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Secondary Metabolites and PI3K Inhibitory Activity of *Colletotrichum gloeosporioides*, a Fungal Endophyte of *Uncaria rhynchophylla*

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Abstract
In the present study, nine compounds (**1–9**) were isolated from *Colletotrichum gloeosporioides* (an endophytic fungus from *Uncaria rhynchophylla*) which was cultured in wheat bran medium. Their structures were elucidated as 4-Epi-14-hydroxy-10, 23-dihydro-24, 25-dehydroaflavinine (**1**), 10, 23-Dihydro-24,25 -dehydro-21–oxoaflavinine (**2**), Ergosterol (**3**), Ergosterol peroxide (**4**), Mellein (**5**), 4, 5-dihydroblumenol A (**6**), Colletotrichine A (**7**), Cyclo(*L*-leucyl-*L*-leucyl) (**8**), and Brevianamide F **(9)** based on NMR spectral data, as well as comparing with previous literature data. This is the first report about the isolation of compounds **1–2**, **6**, and **8–9** from *Colletotrichum* genus. All compounds were tested for their phosphoinositide 3-kinase (PI3Kα) inhibitory activity. Compounds **8** and **9** showed potent PI3K α inhibitory activity with IC_{50} values of 38.1 and 4.8 μM, respectively, while the other compounds showed very weak activity at a concentration of 20 μg/mL.

Introduction

Endophytic fungi are microorganisms that inhabit in the intercellular spaces of plant stems, petioles, roots, and leaves without causing visible disease symptoms [1].They have been proved to be a new source for natural compounds. A large number of new natural compounds including polyketides, alkaloids, phenylpropanoids, terpenoids, and phenols have been isolated from endophytic fungi [2]. During our research on endophytic fungi living in *Uncaria rhynchophylla*, we isolated an endophytic fungus *Colletotrichum gloeosporioides* GT-7 [3]. In the past studies on this fungus, we obtained some novel compounds including novel lactams colletotrilactam A–D [3], new sesquiterpenoid colletotrichine A [4] from the organic extract of liquid potato dextrose broth (PDB) culture medium. Some lines of evidence showed that changing fermentation conditions, such as the alteration of fermentation medias, could lead to the change of the biosynthetic pathways and some new compounds would appear [5, 6]. To obtain more active compounds from this fungus, we cultured it in wheat bran medium and studied on its secondary metabolites, and nine compounds (**1–9**) (Fig. 1) were obtained.

Phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that play key regulatory roles in cell proliferation, survival, and cell translation [7]. It has been proved that PI3Ks are potential targets for chemical therapy, especially PI3K α as one of the most important targets of anti-tumors [7]. Up to now, many PI3K inhibitors have been found, including thienopyrimidine derivatives, quinazoline derivatives, pyridofuropyrimidines, imidazopyridine analogues, imidazoquinoline analogues [8]. However, natural PI3K inhibitors were very rare only including flavonoid IC-8711, liphagal, helenaquinone, resveratrol, caffeine [8]. To obtain natural PI3K inhibitors, we tested PI3K α inhibitory activity of **1–9** and found **8** and **9** were potent PI3K α inhibitors with IC_{50} values of 38.1 and 4.8 μM, respectively.

Experimental

Chemicals and Instrumentation

NMR spectra were obtained on a Bruker Avance-3 spectrometer. HPLC purification was performed using a Waters

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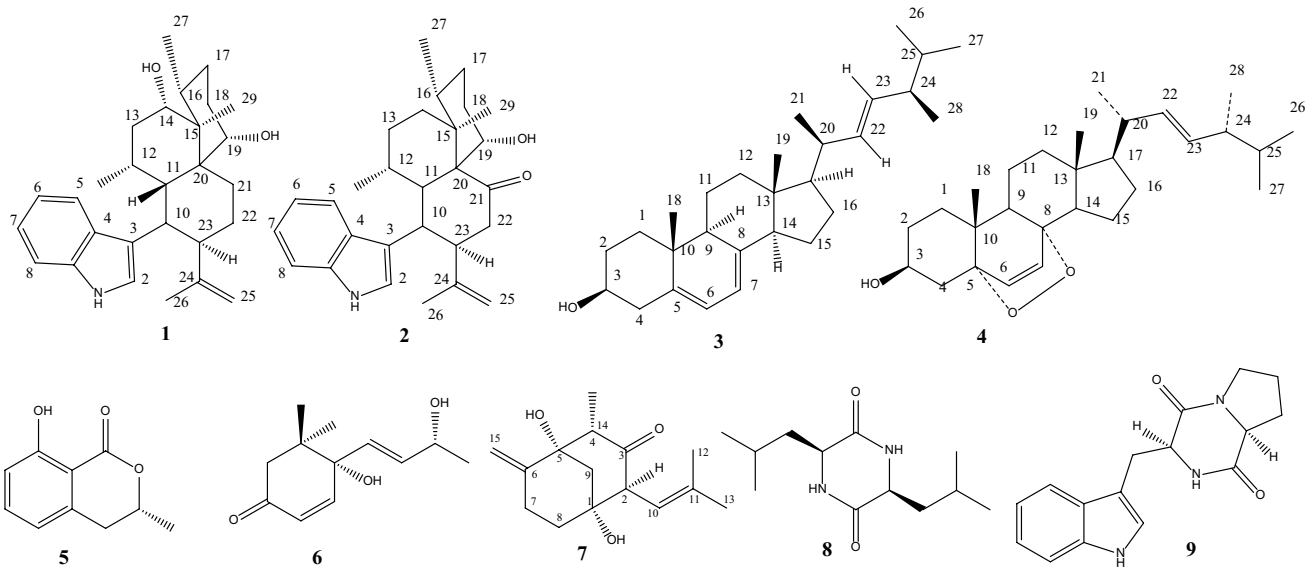

Fig. 1 Structures of compounds **1–9**

HPLC apparatus with two 510 pumps and one 2487 dual λ absorbance detector and a Phenomenex Gemini C18 column (10.0 mm × 250 mm, 5 µm). Silica gel (200–400 mesh) was from Qingdao Marine Chemical Co., Ltd. China. Macroporous resin (HPD-100) was purchased from Zhengzhou Qinshi Technology Co., Ltd., China.

Fungus Material

Colletotrichum gloeosporioides GT-7 (GenBank accession No. KR911618) was isolated from the healthy tissue of *U. rhynchophylla* and identified as *C. gloeosporioides* based on the GenBank search for DNA sequence similarity of the ITS1–5.8S-ITS2 ribosomal RNA gene region and morphological characteristics [3]. The colony of GT-7 on the PDA plate was white at first, then gray–green, with black dots on it, and the colony was fluffy. The back of the colony is yellow–green, nearly circular. Its conidia are colorless, unicellular, cylindrical, and obtuse at both ends.

Extraction and Isolation

The strain GT-7 was inoculated into twenty-five 500 mL Erlenmeyer flasks containing 25 g wheat bran and 20 mL of water. The culture was kept for 35 days at 28 °C under static condition. The culture media was exhaustively extracted with EtOAc. The crude extract (15 g) was chromatographed on a macroporous resin column with a step gradient of EtOH–H_2O (10%, 30%, 50%, 70%, and 90%) to yield 5 fractions (A–E). The fractions C, D were subjected to HPLC separation (Waters-510 pump, Waters 2487 Dual absorbance detector, *Phenomenex Gemini C18 column*, 250*10 mm, 5 µm). The fraction D was eluted with MeOH–water (70:30, flow rate 1.8 mL/min, 254 nm) to yield compounds **1** (8 mg, $t_R = 52$ min) and **2** (7 mg, $t_R = 60$ min). The fraction C was eluted with MeOH–water (52:48, flow rate 1.8 mL/min, 254 nm) to yield compounds **5** (4 mg, $t_R = 44$ min) and **6** (5 mg, $t_R = 54$ min). The fraction E was subjected to silica gel column chromatography eluting with petroleum ether–acetone (20:1) to give compounds **3** (8 mg) and **4** (5 mg). The fraction A was subjected to silica gel column chromatography eluting with $CHCl_3$–MeOH (40:1) to give compounds **7** (10 mg),**8** (3 mg), and **9** (5 mg).

Bioassay Procedure for PI3Kα Inhibition

The PI3Kα activity assay was conducted using ADP-Glo Kinase assay [9]. Briefly, ADP-Glo™ kinase detection kit was from Promega. PI3Kα kinase and the substrate PIP2/PS were from Thermo Fisher Scientific. All assays were performed in a black 384-well plate at room temperature. The kinase buffer contained 50 mM Hepes (pH 7.5), 3 mM MgCl2, 100 mM NaCl, 1 mM EGTA, 0.03% CHAPS, and 2 mM DTT. PI3Kα kinase mixture was prepared by diluting PI3Kα in the kinase buffer to 0.9 ng/µL. The ATP/substrate mixture contained 10 µM PIP2/PS and 50 µM ATP. Compounds for testing were diluted in DMSO to obtain different concentrations. 2 µL of diluted compounds and 4 µL of ATP/substrate mixture were added to individual wells of 384-well assay plates. The reaction was started by adding 4 µL of PI3Kα kinase mixture per well. The assay plates were covered and reactions were allowed to proceed for 1 h, after which 10 µL of Kinase Glo™ reagent per well was added. The plates were incubated for 40 min, and then 20µL of

kinase detection reagent per well was added. The plates then were equilibrated in the dark for 25 min, after which the luminescence was measured. The percentage of inhibition was calculated based on the following equation: % inhibition = $\left[1 - \left(RLU_{compound} - RLU_{min}\right)/\left(RLU_{max} - RLU_{min}\right)\right] \times 100$, where $RLU_{compound}$ is the luminescence reading at a given compound concentration; RLU_{min} is the luminescence reading at the highest concentration (10 mM) of the positive control (compound GDC0941) to completely inhibit PI3Kα kinase activity; and RLU_{max} is luminescence reading in the absence of a compound.

Results and Discussion

This study focused on compounds isolated from *C. gloeosporioides* (an endophytic fungus from *Uncaria rhynchophylla*) which was cultured in wheat bran medium and their PI3Kα inhibitory activity was evaluated. Nine compounds (**1–9**, Fig. 1) were isolated. This is the first report about the isolation of compounds **1–2**, **6**, and **8–9** from *Colletotrichum* genus. Compounds **8** and **9** showed potent PI3Kα inhibitory activity with IC_{50} values of 38.1 and 4.8 μM, while the other compounds showed very weak activity at a concentration of 20 μg/mL (Table 1).

Structure Elucidation of the Isolated Compounds

4-Epi-14-hydroxy-10, 23-dihydro-24, 25-dehydroaflavinine (**1**), white amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, s, H-2), 7.54 (1H, d, *J* = 7.6 Hz, H-5), 7.35 (1H, d, *J* = 8.1 Hz, H-8), 7.18 (1H, dd, *J* = 7.6, 6.8 Hz, H-6), 7.12 (1H, dd, *J* = 8.1, 6.8 Hz, H-7), 4.84 (1H, s, H-25), 4.76 (1H, s, H-25), 4.75(1H, br s, H-14), 4.69 (1H, br s, H-19), 3.69 (1H, dd, *J* = 5.9, 5.8 Hz, H-10), 3.39 (1H, ddd, *J* = 4.6, 13.0, 13.0 Hz, H-23), 2.75 (1H, dd, *J* = 5.9, 5.8 Hz, H-11), 2.17 (1H, m, H-16), 2.12(1H, m, H-21), 1.79 (1H, m, H-21), 1.75 (1H, m, H-18), 1.67 (1H, m, H-17), 1.64 (1H, m, H-13), 1.63 (1H, m, H-22), 1.47 (3H, s, H-26), 1.43 (1H, m, H-12), 1.38 (1H, m, H-18), 1.32 (3H, d, *J* = 7.1 Hz, H-27), 1.19 (1H, m, H-17), 1.14 (3H, s, H-29), 0.87(2H, m, H-13), 0.85 (1H, m, H-13), 0.80 (3H, d, *J* = 6.8 Hz, H-28); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (C-24), 135.9 (C-9), 127.7 (C-4), 123.5 (C-2), 121.7 (C-7), 119.2(C-6), 118.3 (C-5), 116.1 (C-3), 111.6 (C-8), 111.3 (C-25), 71.9 (C-14), 68.7 (C-19), 47.1 (C-20), 39.5 (C-15), 39.5 (C-23), 38.2 (C-11), 35.0 (C-10), 32.4 (C-16), 31.6 (C-18), 30.0 (C-13), 30.0 (C-22), 29.5 (C-12), 28.6 (C-17), 25.0 (C-21), 19.6 (C-29), 18.3 (C-27), 18.1 (C-26), 16.1 (C-28) [10].

10, 23-Dihydro-24, 25-dehydro-21–oxoaflavinine (**2**), white amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, s, H-1), 7.56 (1H, d, *J* = 7.8 Hz, H-5), 7.37 (1H, d, *J* = 7.6 Hz, H-8), 7.20 (1H, dd, *J* = 7.6, 6.8 Hz, H-7), 7.16 (1H, dd, *J* = 7.8, 6.8 Hz, H-6), 7.05 (1H, s, H-2), 5.21 (1H, br s, H-19), 4.83 (1H, s, H-25), 4.70 (1H, s, H-25), 4.07 (1H, dd, *J* = 5.4, 13.2 Hz, H-10), 3.67 (1H, ddd, *J* = 13.0, 12.5, 6.8 Hz, H-23), 3.09 (1H, dd, *J* = 12.4, 14.4 Hz, H-22), 3.01 (1H, dd, *J* = 5.4, 4.6 Hz, H-11), 2.44 (1H, dd, *J* = 6.8, 14.4 Hz, H-22), 2.30(1H, m, H-18), 2.17 (1H, m, H-13), 2.10 (1H, m, H-16), 1.97 (1H, m, H-17), 1.75 (1H, m, H-17), 1.62 (3H, s, H-26), 1.56 (1H, m, H-13), 1.45 (1H, m, H-12), 1.43 (1H, m, H-18), 1.40 (3H, s, H-29), 1.24 (1H, m, H-14), 1.04 (3H, d, *J* = 6.1 Hz, H-27), 0.93 (1H, m, H-14), 0.76 (3H, d, *J* = 6.8 Hz, H-28); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0 (C-21), 146.8 (C-24), 136.1 (C-9), 127.5 (C-4), 122.5 (C-2), 122.1 (C-7), 119.4(C-6), 118.2 (C-5), 115.0 (C-3), 112.6 (C-8), 111.3 (C-25), 72.7 (C-19), 58.2 (C-20), 47.6 (C-23), 44.6 (C-22), 43.2 (C-11), 38.5 (C-15), 34.6 (C-10), 31.4 (C-16), 30.6 (C-18), 29.6 (C-12), 29.6 (C-13), 28.6 (C-14), 24.6 (C-17), 18.2 (C-26), 18.1 (C-29), 18.0 (C-27), 14.6 (C-28) [10].

Ergosterol (**3**), colorless crystal, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (1H, d, *J* = 6.0, H-6), 5.37(1H,dd,, *J* = 6.0, H-7), 5.19 (1H, m, H-23), 5.15(1H, m, H-22), 3.64 (1H, m, H-3), 1.01(3H, d, *J* = 6.8 Hz, H-21), 0.94 (3H, s, H-19), 0.91 (3H, d, *J* = 6.8 Hz, H-26), 0.83 (3H, d, *J* = 6.8 Hz, H-28), 0.80 (3H, d, *J* = 6.0, H-27), 0.64 (3H, s, H-18); ^{13}C-NMR(100 MHz, $CDCl_3$): δ 141.3 (C-8), 139.8 (C-5), 135.5 (C- 22), 132.0 (C- 23), 119.6 (C-6), 116.3 (C-7), 70.4 (C-3), 55.7 (C-17), 54.5 (C-14), 46.2 (C-9), 42.7 (C-13), 40.8 (C-24), 40.8 (C-4), 40.4 (C-20), 39.1(C-12), 38.3 (C-1), 37.0 (C-10), 33.1 (C- 25), 32.1(C-2), 28.2 (C-16), 23.0 (C-15), 21.1 (C-11), 21.1 (C- 21), 19.9 (C-26), 19.6 (C-27), 17.6(C-28), 16.3 (C-19), 12.0 (C-18) [11].

Ergosterol peroxide (**4**), colorless crystal, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (1H, d, *J* = 8.5 Hz, H-6), 6.23 (1H, d, *J* = 8.5 Hz, H-7), 5.22 (1H, dd, *J* = 15.3, 7.5 Hz, H-23), 5.14 (1H, dd, *J* = 15.4, 8.3 Hz, H-22), 3.94 (1H, m, H-3), 1.00 (3H, d, *J* = 6.6 Hz, H-21), 0.90 (3H, d, *J* = 6.8 Hz,

Table 1 The inhibitory activity of compounds **1**–**8** against PI3Kα

Compounds	Inhibition rate at 20 μg/mL (%)	IC_{50} value (μM)
1	13.0	–
2	5.5	–
3	36.5	–
4	13.9	–
5	24.4	–
6	0.07	–
7	34.5	–
8	85.0	38.1
9	83.2	14.8
GDC0941*	94.2	0.0024

*GDC0941 is a positive control

H-28), 0.89 (3H, s, H-19), 0.83 (3H, d, J = 6.8 Hz, H-26), 0.81 (3H, s, H-18), 0.80 (3H, d, J = 6.8 Hz, H-27); ^{13}C-NMR(100 MHz, $CDCl_3$): δ 134.8 (C- 22), 134.6 (C-6), 131.9 (C- 23), 130.2 (C-7), 81.6 (C-5), 78.8 (C-8), 70.1 (C-3), 55.7 (C-17), 51.5 (C-14), 50.8 (C-9), 44.7 (C-13), 42.2 (C-24), 39.8 (C-20), 39.6 (C-4), 37.0 (C-10), 36.9 (C-12), 34.3 (C-1), 33.1 (C- 25), 30.1(C-2), 28.1 (C-16), 23.0 (C-15), 20.9 (C- 21), 20.8 (C-11), 19.9 (C-27), 19.6 (C-26), 17.6 (C-28), 17.5 (C-19), 12.3 (C-18) [12].

Mellein (**5**), white amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0 (1H, s, -OH), 7.40 (1H, t, J = 7.2 Hz, H-6), 6.87 (1H, d, J = 7.2 Hz, H-5), 6.69 (1H, d, J = 7.2 Hz, H-7), 4.73 (1H, m, H-3), 2.93 (2H, d, J = 6.0 Hz, H-4), 1.53 (3H, d, J = 6.0 Hz, -CH_3); ^{13}C-NMR(100 MHz, $CDCl_3$): δ 171.0 (C-1), 162.3 (C-8), 139.4 (C-10), 136.2 (C-6), 118.0 (C-5), 116.4 (C-7), 108.3 (C-9), 76.0 (C-3), 34.5 (C-4), 20.8 (–CH_3), [13].

4, 5-dihydroblumenol A (**6**), white amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (1H, s, H-4), 5.86 (1H, dd, J = 15.6, 5.0 Hz, H-8), 5.78 (1H, d, J = 15.6 Hz, H-7), 4.41 (1H, m, H-9), 2.45 (1H, d, J = 16.8 Hz, H-6α), 2.24 (1H, d, J = 16.8 Hz, H-6β), 1.89 (3H, s, H-13), 1.30 (3H, d, J = 6.3 Hz, H-10), 1.08 (3H, s, H-12), 1.02 (3H, s, H-11); ^{13}C NMR (100 MHz, $CDCl_3$): 197.8 (C-3), 162.0 (C-5), 135.7 (C-7), 128.9 (C-8), 126.8 (C-4), 79.0 (C-6), 67.9 (C-9), 49.7 (C-2), 41.1 (C-1), 24.0 (C-11), 23.7 (C-12), 22.6 (C-10), 18.8 (C-13) [14].

Colletotrichine A (**7**), white amorphous powder, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.27 (1H, d, J = 9.8 Hz, H-10), 5.04 (1H, s, H-15b), 4.92 (1H, s, H-15a), 3.39 (1H, d, J = 9.8 Hz, H-2), 2.58 (1H, q, J = 6.6 Hz, H-4), 2.41 (1H, d, J = 11.8 Hz, H-9a), 2.27 (1H, dd, J = 15.0, 5.7 Hz, H-7a), 2.11 (1H, d, J = 11.8 Hz, H-9b), 1.88 (3H, s, H-13), 1.85 (1H, m, H-8a), 1.69 (3H, s, H-12), 1.62 (1H, td, J = 15.0 13.4 Hz, H-7b), 1.43 (1H, m, H-8b), 0.97 (3H, d, J = 6.6 Hz, H-14); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.8 (C-6), 140.2 (C-11), 116.5 (C-10), 109.4(C-15), 76.1 (C-1), 74.2 (C-5), 59.0 (C-2), 54.1 (C-4), 51.8 (C-9), 36.4 (C-8), 29.8 (C-7), 26.6 (C-13), 20.3 (C-3), 18.8 (C-12), 7.7 (C-14) [4].

Cyclo(*L*-leucyl-*L*-leucyl) (**8**), ^{1}H NMR (400 MHz, CD_3OD): δ 3.91 (1H, dd, J = 9.0, 4.6 Hz), 1.85 (1H, m), 1.72 (1H, m), 1.62 (1H, m), 0.95 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD): 171.2 (2*CON), 54.7 (2*CH), 45.9 (2*CH_2), 25.3 (2*CH), 23.6 (2*Me), 21.9 (2*Me) [15].

Brevianamide F (**9**), White amorphous powder. $[\alpha]_D^{20}$ -68.2° (c = 0.70, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.33 (1H, s, -NH), 7.58 (1H, d, J = 8.0, H-7), 7.38 (1H, d, J = 8.0, H-4), 7.23 (1H, t, J = 8.0, H-6), 7.14 (1H, t, J = 8.0, H-5), 7.08 (1H, s, H-2), 5.76 (1H, s, -NH), 4.36 (1H, d, J = 9.2, H-9), 4.07 (1H, t, J = 8.0, H-12), 3.75 (1H, dd, J = 1.2, 14.4, H-8b), 3.61 (2H, m, H-15), 2.97 (1H, dd, J = 9.2, 14.4, H-8a), 2.32 (1H, m, H-16a), 2.02 (2H, m, H-17), 1.91 (1H, m, H-16b); ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (C-11), 165.5 (C-14), 136.6 (C-7a), 126.6 (C-3a), 123.4 (C-2), 122.7 (C-5), 119.7 (C-6), 118.5 (C-4), 111.5 (C-7), 109.5 (C-3), 59.1 (C-12), 54.5 (C-9), 45.3 (C-15), 28.2 (C-17), 26.8 (C-8), 22.5 (C-16) [16].

Compound **8** is a cyclic dipeptide which was often isolated from plants and fungi such as from corn oil [17], *Dioscorea collettii* [18], *Streptomyces rutgersensis* [19], and mangrove endophytic fungus [20]. It has been reported that this compound showed weak activity of antibiosis [21] and scavenging radicals [22]. Up to now, there were no reports about PI3Kα inhibitory activity of **8**. We first found **8** is a potent PI3Kα inhibitor, which will be a promising antitumor lead compound. Compound **9** is a common constituent of plant endophytic fungi, which was often found in *Streptomyces* [23], *Aspergillus* [24], *Penicillium* [25] genus fungi. Wen et al. [24]. reported compound **9** isolated from *Aspergillus ochraceus* showed 41.9% inhibition ratio of cytokine TNF-a at 20 μM. Compound **9** has also been reported to show antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* with MIC of 12.6 and 11.9 μg/mL, respectively [26]. In the present study, PI3Kα inhibitory activity of **9** was first found by us, which might become a new antitumor lead compound.

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