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Tricycloalternarene derivatives from the endophytic fungus *Guignardia bidwellii* PSU-G11

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ABSTRACT

Four new tricycloalternarene derivatives, guignarenones A–D (**1**–**4**), along with known (6*S*,9*R*)-vomifoliol were isolated from the endophytic fungus *Guignardia bidwellii* PSU-G11. Their structures were determined on the basis of spectroscopic data. The absolute configurations in **1** were assigned using a combination of the modified Mosher's method and NOEDIFF data. Compound **1** displayed mild cytotoxic activity against oral cavity cancer and African green monkey kidney fibroblast (Vero) cell lines.

1. Introduction

The genus *Guignardia* is a rich source of bioactive natural products such as isovernin aldehyde (Otomo et al., 1983), (*R*)-guignardic acid (Ferreira et al., 2002), and vermistatin (Xia et al., 2007). As part of our ongoing search for bioactive fungal metabolites, the endophytic fungus *Guignardia bidwellii* PSU-G11 was isolated from the leaves of *Garcinia hombroniana*. The EtOAc extract from the culture broth was subjected to chemical investigation. We reported herein the isolation of four new tricycloalternarene derivatives, guignarenones A–D (**1**–**4**), along with one known metabolite, (6*S*,9*R*)-vomifoliol (**5**) (Yamano and Ito, 2005) from the culture broth. Their cytotoxic activity against oral cavity cancer (KB), and African green monkey kidney fibroblast (Vero) cell lines was examined.

2. Results and discussion

Fig. 1 the structures of **1**–**5** were elucidated by analysis of spectroscopic data. Their relative congurations were assigned using NOEDIFF data. The absolute configurations in guignarenone A (**1**) were determined by employing a combination of the modified Mosher's method (Ohtani et al., 1991) and NOEDIFF data. As guignarenones A–D (**1**–**4**) were co-metabolites, we proposed that they would have the same biosynthetic pathway. Consequently, the absolute configurations of rings A and B in **2**–**4** would be identical to those of **1**. This is the first report on the complete assignment of the absolute configurations of tricycloalternarenes using chemical and spectroscopic methods since those of previously isolated tricycloalternarenes, except for guignardones A–C (Yaun et al., 2010), have never been determined (Liebermann et al., 1997; Sugawara et al., 1998; Nussbaum et al., 1999; Qiao et al., 2007; Yuan et al., 2008). However, the absolute configurations of guignardones A–C were assigned by comparison of their circular dichroism spectra with the calculated ECD spectra (Yaun et al., 2010). For the known compound **5**, the structure was confirmed by comparison of the ^{1}H and ^{13}C NMR data as well as the specific rotation with those previously reported (Yamano and Ito, 2005).

Guignarenone A (**1**) was obtained as a colorless gum. Its molecular formula was determined as $C_{22}H_{32}O_4$ by HREIMS, indicating that **1** had seven degrees of unsaturation. A UV absorption band at 263 nm was attributed to a conjugated carbonyl chromophore whereas the IR spectrum showed hydroxyl and carbonyl absorption bands at 3373 and 1709 cm^{-1}, respectively. The ^{1}H NMR spectrum of **1** (Table 1) contained signals for a

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Table 1
^{1}H and ^{13}C NMR data for guignarenones A (**1**) and B (**2**) ($CDCl_3$, δ ppm).

Position	**1**		**2**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	–	194.9	–	194.9
2	–	106.0	–	105.7
3	–	167.6	–	168.3
4	4.24 m	65.7	4.27 m	65.8
4-OH	3.27 d (7.2)	–	3.25 d (7.0)	–
5	2.38 ddd (13.8, 4.8, 3.6) 2.24 ddd (13.8, 6.6, 5.4)	34.6	2.38 ddd (13.5, 4.5, 4.0) 2.24 ddd (13.5, 7.0, 5.5)	34.7
6	3.70 dd (6.6, 3.6)	79.1	3.72 dd (7.0, 4.0)	79.2
7	3.47 s	58.4	3.49 s	58.4
8	2.35 m 2.15 m	16.3	2.68 brd (17.5) 2.28 dd (17.5, 6.5)	18.7
9	1.98 m	43.6	1.67 m	50.0
10	–	87.7	–	88.9
11	1.33 s	22.4	1.34 s	23.6
12	2.13 m 1.80 m	37.4	2.04 m 1.65 m	38.3
13	1.94 m 1.49 m	27.9	1.77 m 1.53 m	24.6
14	2.16 m	48.3	2.11 dd (8.0, 7.0)	50.0
15	–	149.8	–	75.1
16	4.76 d (1.5) 4.72 brs	109.1	1.15, s	22.2
17	2.07 m	33.5	1.48 m	40.9
18	1.95 m	26.6	2.00 m	22.3
19	5.07 tm (6.9)	124.0	5.12 tm (7.0)	124.2
20	–	131.7	–	132.2
21	1.66, s	25.6	1.68 d (0.6)	25.7
22	1.58, s	17.7	1.61 s	17.7

4-methylpent-3-enyl group [δ 5.07 (tm, J = 6.9 Hz), 2.07 (m), 1.95 (m), 1.66 (s) and 1.58 (s)], two geminal olefinic protons (δ 4.76, d, J = 1.5 Hz, and 4.72, brs), two oxymethine protons (δ 4.24, q, J = 5.7 Hz, and 3.70, dd, J = 6.6 and 3.6 Hz), one hydroxy proton (δ 3.27, d, J = 7.2 Hz), two coupled methine protons (δ 2.16 and 1.98, each m), two sets of coupled methylene protons (δ 2.13, 1.80 and 1.94, 1.49, each 1H, m), two sets of nonequivalent methylene protons (δ 2.38, ddd, J = 13.8, 4.8 and 3.6 Hz, 2.24, ddd, J = 13.8, 6.6 and 5.4 Hz, each 1H, and 2.35, 2.15, each 1H, m), one methoxyl group (δ 3.47, s) and one methyl group (δ 1.33, s). The ^{13}C NMR spectrum of **1** displayed three carbons of a fully substituted β-alkoxy-α,β-unsaturated ketone (δ 194.9, 167.6 and 106.0), six carbons of the 4-methylpent-3-enyl unit (δ 131.7, 124.0, 33.5, 26.6, 25.6 and 17.7), two carbons of a *gem*-disubstituted ethylene (δ 149.8 and 109.1), one oxyquaternary (δ 87.7), two oxymethine (δ 79.1 and 65.7), two methine (δ 48.3 and 43.6), four methylene (δ 37.4, 34.6, 27.9 and 16.3), one methoxy (δ 58.4) and one methyl (δ_C 22.4) carbons. A cyclohexenone having hydroxyl and methoxyl groups at C-4 (δ_C 65.7) and C-6 (δ 79.1) was established by the HMBC correlations observed from H-4 (δ 4.24) to C-3 (δ 167.6) and C-6, from H_2-5 (δ 2.38 and 2.24) to C-6 and from H-6 (δ 3.70) to C-2 (δ 106.0) and C-4 (Fig. 2). The ^{1}H–^{1}H COSY correlations revealed the connection from H-12 (δ 2.13 and 1.80) to H-14 (δ 2.16) and from H-14 to H-9 (δ 1.98) (Fig. 2). In addition, the HMBC cross peaks of H_3-11 (δ 1.33) with C-9, C-10 (δ 87.7) and C-12, and the chemical shift of C-10 constructed a cyclopentane with a methyl group and an oxy substituent at C-10. A tricycloalternarene skeleton was established on the basis of the ^{1}H–^{1}H COSY correlations of H-9 (δ 1.98) with H_2-8 (δ 2.35 and 2.15) as well as the ^{3}J HMBC data from H_2-8 to C-1, C-3, C-10 and C-14. The

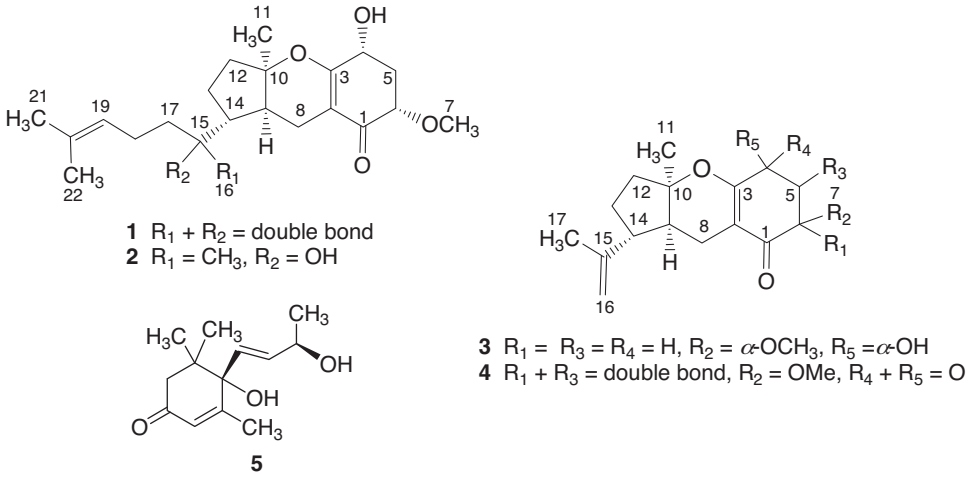


Fig. 1. Structures of metabolites isolated from the endophytic fungus *G. bidwellii* PSU-G11.

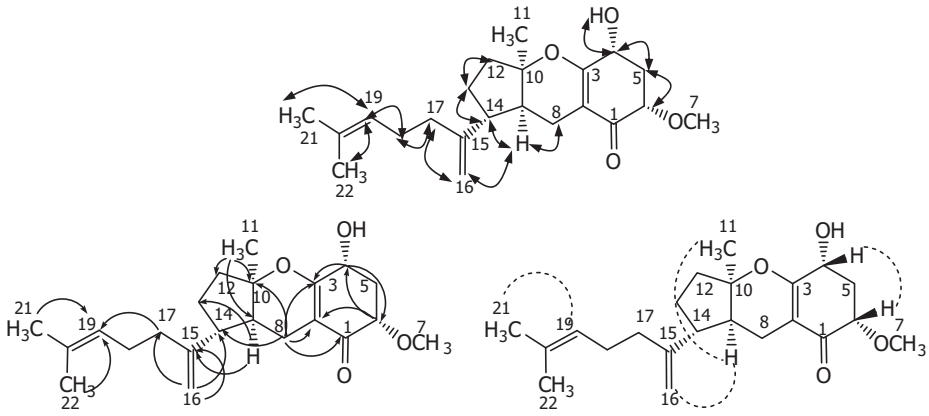
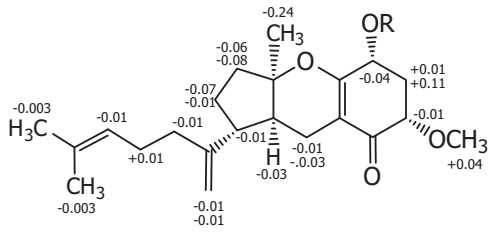


Fig. 2. ^{1}H–^{1}H COSY (⟷), selected HMBC (⟶) and selected NOEDIFF (⇢) data of **1**.

^{1}H–^{1}H COSY and HMBC correlations shown in Fig. 2 constructed the 4-methylpent-3-enyl unit. This unit was connected to C-15 (δ_C 149.8) of the *gem*-disubstituted ethylenyl unit to form a 2-substituted-6-methyl-1,5-heptadienyl moiety according to the ^3J HMBC correlations of H_2-16 (δ 4.76 and 4.72) with C-17 (δ 33.5) of the pentenyl unit. This moiety was then attached at C-14 of the tricycloalternarene skeleton due to the HMBC correlations from H_2-16 to C-14 and from H-9 to C-15.

Irradiation of H-9 enhanced the signal intensity of H-16 (δ 4.72) of the 2-substituted-6-methyl-1,5-heptadienyl unit and H_3-11, but not H-14 (δ 2.16), indicating that H-9, H_3-11 and the heptadienyl unit were all *cis*. Signal enhancement of H-6 upon irradiation of H-4 indicated that 4-OH and 6-OCH_3 were placed on the same side of the molecule. However, these data were inadequate to assign overall relative configuration of **1**. The absolute configuration at C-4 was determined on the basis of the Mosher's method using the (*S*)- and (*R*)-MTPA esters (Fig. 3). The differences in the ^{1}H NMR chemical shifts between the *S*- and *R*-MTPA derivatives ($\Delta\delta_H = \delta_S - \delta_R$) near C-4 (Fig. 3) established the absolute configuration at this position to be *R*. Thus, C-6 would have an *S* configuration. Irradiation of H_3-11 of the *S*- and *R*-MTPA derivatives affected signal intensity of the methoxyl and phenyl protons of the ester moiety in the NOEDIFF experiments, indicating the close proximity of this methyl group and the ester unit. Consequently, C-10 had *R* configuration. The absolute configurations of **1** were then assigned as 4*R*, 6*S*, 9*S*, 10*R*, and 14*R*.

Guignarenone B (**2**) was obtained as a colorless gum with the molecular formula $C_{22}H_{34}O_5$ from HREIMS. The ^{1}H NMR data (Table 1) were similar to those of **1** except that signals of two geminal olefinic protons in **1** were replaced by a methyl signal (H_3-16, δ 1.15) in **2**. The location of the methyl group at C-15 (δ 75.1) was confirmed by the HMBC cross peaks from H_3-16 to C-14 (δ 50.0), C-15 and C-17 (δ 40.9). The other substituent at this carbon was identified as a hydroxyl group on the basis of the chemical shift of C-15. The absolute configurations of **2** were proposed to be identical to those of **1** on the basis of their identical NOEDIFF data as well as their co-occurrence. However, the absolute configuration at C-15 remained unidentified due to inadequate NOEDIFF data. Consequently, **2** was identified as a new hydrate derivative of **1**.



1a: R = (*S*)-MTPA

1b: R = (*R*)-MTPA

Fig. 3. $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained form MTPA esters **1a** and **1b**.

Guignarenone C (**3**) with the molecular formula $C_{17}H_{24}O_4$ from HREIMS was obtained as a colorless gum. The UV and IR absorption bands of **3** were similar to those of **1** and **2**. The ^{1}H NMR data (Table 2) were different from those of **1** by the replacement of signals for the 4-methylpent-3-enyl group in **1** with a singlet signal of a methyl group (δ 1.67) in **3**. The HMBC cross peaks from the methyl protons (H_3-17) to C-14 (δ 49.0), C-15 (δ 145.5) and C-16 (δ 111.2) confirmed the attachment of the methyl group, instead of the 4-methylpent-3-enyl group, at C-15 in **3**. The absolute configurations in **3** were proposed to be identical to those in **1** based on their similar specific rotations, NOEDIFF and CD data. Consequently, guignarenone C would have structure **3**.

Guignarenone D (**4**) was obtained as a colorless gum. The molecular formula $C_{17}H_{20}O_4$ determined by HREIMS revealed that **4** had four fewer hydrogen atoms than **3**. The UV spectrum showed a maximum absorption band at a longer wavelength (λ_{max} 286 nm) than that in **1**–**3**, indicating that it possessed a longer conjugated chromophore. The absorption bands of two typical ketone carbonyl groups of a 1,4-quinone at 1698 and 1680 cm^{-1}, were observed in the IR spectrum. The ^{1}H NMR data of **4** were similar to those of **3**. The difference was the replacement of signals for H-4, H-6 and H_2-5 in **3** by an olefinic proton signal of a trisubstituted double bond (δ 5.80) in **4**. In addition, the methoxy protons (δ 3.82) in **4** resonated at a lower field. This olefinic proton was attributed to H-5 on the basis of its HMBC correlations with C-1 (δ 181.3), C-3 (δ 152.0), C-4 (δ 181.3) and C-6 (δ 159.4). The chemical shifts of C-5 (δ 104.9) and C-6 as well as the HMBC correlation from the methoxy protons (δ 3.82) to C-6 established a double bond at C5–C6 with the methoxyl group at C-6. These data suggested that the oxymethine carbon, C-4, in **3** was presumably oxidized to a ketone carbonyl carbon in **4**. Signal enhancement of H_3-11 (δ 1.36) and H_3-17 (δ 1.68) upon irradiation of H-9 (δ 2.00) established the relative configurations of the fused cyclopentane, identical to those of **1**–**3**. As they were co-metabolites, the absolute configurations of the fused cyclopentane in **4** were proposed to be identical to those of **1**–**3**. Thus, **4** was identified as an oxidized derivative of **3**.

Compounds **1** and **3** in sufficient amount were evaluated for cytotoxic activity against Vero and KB cell lines. Compound **1** displayed mild cytotoxic activity against both KB and Vero cell lines with the IC_{50} values of 138.1 and 136.6 μM, respectively, whereas **3** was inactive against both cell lines.

Table 2
^{1}H and ^{13}C NMR data for guignarenones C (**3**) and D (**4**) ($CDCl_3$, δ ppm).

Position	**3**		**4**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	–	194.9	–	181.3
2	–	105.9	–	113.8
3	–	167.6	–	152.0
4	4.26 m	65.8	–	181.3
4-OH	3.27 d (7.5)	–	–	–
5	2.40 ddd (13.8, 4.5, 3.9) 2.27 ddd (13.8, 6.6, 5.4)	104.9	5.80 s	104.9
6	3.72 dd (6.6, 3.9)	79.2	–	159.4
7	3.49 s	58.4	3.82 s	56.3
8	2.35 m 2.12 m	16.2	2.53 m 2.34 m	16.8
9	1.97 m	43.3	2.00 m	43.2
10	–	87.7	–	88.3
11	1.35 s	22.4	1.36 s	22.7
12	2.13 m 1.79 m	37.5	2.34 m 1.84 ddd (14.5, 14.0, 7.0)	37.3
13	1.92 m 1.54 m	27.0	2.00 m 1.55 m	26.9
14	2.21 m	49.0	2.24 q (9.0)	49.1
15	–	145.5	–	145.2
16	4.74 brt (1.5) 4.65 brs	111.2	4.76 qn (1.5) 4.66 qn (1.5)	111.5
17	1.67 s	19.3	1.68 s	19.2

3. Experimental

3.1. General experimental procedures

Optical rotations were measured using a JASCO P-1020 polarimeter. Ultraviolet (UV) spectra were measured in MeOH on a SHIMADZU UV-160A spectrophotometer. Infrared spectra (IR) were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer. ^{1}H- and ^{13}C NMR, along with 2D NMR spectra, were recorded on a 300 or 500 MHz Bruker FTNMR Ultra Shield spectrometer. Mass spectra were obtained on a MAT 95 XL Mass Spectrometer (Thermo Finnigan). Column chromatography (CC) was carried out on Sephadex LH-20 or silica gel (Merck) type 100 (70–230 Mesh ASTM).

3.2. Fungal material

The endophytic fungus *G. bidwellii* PSU-G11 was isolated from the leaves of *G. hombroniana*, collected in Songkhla Province, Thailand, in 2006. This fungus was deposited as PSU-G11 at the Department of Microbiology, Faculty of Science, Prince of Songkla University, and as BCC 35873 in the BIOTEC Culture Collection, National Center for Genetic Engineering and Biotechnology, Thailand.

This endophytic fungus did not produce any conidia or spores. Thus, it was identified based on the analysis of the DNA sequences of the internal transcribed spacer (ITS1-5.8S-ITS2) regions of its ribosomal RNA gene. Its ITS sequence (GenBank accession no HM049170) matched with four *Guignardia* sequences from GenBank comprising *Guignardia sp.* (AB454311) and *G. bidwellii* (AB454268, AB454276 and AB454313) with sequence identity of 93.1%. The endophytic fungus PSU-G11 was then identified as *G. bidwellii*.

3.3. Extraction and isolation

The broth EtOAc extract (750 mg) was prepared using the same procedure as previously described (Sommart et al., 2008) and was subjected to Sephadex LH-20 column chromatography (CC) eluted with MeOH to give four fractions (A–D). Fraction B (430 mg) was applied to silica gel CC eluted with a gradient of MeOH–CH_2Cl_2 to give six subfractions (B1–B6). Subfraction B2 (170 mg) was further purified by silica gel CC using 30% EtOAc-light petroleum to afford five subfractions. The second subfraction (35.9 mg) was subjected to silica gel CC using the same method as fraction B2 to give **1** (12.6 mg). Compound **3** (5.7 mg) was obtained from the fourth subfraction upon purification on silica gel CC eluted with 30% EtOAc-light petroleum. Subfraction B4 (67.5 mg) was purified using the same method as fraction B to give three subfractions. Compounds **2** (1.3 mg) and **4** (1.1 mg) were obtained from the second subfraction (30.9 mg) after purification by silica gel CC using a gradient of EtOAc-light petroleum. Subfraction B5 (33.0 mg) was purified using the same method as the second subfraction of B4 to afford four subfractions. The second subfraction contained **5** (1.0 mg).

3.4. Guignarenone A (1)

Colorless gum; $[\alpha]_D^{26}$ + 63 (*c* 0.76, acetone); UV λ_{max}(MeOH): 263 nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 218 (+8.2), 263 (+48.1), 301 (−9.8) nm; FT-IR (neat) ν_{max}: 3373, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra, see Table 1; HREIMS *m/z* 360.2301 $[M]^+$ (calcd. for $C_{22}H_{32}O_4$, 360.2301).

3.5. Guignarenone B (2)

Colorless gum; $[\alpha]_D^{26}$ + 55 (*c* 0.76, acetone); UV λ_{max}(MeOH): 264 nm; FT-IR (neat) ν_{max}: 3444, 1703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra, see Table 1; HREIMS *m/z* 378.2406 $[M]^+$ (calcd. for $C_{22}H_{34}O_5$, 378.2406).

3.6. Guignarenone C (3)

Colorless gum; $[\alpha]_D^{26}$ + 72 (*c* 0.76, acetone); UV λ_{max}(MeOH): 263 nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$): 217 (+2.7), 262 (+60.6), 298 (−14.9) nm; FT-IR (neat) ν_{max}: 3407, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra, see Table 2; HREIMS *m/z* 292.1664 $[M]^+$ (calcd. for $C_{17}H_{24}O_4$, 292.1675).

3.7. Guignarenone D (4)

Colorless gum; $[\alpha]_D^{26}$ + 45 (*c* 0.76, acetone); UV λ_{max}(MeOH): 286 nm; FT-IR (neat) ν_{max}: 1698, 1680 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra, see Table 2; HREIMS m/z 288.1363 $[M]^+$ (calcd. for $C_{17}H_{20}O_4$, 288.1356).

3.8. (6S,9R)-Vomifoliol (5)

Observed $[\alpha]_D^{27}$ + 201.0 (*c* 0.64, MeOH); $[\alpha]_D^{23}$ + 214.10 (*c* 0.64, MeOH) (Yamano and Ito, 2005).

3.9. Preparation of MTPA esters of guignarenone A (1)

To a solution of **1** (2.5 mg) in pyridine (100 μL) and CH_2Cl_2 (300 μL) was added (*R*)-MTPACl (40 μL). The reaction mixture was then stirred at room temperature for four days. After removal of the solvent, the 4-(*S*)-MTPA ester (**1a**, 4.30 mg) was obtained. Compound **1** (2.5 mg) was treated with (*S*)-MTPACl under the same conditions as **1a** to yield the 4-(*R*)-MTPA ester (**1b**, 4.32 mg).

3.10. Cytotoxic assay

The cytotoxic activity against Vero and KB cell lines was performed according to that of Hunt et al. (Hunt et al., 1999). Ellipticine and doxorubicin were used as the standard drugs and displayed the IC_{50} values of 2.24 and 0.38 μM, respectively.

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