen, W. M. *ACS Chem. Neurosci.* **2016**, *7*, 1442−1451. (b) Liao, Y. M.; Zhuang, X. J.; Huang, X. J.; Peng, Y. H.; Ma, X. Y.; Huang, Z. X.; Liu, F.; Xu, J.; Wang, Y.; Chen, W. M.; Ye, W. C.; Shi, L. *Front. Pharmacol.* **2018**, *9*, 290.

DOI: 10.1021/acs.orglett.8b03432
Org. Lett. 2018, 20, 7703−7707