Science & Technology Development Journal, 23(3):590-597

Open Access Full Text Article

Research Article

Synthesis and evaluation of *α-glucosidase* and *tyrosinase* inhibitory activities of ester derivatives of usnic acid

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ABSTRACT

Introduction: Usnic acid isolated from lichen was a potential bioactivity compound. It has a broad spectrum bioactivity, including antiviral, anti-inflammatory, anticancer… However, low solubility in water limited its application. Many researchs have done to overcome the restriction. Recent results showed that usnic acid derivatives bearing triazole, enamine, pyrazole and benzylidene groups had strong antiviral and anticancer activities. Thus, investigation of usnic acid derivatives synthesis was an attractive aspect due to the diversity of bioactivities of usnic acid derivatives. **Methods**: Usnic acid was isolated from lichen, six ester derivatives of usnic acid were synthesized from usnic acid with acetyl chloride and benzoyl chloride under stirring at room temperature. The products were evaluated *α-glucosidase* and *tyrosinase* inhibitory activities. **Results**: All the ester derivatives were created with good yields. All derivatives exhibited the same or higher activity comparing with usnic acid. Ester of usnic acid bearing benzoyl group showed excellent *α-glucosidase* activity with IC_{50} 26.7±0.57 and 68.8±0.15 μM. **Conclusion**: Among the ester derivatives, UE1 and UE6 were reported as as new compounds. Interestingly, all products displayed the same or higher biological activity than the starting material, usnic acid when evaluated against *α-glucosidase* and *tyrosinase*.

Key words: Acetyl chloride, benzoyl chloride, ester derivatives, α-glucosidase, tyrosinase, usnic acid

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History

- Received: 2020-03-25
- Accepted: 2020-07-12
- Published: 2020-07-27

DOI : 10.32508/stdj.v23i3.1850

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INTRODUCTION

Isolated compounds from lichens exhibited a wide range of biological properties, such as antimicrobial, antiviral, anti-inflammatory, anticaner…[1]. Usnic acid, a dibenzofuran derivative found only in lichens was a remarkable substance. Usnic acid has a broad spectrum of bioactivity, especially against gram-positive bacteria such as *Staphylococcus, Streptococcus,* and antifungal[2]. Futhermore, it also has antiviral, anti-inflammatory, antipyretic… activities[2]. *In vitro* experiments showed that usnic acid could inhibit many human cancer cell lines growth[3]. However, toxicity with liver and low solubility in water of usnic acid has limited application of it in cancer treatment. This attracts interests of many researchers to overcome the limit.

The first research of usnic acid derivatives synthesis was carried out by Takai in 1979, the solubility of products were improved by preparing glycoside and imine derivatives of usnic acid[4]. Recently, many researchs showed that usnic acid bearing triazole, enamine, pyrazole and benzylidene groups had strong antiviral and anticancer activities[5–8]. The diversity of bioactivities of usnic acid derivatives showed that they could be a potential drugs in medicinal treatments. Herein, we described a procedure of ester derivatives synthesis from usnic acid, these compounds were evaluated of *α-glucosidase* and *tyrosinase* inhibitory activities.

MATERIALS AND METHODS

Materials

(+)-Usnic acid isolated from lichen.

Acetyl chloride, benzoyl chloride (Sigma-Aldrich).

Silica gel 60 (HiMedia, India).

Bruker Advance III (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer with TMS as internal standard recorded NMR spectra.

The HR–ESI–MS were recorded on a HR–ESI–MS Bruker microTOF Q-II.

Column chromatography was performed with silica gel 60.

General experimental procedure

A mixture of (+)-usnic acid (0.250 g, 0.727 mmol) in $CHCl_3$ (5.0 mL) was stirred at room temperature for 5 minutes. Acetyl chloride (0.341 g, 4.350 mmol) was added, followed by pyridine (3.5 mL, 43.502 mmol) and stirred at room temperature for 6 h. Then, the organic layer was extracted with water and saturated

Cite this article : Dung P D, Huy D T, Kieu N V. **Synthesis and evaluation of *α-glucosidase* and *tyrosinase* inhibitory activities of ester derivatives of usnic acid**. *Sci. Tech. Dev. J.;* 23(3):590-597.

with aqueous $NaHCO_3$, respectively, and dried over anhydrous Na_2SO_4. The mixture was filtered and evaporated using rotatory vacuum evaporator. The products, **UE1**-**4** were purified by subjecting to silica gel column.

A mixture of (+)-usnic acid (0.250 g, 0.727 mmol) in $CHCl_3$ (5.0 mL) was stirred at room temperature for 5 minutes. enzoyl chloride (0.611 g, 4.350 mmol) was added, followed by pyridine (3.5 mL, 43.502 mmol) and stirred at room temperature for 6 h. The products, **UE 5** were purified by subjecting to silica gel column.

A mixture of **UE3** (0.280 g, 0.727 mmol) in $CHCl_3$ (5.0 mL) was stirred at room temperature for 5 minutes. enzoyl chloride (0.611 g, 4.350 mmol) was added, followed by pyridine (3.5 mL, 43.502 mmol) and stirred at room temperature for 6 h. The products, **UE 6** were purified by subjecting to silica gel column.

Biological activities investigation

These inhibitory activities were evaluated according to[9]. Enzymatic activity was calculated by measuring absorbance at 405 nm (ALLSHENG micro plate reader AMR-100). All samples were analyzed in triplicate at various concentrations to obtain the IC_{50} value of each compound. The mean values and standard deviation were also identified.

Structure determination of products

The products were verified structures by ^1H and ^{13}C NMR method using $CDCl_3$ as solvent and HR-ESI-MS method.

UE1: Light yellow powder, m = 0.0342 g, yield: 10 %; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 6.38 (1H, s), 2.65 (3H, s), 2.40 (3H, s), 2.35 (3H, s), 2.23 (3H, s), 2.22 (3H, s), 2.19 (3H, s), 2.02 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 203.0, 202.9, 195.0, 169.1x2, 168.5, 151.2, 147.8, 145.7, 145.5, 144.5, 121.5, 120.3, 115.5, 113.7, 108.5, 47.0, 31.8, 29.5, 21.1, 20.7, 20.5, 9.7, 9.2. HR-ESI-MS m/z $[M+H]^+$ calcd. for $C_{24}H_{23}O_{10}$: 471.1291; found: 471.1297.

UE2: Light yellow powder, m = 0.1055 g, yield: 34 %; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.90 (1H, s), 2.60 (3H, s), 2.54 (3H, s), 2.46 (3H, s), 2.33 (3H, s), 1.98 (3H, s), 1.81 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 198.6, 195.0, 192.8, 190.9, 177.8, 168.9, 168.8, 153.7, 149.0, 148.5, 123.6, 118.9, 116.1, 106.2, 98.8, 59.5, 32.1, 31.1, 26.2, 21.4, 20.8, 10.4.

UE3: Light yellow powder, m = 0.0420 g, yield: 15 %; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 13.22 (1H, s), 5.91 (1H, s), 2.74 (3H, s), 2.54 (3H, s), 2.45 (3H, s), 2.03 (3H, s), 1.78 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 201.9, 198.4, 193.3, 190.9, 178.1, 168.6, 163.3, 155.7, 151.5, 117.7, 111.1, 106.3, 105.4, 98.8, 59.4, 32.0, 31.2, 26.0, 21.4, 9.3.

UE4: Light yellow powder, m = 0.0505 g, yield: 18 %; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 11.07 (1H, s), 5.97 (1H, s), 2.66 (3H, s), 2.57 (3H, s), 2.35 (3H, s), 2.06 (3H, s), 1.80 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 201.9, 197.8, 194.0, 191.8, 179.3, 169.2, 155.5, 154.2, 149.7, 117.4, 110.0, 109.9, 105.4, 98.5, 59.1, 32.4, 32.0, 28.0, 20.9, 8.9.

UE5: Light yellow powder, m = 0.3250 g, yield: 81 %; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 13.32 (1H, s), 10.52 (1H, s), 8.01 (2H, d, J = 8.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.66 (2H, t, J = 8.0 Hz), 7.53 (2H, t, J = 8.0 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.32 (1H, t, J = 8.0 Hz), 6.03 (1H, s), 5.43 (1H, d, 1.2), 5.24 (1H, d, 1.2), 2.65 (3H, s), 2.12 (3H, s), 1.88 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 200.9, 200.5, 174.0, 165.1, 164.5, 164.0, 163.0, 157.5, 156.4, 143.5, 134.6, 133.6, 130.7, 130.1, 128.9, 128.5, 128.4, 127.9, 114.6, 109.8, 109.2, 104.0, 101.9, 96.6, 60.7, 31.3, 31.1, 7.7.

UE6: Light yellow powder, m = 0.2529 g, yield: 71 %; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.18 (2H, d, 8.0), 7.66 (1H, t, 8.0), 7.53 (2H, t, 8.0), 5.92 (1H, s), 2.60 (3H, s), 2.56 (3H, s), 2.48 (3H, s) 2.04 (3H, s), 1.85 (3H, s). ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 202.5, 198.7, 195.0, 190.9, 177.9, 168.9, 164.6, 153.5, 148.9, 148.5, 134.2, 130.6, 128.9, 128.7, 119.1, 116.7, 114.5, 114.0, 98.9, 59.6, 32.0, 29.8, 26.2, 21.5, 10.6. HR-ESI-MS m/z $[M+Na]^+$ calcd. for $C_{27}H_{22}O_9Na$: 513.1162; found 513.1122.

RESULTS

Figure 1 showed esterification of usnic acid with acetyl chloride and benzoyl chloride. Six ester derivatives (**UE1-6**) were synthesized from usnic acid. Table 1 showed the results in the synthesis of six ester derivatives of usnic acid. Yields of the reactions using acetyl chloride or benzoyl chloride were good (> 70%). Proposed mechanism of **UE3** synthesis from usnic acid was shown in Scheme 1.

Table 2 and Table 3 summarized data of nuclear magnetic resonance spectra of these ester products. These signals demonstrated that six ester derivatives had been synthesized successfully.

α-glucosidase and *tyrosinase* inhibitory activities of **UE1-6** were listed in Table 4. All derivatives exhibited the same or higher activity comparing with starting material (usnic acid).

DISCUSSION

Ester derivatives synthesis from usnic acid

There are three hydroxy groups in usnic acid structure at C-3, C-8 and C-10 could be esterified. In the

Table 2: ^{1}H NMR data of ester derivatives

Position	Usnic acid ($\delta_H J$, Hz)	UE1 ($\delta_H J$, Hz)	UE2 ($\delta_H J$, Hz)	UE3 ($\delta_H J$, Hz)	UE4 ($\delta_H J$, Hz)	UE5 ($\delta_H J$, Hz)	UE6 ($\delta_H J$, Hz)
1	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-
4	5.97 s	6.38 s	5.90 s	5.91 s	5.97 s	6.03 s	5.92 s
5	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-
13	1.76 s	2.02 s	1.81 s	1.78 s	1.80 s	1.88 s	1.85 s
14	-	-	-	-	-	-	-
15	2.66 s	2.40 s	2.54 s	2.54 s	2.57 s	5.43 d (1.2) 5.24 d (1.2)	2.56 s
16	2.11 s	2.35 s	2.46 s	2.45 s	2.35 s	2.12 s	2.48 s
17	-						
18	2.68 s	2.65 s	2.60 s	2.74 s	2.66 s	2.65 s	2.60 s
3-OH	-	-	-	-	-	-	-
8-OH	13.29 s	-	-	13.22 s	-	13.32 s	-
10-OH	11.01 s	-	-	-	11.07 s	10.52 s	-
2’		2.23 s	2.33 s	2.03 s	2.06 s	-	-
2”		2.22 s	1.98 s		-	-	2.04 s
2”’		2.19 s	-	-	-	-	-
3’,7’						8.01 d (8.0)	8.18 d (8.0)
3”,7”						7.88 d (8.0)	-
4’-6’						7.66 t (8.0)	7.66 t (8.0)
4”-6”						7.53 t (8.0)	-
5’						7.46 t (8.0)	7.53 t (8.0)
5”						7.32 t (8.0)	-

Table 3: ^{13}**C NMR data of ester derivatives**

Position	Usnic acid (δ_C)[9]	UE1 (δ_C)	UE2 (δ_C)	UE3 (δ_C)	UE4 (δ_C)	UE5 (δ_C)	UE6 (δ_C)
1	198.1	195.0	192.8	193.3	194.0	200.5	195.0
2	105.3	120.3	118.9	111.1	110.0	109.2	116.7
3	191.7	151.2	190.9	190.9	191.8	165.1	190.9
4	98.3	108.5	98.8	98.8	98.5	96.6	98.9
5	179.4	147.8	177.8	178.1	179.3	174.0	177.9
6	155.2	145.5	149.0	155.7	154.2	156.4	148.5
7	101.6	113.7	106.2	105.4	105.4	101.9	114.0
8	163.9	145.7	153.7	163.3	155.5	157.5	153.5
9	109.4	121.5	123.6	117.7	117.4	114.6	119.1
10	157.5	144.5	148.5	151.5	149.7	143.5	148.9
11	103.9	115.5	116.1	106.3	109.9	104.0	114.5
12	59.1	47.0	59.5	59.4	59.1	60.7	59.6
13	7.5	9.2	10.4	9.3	8.9	7.7	10.6
14	200.3	203.0	198.6	201.9	201.9	163.0	202.5
15	27.8	29.5	31.1	31.2	32.0	109.8	29.8
16	32.2	9.7	26.2	21.4	28.0	31.1	26.2
17	201.7	202.9	195.0	198.4	197.8	200.9	198.7
18	31.2	31.8	32.1	32.0	32.4	31.3	32.0
1’		169.1	168.9	168.6	169.2	164.5	168.9
1”		169.1	168.8			164.0	164.6
1”’		168.5			-	-	-
2’		21.1	21.4	26.0	20.9	127.9	128.7
2”		20.7	20.8			128.4	21.5
2”’		20.5			-	-	-
3’						130.7	130.6
3”						130.1	-
4’						128.9	128.9
4”						128.5	-
5’						134.6	134.2
5”						133.6	-
6’						128.9	128.9
6”						128.5	-
7’						130.7	130.6
7”						130.1	-

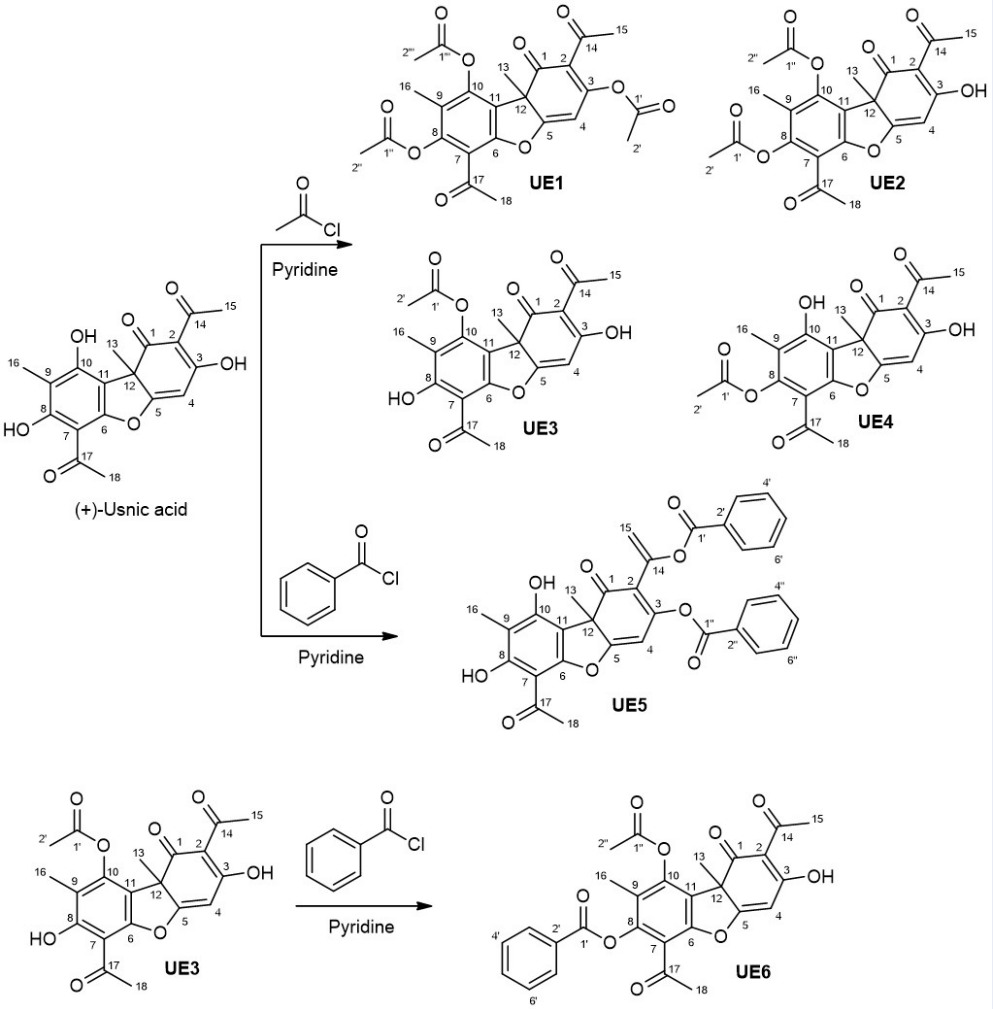

Figure 1: Esterification of usnic acid

Table 4: α-*Glucosidase* and *tyrosinase* inhibitory activities of usnic acid derivatives

Entry	Compound	α-*Glucosidase* IC_{50} (μM)	*Tyrosinase* IC_{50} (μM)
1	UE1	>200	NA
2	UE2	>200	>200
3	UE3	>200	NA
4	UE4	>200	>200
5	UE5	26.7 ± 0.57	>200
6	UE6	68.8 ± 0.15	NA
7	Usnic acid	>200	NA
8	Acarbose	93.6±0.49	
9	Kojic acid		36.1 ± 1.07

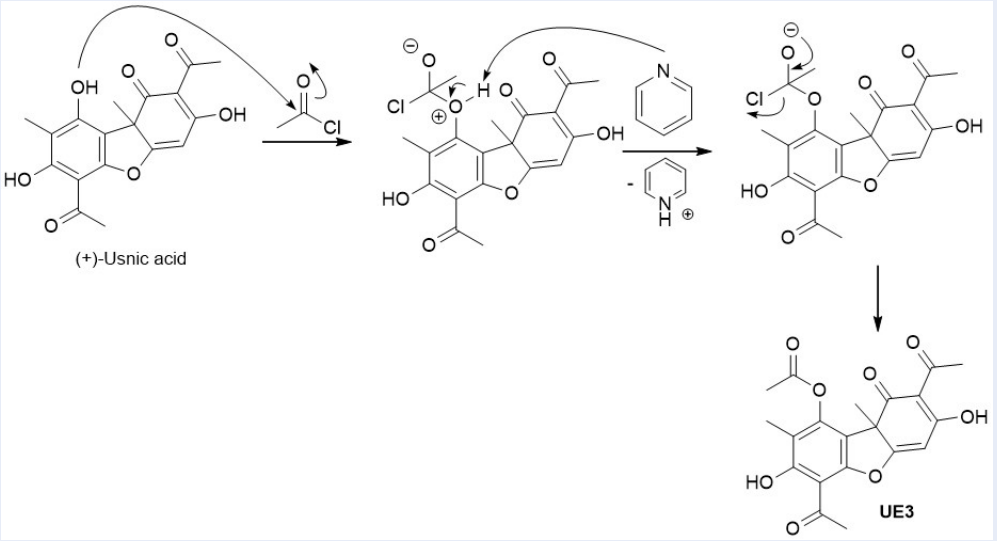

Figure 2: Proposed mechanism of **UE3** synthesis from usnic acid

Table 1: Ester derivatives synthesis of usnic acid

Entry	Ester compound	Yield (%)[a]
1	UE1	10
2	UE2	34
3	UE3	15
4	UE4	18
5	UE5	81
6	UE6	71

[a] Isolated yields

reaction, we use large amounts of acetyl chloride in order to react at three hydroxy groups completely. However, the reaction produced four ester derivatives (**UE1-4**) depending on the number and position of hydroxy groups that participated in the reaction when acetyl chloride was used as a reactant. Besides, only one product (**UE5**) was created when benzoyl chloride was used. Moreover, the ester product (**UE6**) was also generated when **UE3** product reacted with benzoyl chloride in the same conditions (Figure 1). The synthesis results were listed in Table 1 below showed that yields of the reactions using acetyl chloride or benzoyl chloride were good (> 70%).

The ^{1}H NMR spectrum of **UE1** showed an olefin proton at δ_H 6.38, and seven methyl groups at δ_H 2.65, 2.40, 2.35, 2.23, 2.22, 2.19 and 2.02. The ^{13}C NMR spectrum of **UE1** displayed twenty-three carbon signals, including three ketone carbons at δ_C 203.0, 202.9 and 195.0, three carboxyl carbons at δ_C 169.1x2 and 168.5, ten olefin carbons in the range of δ_C 155.0-100.0, one tertiary carbon at δ_C 47.0 and seven methyl carbons at δ_C 31.8, 29.5, 21.1, 20.7, 20.5, 9.7 and 9.2. The lack of 8- and 10-OH signal in usnic acid along with the appearance of seven methyl groups (usnic acid has only four methyl groups [10]) indicated the esterification reaction occurred on 3-, 8-, and 10-OH of usnic acid. Thus, **UE1** is established as 3,8,10-triacetoxyusnic acid.

The ^{1}H NMR spectrum of **UE2** showed an olefin proton at δ_H 5.90, and six methyl groups at δ_H 2.60, 2.54, 2.46, 2.33, 1.98 and 1.81. The lack of both of 10-OH and 8-OH in usnic acid along with the appearance of only two acetoxycarbonyl groups (δ_H 2.33 and 1.98; δ_C 168.9 and 168.8) indicated the esterification reaction occurred on both of 10-OH and 8-OH of usnic acid. Thus, the structure of **UE2**, 8,10-*O*-diacetylusnic acid [10], is elucidated as shown in Figure 1.

The ^{1}H NMR spectrum of **UE3** showed a singlet of hydroxy chelated signal at δ_H 13.22, an olefin proton at δ_H 5.91, and five methyl groups at δ_H 2.74, 2.54, 2.45, 2.03, and 1.78. Similar to **UE2**, the lack of 10-OH in usnic acid [10] along with the appearance of only one acetoxycarbonyl group (δ_H 2.03, δ_C 168.6 and 26.0) indicated the esterification reaction occurred on 10-OH of usnic acid. Thus, the structure of **UE3**, 10-*O*-acetylusnic acid [11], is elucidated as shown in Figure 1.

The examination of the ^{1}H and ^{13}C NMR spectra of **UE4** revealed the similar spectra to those of **UE3**, excepted for the lack of 8-OH and the occurrence of

10-OH that indicated the reaction occurred at 8-OH. Thus, **UE4**, 8-*O*-acetylusnic acid [11], is established as shown in Figure 1.

The ^{1}H NMR of **UE5** displayed the presence of two chelated hydroxyl groups at δ_H 13.32 and 10.52, ten aromatic protons at δ_H 7.00-8.50, three olefin protons at δ_H 6.03, 5.43, and 5.24, and three methyl groups at δ_H 2.65, 2.12 and 1.88. Comparison with those of usnic acid indicated the hydroxyl groups at δ_H 13.32 and 10.52 belonging to 8-OH and 10-OH, respectively. Moreover, the appearance of ten aromatic protons at δ_H 7.00-8.50 ppm along with a couple gem olefin proton at δ_H 5.43 (1H, d, J = 1.2 Hz) and 5.24 (1H, d, J = 1.2 Hz) implied the disubstitution on C-14 and C-3. Finally, **UE5** is established as benzoic acid 1-(6-acetyl-3-benzoyloxy-7,9-dihydroxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl)-6inyl ester as shown in Figure 1 [11].

The ^{1}H NMR spectrum of **UE6** showed five aromatic protons at δ_H 8.5-7.5, that implied monobenzoyl chloride reacted with **UE3**. A singlet signal at δ_H 5.86 (1H, s), belonging to H-4 in starting material, and five methyl groups at δ_H 2.60, 2.56, 2.48, 2.04 and 1.85. The examination of the ^{13}C NMR spectrum revealed some important structural differences from **UE3** including the occurrence of five aromatic carbons at δ_C 134.2, 130.6 x2 and 128.9x2 confirmed the addition of monobenzoyl chloride. Moreover, the lack of chelated hydroxyl proton 8-OH at δ_H 13.22 (**UE3**) identificated that the reaction occurred at 8-OH. Finally, the structure of **UE6** was established as shown in Figure 1.

Biological activities of usnic acid derivatives

Six usnic acid derivatives including via esterification (**UE1**-**6**) were further tested with α-*glucosidase* and *tyrosinase* inhibitory activities. From the results, all derivatives exhibited the same or higher activity comparing with starting material (usnic acid: >200 μM and no activity (NA) for α-*glucosidase* and *tyrosinase*, respectively). Especially, **UE5** and **UE6** showed excellent α-*glucosidase* activity with IC_{50} 26.7$\pm$0.57, and 68.8$\pm$0.15 μM, respectively. These compounds not only displayed higher activity than that of usnic acid, but also with that of a positive control, acarbose (IC_{50}: 93.6$\pm$0.49 μM) as shown in Table 4. In this case, **UE5** displayed the strongest activity (IC_{50}: 26.7$\pm$0.57 μM).

CONCLUSION

From usnic acid, six derivatives were synthesized via esterification reactions (**UE1**-**6**). Their chemical structures were elucidated by NMR and HRESIMS as well as comparison with those from literature. Among them, **UE1** and **UE6** were reported as as new compounds. Interestingly, all products displayed the same or higher biological activity than the starting material, usnic acid when evaluated against α-*glucosidase* and *tyrosinase*. In the α-*glucosidase* assay, **UE5** and **UE6** showed excellent activity (IC_{50} 26.7$\pm$0.57, and 68.8$\pm$0.15 μM, respectively). On the other hand, all tested compounds revealed weak or no inhibitory activity in the *tyrosinase* assay.

ABBREVIATIONS

^{1}H NMR: Proton nuclear magnetic resonance;
^{13}C NMR: Carbon-13 nuclear magnetic resonance;
s: singlet;
d: doublet;
t: triplet.

CONFLICTS OF INTEREST

The authors declare that they have no competing financial interest.

AUTHOR CONTRIBUTION

All authors contributed in conducting experiments, acquisition of data, interpretation of data, searching the bibliography and gave final approval of the manuscript to be submitted.

ACKNOWLEDGEMENT

The authors are indebted to Dr. Warinthorn Chavasiri and Mrs. Asshaima Paramita Devi (Center of Excellence in Natural Products Chemistry, Department of Chemistry, Faculty of Science, Chulalongkorn University, Thailand) for performing the enzyme inhibitory against α–*glucosidase* and *tyrosinase*.

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