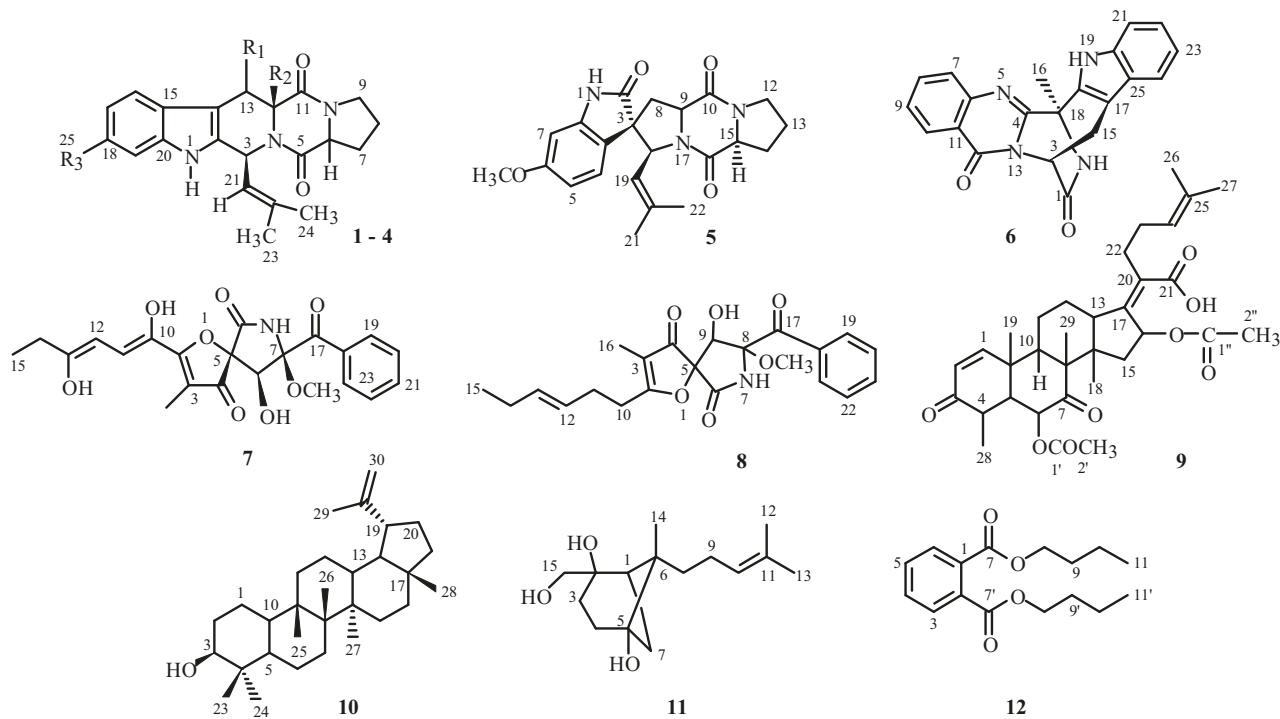


CHEMICAL CONSTITUENTS AND BIOACTIVITY OF A FUNGAL ENDOPHYTE FROM *Lamium amplexicaule*

Jian-Hui Sun, Zhong-Duo Yang,*
and Yi-Fei Zhang

Endophytic fungi are microorganisms that inhabit the intercellular spaces of plant stems, petioles, roots, and leaves without causing visible disease symptoms [1]. Recently, many bioactive compounds with antitumor, antimicrobial, and antituberculosis properties were isolated from secondary metabolites of fungal endophytes [2]. In this paper, we described the isolation and identification of 12 compounds (**1–12**) from an endophytic fungus BGC-2 (identified as *Alternaria alternata*) from *Lamium amplexicaule*. The fungal strain (BGC-2) was isolated from the stems of *Lamium amplexicaule* and identified as *Alternaria alternata* based on both morphology on PDA and analysis of the DNA sequences of the ITS1-5.8S-ITS2 ribosomal RNA gene region. A GenBank search for DNA sequence similarity revealed that ITS1-5.8S-ITS2 of BGC-2 was 99% homologous to that of *Alternaria alternata* reference strains (KU324787.1).

The endophytic fungus BGC-2 was cultivated in PDA medium (50 L) for 5 days at 28°C in a fermentor. The culture was filtered, and the broth was extracted with EtOAc (50 L) to afford the crude extract (30 g), which was subjected to a series of chromatographic techniques using silica gel (mesh 200–300), Sephadex LH-20, MCI-CHP20P gel, and HPLC separation (Waters-510 pump, Waters 2487 Dual λ Absorbance Detector, YMC-Pack ODS-A column, 250 × 10 mm, 5 μm). A total of 12 compounds was isolated and identified based on NMR spectra.



1: R₁ = R₂ = OH, R₃ = OCH₃; **2:** R₁ = R₃ = OCH₃, R₂ = OH; **3:** R₁ = R₂ = H, R₃ = OCH₃; **4:** R₁ = R₂ = R₃ = H

School of Life Science and Engineering, Lanzhou University of Technology, 730050, Lanzhou, P. R. China, fax: 86 931 2973924, e-mail: yangzhongduo@126.com. Published in *Khimiya Prirodnnykh Soedinenii*, No. 4, July–August, 2019, pp. 663–665. Original article submitted March 1, 2018.

TABLE 1. The Inhibition Rate and IC₅₀ of MAO and AChE

Compound	Inhibition rate against MAO (%) at 50 µg/mL	IC ₅₀ , µg/mL	Inhibition rate against AChE (%) at 30 µg/mL	IC ₅₀ , µg/mL
1	22.79	N.d.	39.88	N.d.
2	23.50	N.d.	28.94	N.d.
3	9.09	N.d.	66.32	24.37
4	8.13	N.d.	28.91	N.d.
5	24.67	N.d.	65.24	17.91
6	35.01	N.d.	26.77	N.d.
7	43.31	49.72	27.96	N.d.
8	35.99	N.d.	52.48	33.49
9	42.99	62.48	33.01	N.d.
10	26.65	N.d.	32.55	N.d.
11	8.16	N.d.	6.72	N.d.
12	2.42	N.d.	22.26	N.d.

The positive drugs were phosphoric acid isopropyl hydrazine (IC₅₀ = 6.54 µg/mL) and huperzine A (IC₅₀ = 0.31 µg/mL); N.d.: not detected.

Cyclotryprostatin A (1), C₂₂H₂₅N₃O₅, pale yellow crystals. ¹H NMR (600 MHz, CDCl₃, δ, ppm, J/Hz): 7.85 (1H, s, NH-1), 7.45 (1H, d, J = 8.5, H-16), 6.87 (1H, d, J = 2.0, H-19), 6.83 (1H, dd, J = 8.5, 2.0, H-17), 6.65 (1H, d, J = 9.8, H-3), 5.61 (1H, dm, J = 9.8, H-21), 5.10 (1H, s, H-13), 4.43 (1H, dd, J = 10.6, 6.4, H-6), 4.43 (1H, br.s, 12-OH), 3.83 (1H, s, 18-OCH₃), 3.75 (1H, m, H-9a), 3.68 (1H, m, H-9b), 2.48 (1H, m, H-7a), 2.22 (1H, br.s, 13-OH), 2.12 (1H, m, H-8b), 2.05 (3H, s, H-24), 2.01 (1H, m, H-8a), 2.01 (1H, m, H-7b), 1.78 (3H, s, H-23). ¹³C NMR (150 MHz, CDCl₃, δ, ppm): 133.4 (C-2), 49.0 (C-3), 166.1 (C-5), 59.8 (C-6), 30.8 (C-7), 22.3 (C-8), 46.4 (C-9), 167.2 (C-11), 85.2 (C-12), 67.9 (C-13), 107.2 (C-14), 121.6 (C-15), 119.1 (C-16), 110.2 (C-17), 156.9 (C-18), 96.0 (C-19), 137.4 (C-20), 123.5 (C-21), 139.0 (C-22), 25.7 (C-23), 18.6 (C-24), 56.2 (18-OCH₃) [3].

Cyclotryprostatin B (2), C₂₃H₂₇N₃O₅, yellow crystals. ¹H NMR (600 MHz, CDCl₃, δ, ppm, J/Hz): 7.84 (1H, s, NH-1), 7.43 (1H, d, J = 8.6, H-16), 6.87 (1H, d, J = 2.2, H-19), 6.81 (1H, dd, J = 8.6, 2.2, H-17), 6.63 (1H, d, J = 9.8, H-3), 5.55 (1H, dm, J = 9.8, H-21), 4.73 (1H, s, H-13), 4.38 (1H, dd, J = 10.6, 6.4, H-6), 4.34 (1H, br.s, 12-OH), 3.83 (1H, s, 18-OCH₃), 3.73 (1H, m, H-9a), 3.68 (1H, m, H-9b), 3.35 (1H, s, 13-OCH₃), 2.48 (1H, m, H-7a), 2.14 (1H, m, H-8b), 2.05 (3H, s, H-24), 2.02 (1H, m, H-8a), 2.02 (1H, m, H-7b), 1.78 (3H, s, H-23). ¹³C NMR (150 MHz, CDCl₃, δ, ppm): 134.4 (C-2), 49.2 (C-3), 167.1 (C-5), 59.8 (C-6), 30.6 (C-7), 22.4 (C-8), 45.8 (C-9), 165.8 (C-11), 85.0 (C-12), 77.0 (C-13), 105.6 (C-14), 122.6 (C-15), 118.6 (C-16), 110.0 (C-17), 156.4 (C-18), 95.4 (C-19), 137.2 (C-20), 123.5 (C-21), 138.3 (C-22), 26.2 (C-23), 18.2 (C-24), 56.5 (13-OCH₃), 55.7 (18-OCH₃) [3].

Fumitremorgin C (3), C₂₂H₂₅N₃O₃, white powder. ¹H NMR (600 MHz, CDCl₃, δ, ppm, J/Hz): 7.90 (1H, s, H-1), 7.43 (1H, d, J = 8.2, H-16), 6.83 (1H, d, J = 2.3, H-19), 6.81 (1H, dd, J = 8.2, 2.3, H-17), 5.99 (1H, d, J = 9.5, H-3), 4.91 (1H, d, J = 9.5, H-21), 4.18 (1H, dd, J = 11.0, 5.0, H-12), 4.11 (1H, dd, J = 9.5, 7.5, H-6), 3.84 (3H, s, H-25), 3.65 (2H, m, H-9), 3.51 (1H, dd, J = 15.8, 5.0, H-13a), 3.10 (1H, dd, J = 15.8, 11.0, H-13b), 2.39 (1H, m, H-7a), 2.23 (1H, m, H-7b), 2.06 (1H, m, H-8a), 1.94 (3H, s, H-24), 1.92 (1H, m, H-8b), 1.64 (3H, s, H-23). ¹³C NMR (150 MHz, CDCl₃, δ, ppm): 132.4 (C-2), 51.3 (C-3), 169.8 (C-5), 60.1 (C-6), 29.3 (C-7), 23.6 (C-8), 45.7 (C-9), 166.2 (C-11), 56.1 (C-12), 22.4 (C-13), 106.1 (C-14), 120.9 (C-15), 119.3 (C-16), 109.8 (C-17), 156.7 (C-18), 95.9 (C-19), 137.4 (C-20), 124.5 (C-21), 134.3 (C-22), 25.8 (C-23), 18.6 (C-24), 55.9 (C-25) [4].

Demethoxyfumitremorgin C (4), C₂₁H₂₃N₃O₂, white powder. ¹H NMR (600 MHz, CDCl₃, δ, ppm, J/Hz): 8.12 (1H, br.s, H-1), 7.57 (1H, d, J = 7.5, H-16), 7.32 (1H, d, J = 7.5, H-19), 7.23 (1H, t, J = 7.5, H-18), 7.15 (1H, t, J = 7.5, H-17), 6.01 (1H, d, J = 9.2, H-3), 4.93 (1H, d, J = 9.6, H-21), 4.15 (1H, dd, J = 10.8, 5.0, H-12), 4.08 (1H, dd, J = 7.8, 8.2, H-6), 3.62 (2H, m, H-9), 3.53 (1H, dd, J = 15.6, 4.6, H-13a), 3.12 (1H, dd, J = 15.6, 10.8, H-13b), 2.39 (1H, m, H-7a), 2.22 (1H, m, H-7b), 2.06 (1H, m, H-8a), 1.97 (3H, s, H-24), 1.92 (1H, m, H-8b), 1.63 (3H, s, H-23). ¹³C NMR (150 MHz, CDCl₃, δ, ppm): 132.5 (C-2), 51.1 (C-3), 169.7 (C-5), 58.8 (C-6), 28.7 (C-7), 22.7 (C-8), 45.2 (C-9), 166.3 (C-11), 55.2 (C-12), 21.8 (C-13), 106.4 (C-14), 126.1 (C-15), 118.6 (C-16), 120.3 (C-17), 121.9 (C-18), 111.0 (C-19), 136.0 (C-20), 124.5 (C-21), 134.2 (C-22), 25.9 (C-23), 18.2 (C-24) [5].

Spirotryprostatin A (5), $C_{22}H_{25}N_3O_4$, white powder. 1H NMR (600 MHz, $CDCl_3$, δ , ppm, J/Hz): 7.85 (1H, br.s, H-1), 6.91 (1H, d, $J = 8.3$, H-4), 6.48 (1H, dd, $J = 2.2$, 8.4, H-5), 6.43 (1H, d, $J = 2.2$, H-7), 5.02 (1H, d, $J = 9.1$, H-19), 4.99 (1H, dd, $J = 7.1$, 10.5, H-9), 4.78 (1H, d, $J = 9.1$, H-18), 4.29 (1H, t, $J = 8.0$, H-12), 3.78 (3H, s, 6-OCH₃), 3.50–3.68 (1H, m, H-15), 2.60 (1H, dd, $J = 10.8$, 13.4, H-8b), 2.38 (1H, dd, $J = 7.0$, 13.4, H-8a), 2.20–2.39 (2H, m, H-13), 1.86–2.08 (2H, m, H-14), 1.64 (3H, s, H-21), 1.15 (3H, s, H-22) [6].

Fumiquinazoline J (6), $C_{21}H_{16}N_4O_2$, white solid. 1H NMR (600 MHz, $CD_3OD + CDCl_3$, δ , ppm, J/Hz): 8.15 (1H, dd, $J = 8.0$, 1.4, H-10), 8.13 (1H, br.s, H-19), 7.69 (1H, dt, $J = 8.1$, 1.4, H-8), 7.61 (1H, d, $J = 8.1$, H-7), 7.44 (1H, dt, $J = 8.0$, 0.9, H-9), 7.42 (1H, br.d, $J = 7.6$, H-24), 7.38 (1H, br.s, H-2), 7.33 (1H, t, $J = 8.7$, H-21), 7.11 (1H, t, $J = 7.2$, H-22), 7.00 (1H, t, $J = 7.2$, H-23), 5.97 (1H, dd, $J = 4.6$, 2.7, H-14), 3.50 (1H, dd, $J = 17.2$, 2.7, H-15a), 3.35 (1H, dd, $J = 7.2$, 4.6, H-15b), 2.22 (3H, s, H-16). ^{13}C NMR (150 MHz, $CD_3OD + CDCl_3$, δ , ppm): 171.4 (C-1), 55.2 (C-3), 153.9 (C-4), 147.2 (C-6), 127.0 (C-7), 134.5 (C-8), 127.4 (C-9), 125.8 (C-10), 120.2 (C-11), 160.6 (C-12), 56.3 (C-14), 26.1 (C-15), 16.3 (C-16), 106.2 (C-17), 133.0 (C-18), 135.2 (C-20), 111.4 (C-21), 120.4 (C-22), 119.4 (C-23), 117.5 (C-24), 127.6 (C-25) [7].

Pesurotin G (7), $C_{22}H_{23}NO_8$, white powder. 1H NMR (600 MHz, $CDCl_3$, δ , ppm, J/Hz): 8.34 (2H, t, $J = 7.4$, H-19, 24), 7.64 (1H, t, $J = 7.4$, H-21), 7.49 (2H, t, $J = 7.4$, H-20, 22), 7.16 (1H, d, $J = 3.6$, H-11), 6.35 (1H, d, $J = 3.6$, H-12), 4.57 (1H, s, H-9), 3.35 (3H, s, 8-OCH₃), 2.78 (2H, m, H-14), 2.01 (3H, s, H-16), 1.27 (3H, t, $J = 7.5$, H-15). ^{13}C NMR (150 MHz, $CDCl_3$, δ , ppm): 172.4 (C-2), 108.9 (C-3), 196.6 (C-4), 93.5 (C-5), 169.1 (C-6), 92.9 (C-8), 77.2 (C-9), 144.4 (C-10), 118.7 (C-11), 108.7 (C-12), 164.6 (C-13), 21.7 (C-14), 11.7 (C-15), 6.1 (C-16), 197.4 (C-17), 135.6 (C-18), 131.5 (C-19), 128.9 (C-20), 135.8 (C-21), 128.9 (C-22), 131.5 (C-23), 51.6 (8-OCH₃) [8].

Cephalimysin A (8), $C_{22}H_{25}NO_6$, white powder. 1H NMR (600 MHz, $CDCl_3$, δ , ppm, J/Hz): 8.31 (2H, d, $J = 7.9$, H-19, 23), 7.65 (1H, t, $J = 7.9$, H-21), 7.50 (2H, t, $J = 7.9$, H-20, 22), 7.39 (1H, br.s, H-7), 5.52 (1H, dt, $J = 15.1$, 6.2, H-13), 5.39 (1H, dt, $J = 15.1$, 6.2, H-12), 4.60 (1H, d, $J = 12.5$, H-9), 2.64 (2H, m, H-10), 2.34 (2H, m, H-11), 1.98 (2H, m, H-14), 1.68 (3H, s, H-16), 0.93 (3H, t, $J = 7.1$, H-15), 4.06 (1H, d, $J = 12.5$, 9-OH), 3.39 (3H, s, 8-OCH₃). ^{13}C NMR (150 MHz, $CDCl_3$, δ , ppm): 190.3 (C-2), 111.5 (C-3), 196.8 (C-4), 91.2 (C-5), 165.5 (C-6), 89.4 (C-8), 73.8 (C-9), 29.1 (C-10), 28.6 (C-11), 126.3 (C-12), 134.8 (C-13), 25.1 (C-14), 13.3 (C-15), 5.4 (C-16), 193.8 (C-17), 132.1 (C-18), 130.3 (C-19), 128.7 (C-20), 134.5 (C-21), 128.4 (C-22), 130.1 (C-23), 51.3 (8-OCH₃) [9].

CS-E (9), $C_{32}H_{44}O_8$, colorless needles. 1H NMR (600 MHz, $CDCl_3$, δ , ppm, J/Hz): 7.31 (1H, d, $J = 10.2$, H-1), 5.88 (1H, d, $J = 10.2$, H-2), 5.89 (1H, d, $J = 8.3$, H-16), 5.24 (1H, s, H-6), 5.11 (1H, d, $J = 7.2$, H-24), 2.78 (1H, dq, $J = 12.5$, 6.8, H-4), 2.62 (1H, dd, $J = 13.0$, 2.6, H-9), 2.54 (1H, br.d, $J = 11.0$, H-13), 2.47 (2H, m, H-22), 2.42 (1H, m, H-12a), 2.28 (1H, d, $J = 12.5$, H-5), 2.25 (dd, $J = 14.7$, 8.3, H-15), 2.16 (m, H-23), 2.13 (3H, s, 6-OCOCH₃), 1.98 (m, H-11), 1.95 (3H, s, 16-OCOCH₃), 1.92 (d, $J = 14$, H-15), 1.83 (dd, $J = 12.7$, 3.4, H-12b), 1.70 (3H, s, H-27), 1.59 (3H, s, H-26), 1.46 (3H, s, H-19), 1.30 (3H, d, $J = 6.8$, H-28), 1.16 (3H, s, H-29), 0.91 (3H, s, H-18). ^{13}C NMR (150 MHz, $CDCl_3$, δ , ppm): 157.0 (C-1), 127.8 (C-2), 201.3 (C-3), 40.4 (C-4), 47.2 (C-5), 73.7 (C-6), 208.7 (C-7), 52.6 (C-8), 41.7 (C-9), 38.1 (C-10), 23.9 (C-11), 25.9 (C-12), 49.3 (C-13), 46.6 (C-14), 40.6 (C-15), 73.4 (C-16), 147.6 (C-17), 17.9 (C-18), 27.5 (C-19), 130.2 (C-20), 173.8 (C-21), 28.6 (C-22), 28.3 (C-23), 122.8 (C-24), 132.9 (C-25), 17.8 (C-26), 25.7 (C-27), 13.1 (C-28), 18.3 (C-29), 168.8 (6-OCOCH₃), 170.1 (16-OCOCH₃), 20.7 (6-OCOCH₃), 20.5 (16-OCOCH₃) [10].

Lupeol (10), $C_{30}H_{50}O$, white microcrystalline powder. 1H NMR (600 MHz, $CDCl_3$, δ , ppm, J/Hz): 4.69, 4.57 (each 1H, br.s, H-29), 3.21 (1H, dd, $J = 4.8$, 11.6, H-3), 2.36 (1H, dt, $J = 4.0$, 9.6, H-19), 1.70 (3H, s, H-30), 1.05 (3H, s, H-28), 0.99 (3H, s, H-27), 0.94 (3H, s, H-26), 0.85 (3H, s, H-25), 0.80 (3H, s, H-24), 0.76 (3H, s, H-23). ^{13}C NMR (150 MHz, $CDCl_3$, δ , ppm): 38.7 (C-1), 27.8 (C-2), 79.0 (C-3), 38.8 (C-4), 55.3 (C-5), 18.7 (C-6), 34.3 (C-7), 40.8 (C-8), 50.4 (C-9), 37.2 (C-10), 21.2 (C-11), 25.2 (C-12), 38.1 (C-13), 42.8 (C-14), 27.4 (C-15), 35.6 (C-16), 43.0 (C-17), 48.0 (C-18), 48.3 (C-19), 150.9 (C-20), 29.9 (C-21), 40.0 (C-22), 28.0 (C-23), 15.3 (C-24), 16.1 (C-25), 16.0 (C-26), 14.5 (C-27), 18.3 (C-28), 109.3 (C-29), 19.3 (C-30) [11].

β -trans-2 β ,5,15-Trihydroxybergamot-10-ene (11), $C_{15}H_{26}O_3$, colorless needles. 1H NMR (400 MHz, $CDCl_3$, δ , ppm, J/Hz): 5.16 (1H, t, $J = 7.1$, H-10), 3.50, 3.37 (each 1H, d, $J = 10.8$, H-15), 2.15 (1H, m, H-7b), 2.13 (1H, m, H-1), 2.09 (1H, m, H-9b), 2.04 (1H, m, H-4b), 2.02 (1H, m, H-9a), 1.83 (2H, m, H-3a), 1.87 (2H, m, H-3b), 1.74 (1H, m, H-4a), 1.69 (3H, s, H-13), 1.68 (1H, m, H-8b), 1.62 (3H, s, H-12), 1.45 (1H, m, H-7a), 1.43 (1H, m, H-8a), 1.15 (3H, s, H-14). ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 40.7 (C-1), 76.9 (C-2), 29.4 (C-3), 31.1 (C-4), 76.8 (C-5), 46.3 (C-6), 35.6 (C-7), 34.4 (C-8), 23.2 (C-9), 124.6 (C-10), 131.6 (C-11), 17.8 (C-12), 25.7 (C-13), 17.5 (C-14), 69.6 (C-15) [12].

1,2-Benzenedicarboxylic acid, dibutyl ester (12), $C_{16}H_{22}O_4$, colorless oil. 1H NMR (600 MHz, CD_3OD , δ , ppm, J/Hz): 7.72 (2H, dd, $J = 6.0$, 3.3, H-3, 6), 7.58 (2H, dd, $J = 6.0$, 3.3, H-4, 5), 4.31 (4H, t, $J = 6.6$, H-8, 8'), 1.70 (4H, m, H-9, 9'), 1.46 (4H, m, H-10, 10'), 0.96 (6H, t, $J = 7.2$, CH₃-11, 11'). ^{13}C NMR (150 MHz, CD_3OD , δ , ppm): 132.8 (C-1, 2), 128.8 (C-3, 6), 130.9 (C-4, 5), 167.7 (C-7, 7'), 65.5 (C-8, 8'), 30.6 (C-9, 9'), 19.1 (C-10, 10'), 13.7 (C-11, 11') [13].

Isolates were tested for monoamine oxidase (MAO) [14], acetylcholinesterase (AChE) [15], and phosphoinositide 3-kinase (PI3K α) [16] inhibitory activity. Compounds **7** and **9** showed relatively high anti-monoamine oxidase activity with IC₅₀ of 49.72 and 62.48 μ g/mL. Compounds **3**, **5**, and **8** showed relatively high anti-acetylcholinesterase activity with IC₅₀ of 24.37, 17.91, and 33.49 μ g/mL (Table 1), and compound **8** showed PI3K α inhibitory activity with IC₅₀ of 2.0 μ g/mL.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (No. 21762027) and the Project of Science and Technology Department of Gansu Province, China (No. 1604FKCA084).

REFERENCES

1. Z. Sun, M. Zhang, J. Zhang, and J. Feng, *Phytomedicine*, **18**, 859 (2011).
2. B. Schulz, C. Boyle, S. Draeger, A. K. Rommert, and K. Krohn, *Mycol. Res.*, **106**, 996 (2002).
3. C. B. Cui, H. Kakeya, and H. Osada, *Tetrahedron*, **53**, 59 (1997).
4. T. Hino, T. Kawate, and M. Nakagawa, *Tetrahedron*, **45**, 1941 (1989).
5. W. R. Abraham and H. A. Arfmann, *Phytochemistry*, **29**, 1025 (1990).
6. T. Onishi, Sebahar, and R. M. Williams, *Org. Lett.*, **60**, 9503 (2004).
7. X. Pu, G. Z. Li, Q. Xiao, J. H. Yi, Y. Q. Tian, G. L. Zhang, L. X. Zhao, and Y. G. Luo, *Chin. J. Appl. Environ. Biol.*, **5**, 787 (2013).
8. M. S. Lee, S. W. Wang, G. J. Wang, K. L. Pang, C. K. Lee, Y. H. Kuo, H. J. Cha, R. K. Lin, and T. H. Lee, *J. Nat. Prod.*, **79**, 2983 (2016).
9. T. Yamada, E. Imai, K. Nakataji, A. Numata, and R. Tanaka, *Tetrahedron Lett.*, **48**, 6294 (2007).
10. H. Fujimoto, E. Negishi, K. Yamaguchi, N. Nishi, and M. Yamazaki, *Chem. Pharm. Bull.*, **44**, 1843 (1996).
11. J. Fotie, D. S. Bohle, M. L. Leimanis, E. Georges, G. Rukunga, and A. E. Nkengfack, *J. Nat. Prod.*, **69**, 62 (2006).
12. Y. Wang, D. H. Li, Z. L. Li, Y. J. Sun, H. M. Hua, T. Liu, and J. Bai, *Molecules*, **21**, E31 (2015).
13. L. L. Chen, N. Han, Y. C. Wang, T. Huang, R. Xue, and J. Yin, *J. Shenyang Pharm. Univ.*, **28**, 875 (2011).
14. Z. D. Yang, J. B. Liang, W. W. Xue, J. Sheng, Y. Shi, X. J. Yao, J. Ren, and L. Liu, *Chem. Nat. Compd.*, **50**, 1118 (2014).
15. I. Orhan, B. Sener, M. I. Choudhary, and A. Khalid, *J. Ethnopharmacol.*, **91**, 57 (2004).
16. F. B. Han, S. W. Lin, P. Liu, X. Liu, J. Tao, X. Deng, C. Yi, and H. Xu, *Acs. Med. Chem. Lett.*, **6**, 434 (2015).