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Secondary Metabolites with α-Glucosidase Inhibitory Activity from Mangrove Endophytic Fungus Talaromyces sp. CY-3

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Abstract: Eight new compounds, including two sambutoxin derivatives (1–2), two highly oxygenated cyclopentenones (7–8), four highly oxygenated cyclohexenones (9–12), together with four known sambutoxin derivatives (3–6), were isolated from semimangrove endophytic fungus Talaromyces sp. CY-3, under the guidance of molecular networking. The structures of new isolates were elucidated by analysis of detailed spectroscopic data, ECD spectra, chemical hydrolysis, 13C NMR calculation, and DP1+ analysis. In bioassays, compounds 1–5 displayed better α-glucosidase inhibitory activity than the positive control 1-deoxynojirimycin (IC50 = 80.8 ± 0.3 µM), and the IC50 value was in the range of 12.6 ± 0.9 to 57.3 ± 1.3 µM.

Keywords: Talaromyces sp.; molecular networking; sambutoxin; polyketides; α-glucosidase

1. Introduction

According to the WHO forecast, the number of diabetes patients will reach 693 million in 2045. Type II diabetes accounts for 90%, and α-glucosidase inhibitors originating from natural products, such as acarbose, miglitol, and voglibose, are used to treat type II diabetes [1]. However, most clinical antidiabetic drugs cause side effects [2]. Therefore, there is an urgent need to find and discover new antidiabetic drugs.

Mangrove endophytic fungi are an important resource to provide a large number of structurally unique secondary metabolites [3,4] with good biological activities, such as α-glucosidase inhibitory activities [5], antibacterial [6], antifungal [7], anti-insect [8], antitumor [9], antiviral [10], antioxidant [11], and anti-inflammatory activities [12]. As part of our ongoing search for new compounds with α-glucosidase inhibitory activities from mangrove-derived fungi [5,12–14], secondary metabolites of fungus Talaromyces sp. CY-3, collected from the fresh leaves of the semimangrove Hibiscus tiliaescens in Zhanjiang, were studied.

Recently, the advent of visual molecular networking technology has led to a new perspective in the research of natural products [15]. Global Natural Product Social (GNPS) can establish a molecular network to classify compounds with the same LC–MS/MS ion fragments into similar clusters. Moreover, it can rapidly discover novel compounds through accurate MS data and database comparison [16].

Extracts of CY-3 were analyzed by LC–MS/MS, and a visible molecular network was generated (Figure 1). Guided by MS/MS-based molecular networking through the GNPS platform, small clusters of compounds were tracked for isolation with m/z 492 [M+K]⁺, 336 [M+H]⁺, 438 [M+H]⁺, 474 [M+Na]⁺, 201 [M+H]⁺, and 187 [M+H]⁺. Two new sambutoxin derivatives (1–2), six highly oxygenated new polyketides (7–12), and...
four known sambutoxin derivatives (3–6) were isolated (Figure 2). Herein, the isolation, structure elucidation, and α-glucosidase inhibitory activity of all compounds are presented.

Figure 1. Clusters of nodes from Talaromyces sp. for compounds 1–3, 5, 8, and 10–12.

Figure 2. Structure of compounds 1–12.

2. Results
2.1. Structure Identification

Sambutoxin A (1), obtained as a light-yellow oil, was displayed to have a molecular formula of C_{28}H_{37}NO_{4} with 10 degrees of unsaturation at m/z 438.2999 [M+H]^+ (calcd. 438.3002), as shown by a positive HR–ESI–MS spectrum. The 1H NMR of 1 showed six methyls (δH 0.74, 0.82, 0.83, 0.90, 1.61, and 3.50), four methylenes (δH 1.03, 1.19, 1.34, 1.44, 1.64, 1.91, and 2.09), five methines (δH 1.30, 1.69, 2.45, 3.53, and 5.02), seven unsaturated
protons (δ_H 5.18, 7.14, 7.32, 7.39, and 7.42), and one exchangeable hydrogen atom (δ_H 9.99). Its 13C NMR displayed a total of 28 carbons resonances, six methy ls (δ_C 11.3, 11.7, 17.8, 19.7, 20.8, and 37.2), four methylenes (δ_C 29.0, 30.8, 32.2, and 44.8), five methines (δ_C 29.7, 32.1, 32.5, 78.0, and 92.7), seven carbons with unsaturated protons (δ_C 127.5, 128.4, 129.3, 136.4, and 138.1), and six quaternary carbons (δ_C 110.4, 115.2, 130.4, 134.2, 161.5, and 162.0). The HMBC from H-13 to C-12, from H-21 to C-13, together with the 1H-1H COSY H-13/H-14(H-20)/H-15/H-16(H-19)/H-17/H-18 formed the side chain D. HMBC from H-11 to C-7, together with 1H-1H COSY H-7/H-8/H-9/H-10(H-22)/H-11, established the ring C moiety. HMBC from H-6 to C-2, C-4, and C-5 and from H-23 to C-2 and C-6, constructed a ring B moiety. 1H-1H COSY H-2'/H-3'/H-4'/H-5'/H-6', together with HMBC from H-2' to C-1' and from H-6' to C-1', constructed ring A. Finally, rings A, B, C, and side chain D were connected by the HMBCs from H-6' to C-5, H-7 to C-2, C-3, and C-4, and H-21 to C-11. The 1D and 2D NMR data were similar to those of 3 (Table 1). The only difference between them was that the 4'-OH (δ_C 156.5) is reduced to a hydrogen atom (δ_H 7.29–7.34, δ_C 127.5). Thus, the planar structure of 1 was shown (Figure 3).

### Table 1. 1H NMR and 13C NMR of 1–3.

| NO. | 1 (CDCl₃) | 2 (CDCl₃) | 3 (CDCl₃) |
|-----|-----------|-----------|-----------|
| δ_C | δ_H (J in Hz) | δ_C | δ_H (J in Hz) | δ_C | δ_H (J in Hz) |
| 2  | 161.5, C   | 161.7, C   | 162.7, C   |
| 3  | 110.4, C   | 110.1, C   | 110.4, C   |
| 4  | 162.0, C   | 162.5, C   | 162.4, C   |
| 5  | 115.2, C   | 115.4, C   | 115.9, C   |
| 6  | 136.4, CH  | 7.14, s    | 136.2, CH  | 7.11, s    | 136.0, CH  | 7.12, s    |
| 7  | 78.0, CH   | 5.02, d, (9.1) | 73.7, CH   | 5.17, dd, (10.5, 3.1) | 77.8, CH   | 5.02, d, (9.0) |
| 8  | 30.8, CH₂  | 1.64–1.69, m, 2.09, d, (11.4) | 29.9, CH₂  | 1.25–1.31, m, 2.25–2.35, m | 30.9, CH₂  | 1.64–1.70, m, 2.09, dd, (11.4) |
| 9  | 32.3, CH₂  | 1.44, d, (10.1) | 1.91, d, (13.1) | 121.9, CH  | 5.72, d, (5.2) | 32.2, CH₂  | 1.44, d, (10.1) |
| 10 | 32.5, CH   | 1.64–1.69, m | 132.9, C   | 32.1, CH   | 1.64–1.70, m | 32.1, CH   | 1.64–1.70, m |
| 11 | 92.7, CH   | 3.53, s    | 86.9, CH   | 4.56, s    | 92.7, CH   | 3.53, s    |
| 12 | 130.4, C   | 130.2, C   | 130.3, C   |
| 13 | 138.1, CH  | 5.18, d, (9.5) | 139.7, CH  | 5.29, d, (9.6) | 138.1, CH  | 5.18, d, (9.5) |
| 14 | 29.7, CH   | 2.42–2.49, m | 30.0, CH   | 2.40–2.50, m | 29.7, CH   | 2.42–2.49, m |
| 15 | 44.8, CH₂  | 1.01–1.07, m | 44.8, CH₂  | 1.25–1.31, m | 44.8, CH₂  | 1.16–1.21, m |
| 16 | 32.1, CH   | 1.29–1.35, m | 32.2, CH   | 1.25–1.31, m | 32.4, CH   | 1.29–1.34, m |
| 17 | 29.0, CH₂  | 1.29–1.35, m | 29.0, CH₂  | 1.25–1.31, m | 29.0, CH₂  | 1.29–1.34, m |
| 18 | 11.3, CH₃  | 0.83, s    | 11.0, CH₃  | 1.53, d, (1.3) | 11.3, CH₃  | 0.83, s    |
| 19 | 19.7, CH₃  | 0.82, d, (6.5) | 20.8, CH₃  | 0.90, d, (6.6) | 19.7, CH₃  | 0.82, d, (6.5) |
| 20 | 20.8, CH₃  | 0.90, d, (6.6) | 19.7, CH₃  | 0.82, d, (6.4) | 20.8, CH₃  | 0.90, d, (6.6) |
| 21 | 11.7, CH₃  | 1.61, s    | 11.3, CH₃  | 1.49, s    | 11.7, CH₃  | 1.61, s    |
| 22 | 17.8, CH₃  | 0.74, d, (6.5) | 19.1, CH₃  | 0.81, s    | 17.7, CH₃  | 0.74, d, (6.5) |
| 23 | 37.2, CH₃  | 3.50, s    | 37.3, CH₃  | 3.50, s    | 37.4, CH₃  | 3.50, s    |
| 1' | 134.2, C   | 125.9, C   | 125.2, C   |
| 2' | 129.3, CH  | 7.35–7.44, m | 130.6, CH  | 7.26, d, (9.0) | 130.5, CH  | 7.26, d, (9.0) |
| 3' | 128.4, CH  | 7.35–7.44, m | 115.5, CH  | 6.87, d, (8.1) | 115.6, CH  | 6.92, d, (8.1) |
| 4' | 127.5, CH  | 7.29–7.34, m | 155.8, C   | 156.5, C   |
| 5' | 128.4, CH  | 7.35–7.44, m | 115.5, CH  | 6.87, d, (8.1) | 115.6, CH  | 6.92, d, (8.1) |
| 6' | 129.3, CH  | 7.35–7.44, m | 130.6, CH  | 7.26, d, (9.0) | 130.5, CH  | 7.26, d, (9.0) |
| 4'-OH | 9.99, s | 9.83, s | 9.83, s |
The relative configuration of ring C and the double bond between C-12 and C-13 of compound 1 were defined by the NOESY spectrum. The correlations of H-22/H-7/H-11 and H-14/H-21 were also observed in the NOESY spectrum (Figure 4), which means H-22, H-7, and H-11 were on the same side, as were H-14 and H-21. Therefore, the relative configuration of C-7, C-10, and C-11 in ring C was deduced to be (7S*, 10R*, 11R*), and the double bond between C-12 and C-13 was assigned to be (E). In the present work, assigning the configurations at C-14 and C-16 in the aliphatic side chains of 1 was a challenging task due to the high conformational flexibility of fatty chains. As described in the literature, the absolute side-chain configurations for C-14 and C-16 were also determined by 13C NMR calculation and DP4+ probability (Figures S68 and S69). Consequently, the absolute configuration of 1 was determined by comparing the calculated ECD spectra (7S, 10R, 11R, 14R, 16S)-1 and (7R, 10S, 11S, 14R, 16S)-1 with the experimental one. The calculated ECD curves (7S, 10R, 11R, 14R, 16S)-1 showed better agreement with the experimental one (Figure 5A). Thus, the absolute configuration of 1 was assigned to be 7S, 10R, 11R, 13E, 14R, 16S. Compounds 1 and 3 share a common biosynthetic pathway for sambutoxin derivatives, which is consistent with the configuration reported in the literature [19,20].

Sambutoxin B (2), also isolated as a light-yellow oil, displayed a molecular formula of C_{28}H_{37}NO_{4} with 11 degrees of unsaturation at m/z 452.2794 [M+H]^+ (calcd. 452.2795) by positive HR–ESI–MS spectrum. Its 1D and 2D NMR were similar to 3. The only difference between them was that the single bond between C-9 ($\delta_H$ 1.44, 1.97, $\delta_C$ 32.2) and C-10 ($\delta_H$ 1.64–1.70, $\delta_C$ 32.1) was converted to a double bond ($\delta_H$ 5.72, $\delta_C$ 121.9, 132.9). Thus, the planar structure of 2 was as shown in Figure 3. The correlations of H-7/H-11 and H-14/H-21 were observed in the NOESY spectrum (Figure 4). Thus, the double bond between C-12 and C-13 was assigned to be (E), and the relative configuration was deduced to be (7S*, 11R*). The calculated ECD spectra of (7S, 11R)-2 and (7R, 11S)-2 were compared to the measured one, and the calculated ECD curve of (7S, 11R)-2 was showed a good agreement with the experimental one (Figure 5B). The stereochemistry of C-14 and C-16 was biogenetically established as 14R, 16S. Moreover, they were also verified by 13C NMR calculation and DP4+ probability (Figures S70 and S71). Thus, the absolute configuration of 2 was determined as 7S, 11R, 13E, 14R, 16S.
Figure 4. NOESY correlations of 1−2 and 7−12.

Talaketides A(7) was isolated as a yellow oil, and its molecular formula was determined as C_{13}H_{20}O_{3} by the HR–ESI–MS data at m/z 279.1197 [M+Na]^+ (calcd. 279.1203). The ¹H NMR of 7 displayed four methyls, one methylene, two methines, and one methoxy (Table 2). Its ¹³C NMR showed a total of 13 carbons resonances, including four methyls, one methylene, two methines, one methoxy, one ester carboxyl, one carbonyl, two olefinic carbons, and one quaternary carbon (Table 3). The HMBC from H-3 to C-4, H-6 to C-1, C-2, and C-3, H-7 to C-4, H-8 to C-1, C-4, and C-5, H-10 to C-2 and C-9, together with the ¹H–¹H COSY correlation from H-13/H-10/H-11/H-12, formed the planar structure. In order to determine the absolute ring configuration of 7, the ECD of (2S, 3S)-7, (2R, 3R)-7, (2S, 3R)-7, and (2R, 3S)-7 was compared with the measured one. (2S, 3S)-7 showed a good agreement with the experimental one (Figure 5C). Furthermore, the side chain of 7 was hydrolysis in 1M NaOH solution and compared to the standard of (S)-2-methylbutanoic acid and (R)-2-methylbutanoic acid through a chiral column by HPLC (Figure 6 and Figure S72). Therefore, the absolute configuration of 7 was determined as 2S, 3S, 10S.

Talaketides C (9) was isolated as a yellow oil, and its molecular formula was determined as C_{15}H_{23}O_{3} by the HR–ESI–MS data at m/z 307.1517 [M+Na]^+ (calcd. 307.1516). The 1D and 2D NMR were also similar to 7, and the only difference between them was compound 9 had one more methoxy group (δc 3.16, δc 51.8) and one more methylene group (δc 2.82, 3.03, δc 31.2) than compound 7. According to the HMBCs, the methylene group was connected oxymethine (δc 5.10, δc 71.7) and a quaternary carbon (δc 188.2), and methoxy was connected to oxymethine (δc 5.10, δc 71.7), thus the planar structure of 9 was established (Figure 3). The NOESY correlation of H-5 to H-12 was observed (Figure 4), and the ECD curves of (2R, 3R) and (2S, 3S) were compared to the measured one. The calculated ECD of (2R, 3R) showed a good agreement with the experimental one (Figure 5E), and the side-chain stereostructure of C-10 was also determined as 10S through chemical hydrolysis. (Figure 6 and Figure S72). Therefore, the absolute configuration of 9 was determined as 2R, 3R, 10S.

Talaketides D (10) was isolated as a light-yellow oil, and its molecular formula was determined as C_{10}H_{13}O_{3} by the HR–ESI–MS data at m/z 209.0783 [M+Na]^+ (calcd. 209.0784). Analysis of the 1D and 2D NMR spectrum found compound 10 to be similar to the known compound phomaligol D [21]. The only difference between them was the departure of hydroxyl at C-4 (δc 73.1 changed to δc 2.55, δc 41.5). Thus, the planar structure of 10 was...
determined (Figure 3), which was dehydroxylated phomaligol D. H-3/H-8 and H-4/H-7 correlations were observed in the NOESY spectrum, which indicated that the relative configuration of 10 was (2S*, 3R*, 4R*) (Figure 4). In order to determine its absoption configuration, the ECD spectra of (2S, 3R, 4R)-10 and (2R, 3S, 4S)-10 were compared with the measured one. The calculated CD curve of (2S, 3R, 4R) showed a good agreement with the experimental one (Figure 5F). Therefore, the absoption configuration of 10 was deduced to be (2S, 3R, 4R) and named Talaketides D.

![ECD spectra of compounds](image)

**Figure 5.** ECD spectra of compounds 1 (A), 2 (B), 7 (C), 8 (D), 9 (E), 10 (F), 11 (G) and 12 (H) in CH$_3$OH.
### Table 2. ¹H NMR of 7–12.

| Position | 7     | 8     | 9     | 10    | 11    | 12    |
|----------|-------|-------|-------|-------|-------|-------|
| 3        | 4.98, s | 5.10, q, (6.3) | 3.51, d, (9.5) | 3.40, d, (7.2) | 3.80, d, (3.2) |
| 4        |       | 2.55, dqd, (11.3, 6.8, 1.7) | 2.77–2.83, m | 3.02, qdd, (7.1, 3.2, 1.9) |
| 5        | 1.30, s | 1.42, s | 1.29, d, (6.4) | 5.30, d, (1.7) | 5.33, d, (1.2) | 5.34, d, (1.9) |
| 6        | 4.16, s | 3.98, s | 4.10, s | 1.28, d, (6.8) | 1.30, d, (7.2) | 1.27, d, (7.1) |
| 7        | 1.67, s | 1.56, t, (1.8) | 1.22, s | 1.34, s | 1.30, s |       |
| 8        |       | 2.20, s | 3.75, s | 3.76, s | 3.75, s |       |
| 9        | 2.37, q, (7.0) | 2.19–2.28, m | 1.34–1.40, m | 1.44–1.50, m | 1.30, d, (7.0) |       |
| 10       | 1.44–1.50, m | 1.58–1.65, m | 1.30, d, (7.0) | 2.82, dq, (18.2, 1.8) |       |       |
| 11       | 0.94, t, (7.5) | 0.80, t, (7.5) |       | 3.03, dq, (18.2, 1.8) |       |       |
| 12       | 1.12, d, (7.0) |       |       |       |       |       |
| 13       |       |       |       |       |       |       |
| 14       |       |       |       |       |       |       |
| 15       |       |       |       |       |       |       |

### Table 3. ¹³C NMR of 7–12.

| Position | 7     | 8     | 9     | 10    | 11    | 12    |
|----------|-------|-------|-------|-------|-------|-------|
| 1        | 202.0 | 200.6 | 205.0 | 203.0 | 200.9 | 203.3 |
| 2        | 86.4  | 80.4  | 84.3  | 78.4  | 75.5  | 77.7  |
| 3        | 73.5  | 92.5  | 71.7  | 78.1  | 78.7  | 79.0  |
| 4        | 179.7 | 192.4 | 188.2 | 41.5  | 40.1  | 39.0  |
| 5        | 115.6 | 103.3 | 117.5 | 180.1 | 180.5 | 178.9 |
| 6        | 19.5  | 23.5  | 14.9  | 99.5  | 99.6  | 99.0  |
| 7        | 59.1  | 60.1  | 58.2  | 14.0  | 14.2  | 13.4  |
| 8        | 6.08  | 207.2 | 5.6   | 19.2  | 21.4  | 23.6  |
| 9        | 177.5 | 27.5  | 176.4 | 57.2  | 57.0  | 57.1  |
| 10       | 42.0  |       | 42.4  |       |       |       |
| 11       | 27.8  |       | 27.8  |       |       |       |
| 12       | 11.8  |       | 11.7  |       |       |       |
| 13       | 16.8  |       | 16.6  |       |       |       |
| 14       |       |       | 31.2  |       |       |       |
| 15       |       |       | 51.8  |       |       |       |

### Figure 6. Confirmation for C-10 of compounds 7 and 9 through chemical hydrolysis.

Talaketides E (11) and Talaketides F (12), were also isolated as a light-yellow oil. Similarities in 1D and 2D NMR and HR–ESI–MS indicated that they shared the same planar structure (Figure 3), but the observed correlations were different: one was H-3/H-7/H-8, and the other was H-3/H-4/H-7 in the NOESY spectrum (Figure 4). This phenomenon indicated that their relative configuration was assigned to be (2R*, 3R*, 4R*) and (2S*, 3S*, 4S*).
4R*), respectively. Their stereostructures were also determined by ECD calculation and comparison, and the absolute configuration of 11 and 12 was confirmed as (2R, 3R, 4R) and (2S, 3S, 4R), respectively (Figure 5G).

The structures of compounds 3–6 were identified as (−)-sambutoxin (3) [19], ilicicolin H (4) [22], deoxyeleporin B (5) [23], and leporine B (6) [24], respectively, by comparison of their NMR data, MS, CD, and optical rotation with those in the literature.

### 2.2. Proposed Biosynthesis Pathway

A hypothetical biosynthetic pathway for compounds 1–2 and 7–12 was proposed (Figure 7) [25,26]. Compounds 1–2 are the PKS-NRPS biosynthetic pathway. Starting from one L-Phe molecule, one acetyl-CoA molecule, six malonyl-CoA molecules, and four SAM molecules through the PKS pathway formed intermediate i. Then, the formation of 1 was constructed by rearranging and reducing. The formation of 2 was similar to 1, and the only difference between them was that L-Phe was replaced by L-Tyr (Figure 7A).

![Figure 7. Proposed biogenetic pathways of 1–2 (A) and 7–12 (B).](image-url)

The remaining compounds 7–12 are considered to be the origin of biosynthetic polyketides. The key intermediate vi was obtained through the PKS pathway, oxidation, and formed 10–12 by electron transfer, methylation, and epimerization. Further electron transfer, methylation, and esterification to form 9. 7 was formed through electron transfer, methylation, epimerization, methyltransferase, and esterification. Together, compound 8 started from two SAM molecules and three acetyl-CoA molecules through the PKS pathway and further rearranging and methylating (Figure 7B).

### 2.3. α-Glucosidase Inhibitory Activity

Compounds 1–12 were tested for their α-glucosidase inhibitory activity (Table 4). Compounds 1–5 displayed better α-glucosidase inhibitory activity with an IC\textsubscript{50} value in the range of 12.6 ± 0.9 to 57.3 ± 1.3 μM compared to the positive control 1-deoxynojirimycin (IC\textsubscript{50} = 80.8 ± 0.3 μM).

The IC\textsubscript{50} value of compound 2 is 37.4 ± 1.4 μM, lower than that of compound 1 (12.6 ± 0.9 μM) and compound 3 (16.9 ± 0.6 μM), which illustrates that the double bond formed between C-9 and C-10 reduced the α-glucosidase inhibitory activity. Different from compounds 1–3, compound 5 presented a much bigger IC\textsubscript{50} value of 57.3 ± 1.3 μM, and...
the IC₅₀ of compound 6 was even bigger than 100 µM. Therefore, it can be considered that the branch chain attached to ring C contributes a lot to the inhibitory activity. Compound 4 showed relatively higher inhibitory activity (IC₅₀ = 16.5 ± 0.7 µM), which may be due to its different structure from the other five.

| Compounds | IC₅₀/µM  | Compounds | IC₅₀/µM  |
|-----------|---------|-----------|---------|
| 1         | 12.6 ± 0.9 | 7         | >100    |
| 2         | 37.4 ± 1.4 | 8         | >100    |
| 3         | 16.9 ± 0.6 | 9         | >100    |
| 4         | 16.5 ± 0.7 | 10        | >100    |
| 5         | 57.3 ± 1.3 | 11        | >100    |
| 6         | >100      | 12        | >100    |
| 1-deoxynojirimycin | 80.8 ± 0.3 |

2.4. Molecular Docking Study

To explain the difference in inhibitory activity of compounds 1–5 to α-glucosidase, molecular docking between them and α-glucosidase was carried out using Autodock. The interaction energies of compounds 1–5 with α-glucosidase were 8.25, 7.99, 8.85, 9.19, and 7.96 kcal/mol, respectively, which is consistent with the change in IC₅₀ value. Compound 1 mainly formed a hydrogen bond with Glu-411 with a bond length of 2.85 Å (Figure 8A), 2 formed a hydrogen bond with Ser-241 with a bond length of 3.06 Å (Figure 8B), and 3 formed two hydrogen bonds with Asp-215 and Glu-411 with bond lengths of 3.06 and 2.85 Å, respectively. Moreover, compound 4 also formed two hydrogen bonds with Asp-242 and Thr-310 with bond lengths of 3.31 and 2.88 Å, respectively, while 5 only formed a hydrogen bond with Lys-156 with a bond length of 2.77 Å. In general, 1, 3, and 4 possess higher interaction energy and stronger interaction with amino acid residue than 2 and 5, which explains their significant activity.

Figure 8. Binding mode of sambutoxins 1 (A), 2 (B), 3 (C), 4 (D), and 5 (E) with α-glucosidase.
3. Experimental Section

3.1. General Experimental Procedures

The 1D and 2D NMR were recorded on a Bruker Avance 400 MHz spectrometer (Karlsruhe, Germany) at room temperature. HR–ESI–MS spectra of all test compounds were acquired on a ThermoFisher LTQ–Orbitrap–LC–MS spectrometer (Palo Alto, CA, USA). UV–vis spectra were recorded on a Shimadzu UV–2600 spectrophotometer (Kyoto, Japan). Optical rotations were acquired on an Anton–Paar MCP500 automatic polarimeter at 25 °C (Graz, Austria). CD curves were recorded on an Applied Photophysics Chirascan spectropolarimeter (Surrey, UK). All spectrophotometric measurements used a 96-well Bio-Rad microplate reader (Hercules, CA, USA). Solvent was removed by a Heidolph rotavapor with a vacuum pump. Semipreparative HPLC chromatography was used on a U3000 separation module coupled with a DAD detector manufactured by ThermoFisher and a chiral semipreparative column (Nu-Analytical Solutions Co., LTD-packed chiral INB, 5 µm, 4.6 × 250 mm) was used for separation. Column chromatography (CC) used silica gel (200–300 mesh (Qingdao Marine Chemical Factory)) and Sephadex LH-20 (Amersham Pharmacia, Stockholm, Sweden). Precoated silica gel plates (Qingdao Huang Hai Chemical Group Co., G60, F-254) were used for TLC analysis. LC–MS analysis was performed on a Q-TOF manufactured by Waters and a Waters Acquity UPLC BEH C18 column (1.7 µm, 2.1 × 100 mm) was used for analysis.

3.2. Fungal Material

Fungus CY-3 was isolated from the fresh leaves of the semimangrove Hibiscus tiliacus (collected in June 2020 from Zhanjiang Mangrove National Nature Reserve in Guangdong Province, China). It was identified as Talaromyces sp. using ITS gene sequencing. The ITS rDNA gene sequence data of the fungi were deposited to GenBank (Accession No. MZ614621), and fungus CY-3 was deposited at Sun Yat-Sen University, China.

3.3. Fermentation

CY-3 was activated on a potato dextrose agar (PDA) Petri dish at 28 °C, then cultured in potato dextrose broth (PDB) in 6 × 500 mL Erlenmeyer flasks at 28 °C for 3 days in a shaker to obtain spore inoculum. The routine-scale fermentation was performed in 60 × 1 L Erlenmeyer flasks, each containing 50 mL of 2% saline and 50 g of rice. The Erlenmeyer flask containing the culture medium was autoclaved at 121 °C for 25 min. After cooling to room temperature, 10 mL of CY-3 inoculum was inoculated in each bottle and incubated at room temperature for 30 days.

3.4. Extraction and Purification

After fermentation, the mycelium and medium were extracted three times with EA (3 × 20 L). Then, the extracts were condensed under 50 °C in vacuo and combined to obtain a crude extract (31 g). The residue was separated by a silica gel column, eluting with a gradient of PE/EA (1:0–0:1) to afford 9 fractions (Frs. 1–8). Fr. 3 (2.4 g) was subjected to Sephadex LH-20 (methanol) to yield five sub-fractions (SFr. 3.1–3.5). SFr. 3–1 (352 mg) was applied to silica gel CC (DCM/MeOH v/v, 200:1) to give compounds 1 (5.3 mg), 2 (4.9 mg), and 3 (27.1 mg). Compounds 10 (6.3 mg, tR = 7.3 min), 11 (5.7 mg, tR = 9.1 min), and 12 (4.5 mg, tR = 14.3 min) were obtained from SFr3-4 (298 mg) using chiral ND (the gradient was hexane/2-propanol v/v, 19:1, flow rate: 1 mL/min). Fr. 4 (2.5 g) was subjected to Sephadex LH-20 (ethanol) to yield three subfractions (SFr. 4.1–4.3). Compounds 4 (8.7 mg), 5 (3.1 mg), and 6 (2.9 mg) were obtained from SFr4-1 (792 mg) using silica gel CC (DCM/MeOH v/v, 200:1). Fr. 6 (4.7 g) was subjected to Sephadex LH-20 (methanol) to yield three subfractions (SFr. 6.1–6.3). Compounds 7 (50.1 mg), 8 (6.2 mg), and 9 (4.6 mg) were obtained from SFr6–3 (503 mg) using silica gel CC. (DCM/MeOH v/v, 50:1).

Sambutoxin A (1): C28H39NO3; yellow oil; [α]D25 = 30.75° (c 0.74 MeOH); UV (MeOH) λmax (log ε) 240 (1.95) nm; ECD (MeOH) λmax (Δε) 210 (+2.65), 230 (−2.04), 243 (−2.03),
279 (–0.59) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Table 1; HR–ESI–MS: m/z 438.2999 [M+H]$^+$ (calcd. for C$_{28}$H$_{46}$NO$_3$, 438.3002).

Sambutoxin B (2): C$_{28}$H$_{37}$NO$_4$; yellow oil; $\alpha$$_{D}$$^{20}$$^\circ$ = 18.90° (c 1.05, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 238 (3.86) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 217 (–3.45), 230 (–3.74), 259 (–3.16) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Table 1; HR–ESI–MS: m/z 425.2794 [M+H]$^+$ (calcd. for C$_{28}$H$_{38}$NO$_4$, 425.2795).

Talaketides A (7): C$_{13}$H$_{20}$O$_5$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ = 14.09° (c 0.26, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 252 (2.70) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 211 (–1.52), 251 (+6.85), 301 (–2.68) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 279.1197 [M+Na]$^+$ (calcd. for C$_{13}$H$_{20}$O$_5$Na, 279.1203).

Talaketides B (8): C$_9$H$_{12}$O$_3$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ + 3.69° (c 0.24, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 240 (3.28), 295 (2.53) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 208 (–2.95), 241 (–5.73), 294 (+2.65) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 223.0574 [M+Na]$^+$ (calcd. for C$_9$H$_{12}$O$_3$Na, 223.0577).

Talaketides C (9): C$_{15}$H$_{23}$O$_5$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ + 2.96° (c 1.12, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 261 (2.94) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 205 (+0.36), 243 (–3.35), 262 (+0.97), 307 (+0.60) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 307.1517 [M+Na]$^+$ (calcd. for C$_{15}$H$_{23}$O$_5$Na, 307.1516).

Talaketides D (10): C$_9$H$_{14}$O$_4$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ + 16.04° (c 0.24, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 251 (2.84) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 205 (+0.52), 252 (–2.08), 296 (+1.02) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 209.0783 [M+Na]$^+$ (calcd. for C$_9$H$_{14}$O$_4$Na, 209.0784).

Talaketides E (11): C$_9$H$_{11}$O$_2$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ – 11.35° (c 0.25, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 252 (2.81) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 216 (–0.23), 249 (+0.60), 323 (–0.26) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 209.0784 [M+Na]$^+$ (calcd. for C$_9$H$_{11}$O$_2$Na, 209.0784).

Talaketides F (12): C$_{19}$H$_{22}$ClO$_5$; yellow oil; $\alpha$$_{D}$$^{25}$$^\circ$ + 49.14° (c 0.19, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log $\varepsilon$) 252 (2.91) nm; ECD (MeOH) $\lambda_{\text{max}}$ (Δε) 201 (+1.09), 256 (–1.52), 294 (+1.24) nm; $^1$H (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) data, see Tables 2 and 3; HR–ESI–MS: m/z 369.1468 [M+H]$^+$ (calcd. for C$_{19}$H$_{22}$ClO$_5$, 369.1468).

3.5. Molecular Networking

The crude extract of CY-3 was analyzed by LC–MS/MS (LTQ Velos Pro-Orbitrap, Waltham, MA, USA) and a C$_{18}$ column (Thermo Fisher Scientific-packed Hypersil GOLD, 1.9 μm, 2.1 × 100 mm). Samples were dissolved in MeCN at 1 mg/mL. A 10 μL of sample was injected and eluted with a gradient of H$_2$O containing 0.1% HCOOH and MeCN containing 0.1% HCOOH with a gradient method as follows: 10% MeCN/H$_2$O for 1 min, 10% MeCN/H$_2$O to 60% in 9 min, 60% MeCN/H$_2$O to 90% in 3 min, held at 90% MeCN/H$_2$O for 3 min, then 90% MeCN/H$_2$O to 10% MeCN/H$_2$O in 0.2 min, and finally held at 10% MeCN/H$_2$O for 3.8 min with the flow rate of 0.3 mL/min. Mass spectra were recorded in positive ESI mode (m/z 200–2000) and with an automated fully dependent MS/MS scan enabled. The molecular networking were made as described previously [27,28].

3.6. ECD and $^{13}$C NMR Calculations

ECD calculations and $^{13}$C NMR calculations were performed by the Gaussian 09 program and Spartan’14. The conformation with a Boltzmann population greater than 5% was selected for optimization and calculation in methanol at B3LYP/6-31+G (d, p). The ECD spectra were generated by the program SpecDis 1.6 (University of Würzburg, Würzburg, Germany) and drawn by OriginPro 8.0 (OriginLab, Ltd., Northampton, MA, USA) from dipole-length rotational strengths by applying Gaussian band shapes with sigma = 0.30 eV [29,30].
3.7. Bioassay

Compounds 1–12 were evaluated for α-glucosidase inhibitory activity, as described previously [31]. Three parallel concentrations of 1-deoxynojirimycin were taken as positive controls. DMSO was used as blank controls.

3.8. Molecular Docking

Because the crystal structure of glucosidase from *Saccharomyces cerevisiae* cannot be obtained, the α-glucosidase homology model (PDB:3AXH) provided by SWISSMODEL Repository was used, and the model quality was evaluated [29]. The α-glucosidase homology model (PDB:3AXH) with compounds 1–5 was performed on Autodock, as described previously [31–34].

4. Conclusions

In summary, two new sambutoxin derivatives (1–2) and six new highly oxygenated polyketides derivatives (7–12), together with four known compounds (3–6), were obtained using guidance through molecular networking from semimangrove endophytic fungus *Talaromyces* sp. CY-3. The structures of new isolates were elucidated by 1D and 2D NMR, HR–ESI–MS, ECD spectra, 13C NMR calculation, and DP4+ analysis, as well as chemical hydrolysis. The absolute configuration of sambutoxin derivatives (1–2) was determined through 13C NMR calculation and DP4+ analysis for the first time. In bioassays, compounds 1–5 displayed better α-glucosidase inhibitory activity with IC50 values in the range of 12.6 ± 0.9 to 57.3 ± 1.3 μM compared to the positive control 1-deoxynojirimycin (IC50 = 80.8 ± 0.3 μM).

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/md19090492/s1, Figure S1 LC–MS/MS of CY-3, Figure S2 1H NMR of 1. Figure S3 13C NMR of 1. Figure S4 DEPT 135 of 1. Figure S5 HSQC spectrum of 1. Figure S6 HMBC spectrum of 1. Figure S7 COSY spectrum of 1. Figure S8 NOESY spectrum of 1. Figure S9 HR–ESI–MS spectrum of 1. Figure S10 UV spectrum of 1. Figure S11 1H NMR of 2. Figure S12 13C NMR of 2. Figure S13 DEPT 135 of 2. Figure S14 HSQC spectrum of 2. Figure S15 HMBC spectrum of 2. Figure S16 COSY spectrum of 2. Figure S17 NOESY spectrum of 2. Figure S18 HR–ESI–MS spectrum of 2. Figure S19 UV spectrum of 2. Figure S20 1H NMR of 7. Figure S21 13C NMR of 7. Figure S22 HSQC spectrum of 7. Figure S23 HMBC spectrum of 7. Figure S24 COSY spectrum of 7. Figure S25 NOESY spectrum of 7. Figure S26 HR–ESI–MS spectrum of 7. Figure S27 UV spectrum of 7. Figure S28 1H NMR of 8. Figure S29 13C NMR of 8. Figure S30 HSQC spectrum of 8. Figure S31 HMBC spectrum of 8. Figure S32 COSY spectrum of 8. Figure S33 NOESY spectrum of 8. Figure S34 HR–ESI–MS spectrum of 8. Figure S35 UV spectrum of 8. Figure S36 1H NMR of 9. Figure S37 13C NMR of 9. Figure S38 HSQC spectrum of 9. Figure S39 HMBC spectrum of 9. Figure S40 COSY spectrum of 9. Figure S41 NOESY spectrum of 9. Figure S42 HR–ESI–MS spectrum of 9. Figure S43 UV spectrum of 9. Figure S44 1H NMR of 10. Figure S45 13C NMR of 10. Figure S46 HSQC spectrum of 10. Figure S47 HMBC spectrum of 10. Figure S48 COSY spectrum of 10. Figure S49 NOESY spectrum of 10. Figure S50 HR–ESI–MS spectrum of 10. Figure S51 UV spectrum of 10. Figure S52 1H NMR of 11. Figure S53 13C NMR of 11. Figure S54 HSQC spectrum of 11. Figure S55 HMBC spectrum of 11. Figure S56 COSY spectrum of 11. Figure S57 NOESY spectrum of 11. Figure S58 HR–ESI–MS spectrum of 11. Figure S59 UV of 11. Figure S60 1H NMR of 12. Figure S61 13C NMR of 12. Figure S62 HSQC spectrum of 12. Figure S63 HMBC spectrum of 12. Figure S64 COSY spectrum of 12. Figure S65 NOESY spectrum of 12. Figure S66 HR–ESI–MS spectrum of 12. Figure S67 UV spectrum of 12. Figure S68 Comparison of the experimental 13C NMR data of the 2,4,6-trimethyl-2-ene side chain for compound 1 and the calculated chemical shifts for four 2,4,6-trimethyl-2-ene side-chain diastereomers (14R,16S-1, 14R,16R-1 14S,16R-1, and 14S, 16S-1). Figure S69 DP4+ analysis of 1. Figure S70 Comparison of the experimental 13C NMR data of the 2,4,6-trimethyl-2-ene side chain for compound 2 and the calculated chemical shifts for four 2,4,6-trimethyl-2-ene side-chain diastereomers (14R,16S-2, 14R,16R-2 14S,16R-2, and 14S, 16S-2). Figure S71 DP4+ analysis of 2. Figure S72 Hydrolysis of 7 and 9 compared with the standard through HPLC chiral column.
Author Contributions: W.Y. performed the large-scale fermentation and isolated all compounds. W.Y. and Y.C. carried out the structure elucidation and edited the manuscript. J.W. carried out the biological assays. Q.T., Y.Y., Y.Z. and L.G. participated in the experiments. B.W. and Z.S. designed and supervised this research. All authors have read and agreed to the published version of the manuscript.

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