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•Research article•

Geranyl phenyl ethers from *Illicium micranthum* and their anti-HBV activity

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[ABSTRACT] Fourteen new geranyl phenyl ethers (**1**–**14**) along with three known compounds (**15**–**17**) were isolated from *Illicium micranthum*, and their structures were elucidated by comprehensive spectroscopic methods. Illimicranins A–H (**1**–**8**) were characterized as geranyl vanillin ethers, while **9** and **10** were dimethyl acetal derivatives. Illimicranins I and J (**11** and **12**) were rare geranyl isoeugenol ethers. Illimicranins K and L (**13** and **14**) represented the first example of geranyl guaiacylacetone ether and geranyl zingerone ether, respectively. Compounds **1**, **2** and **15** exhibited anti-HBV (hepatitis B virus) activity against HBsAg (hepatitis B surface antigen) and HBeAg (hepatitis B e antigen) secretion, and HBV DNA replication.

[KEY WORDS] *Illicium micranthum*; Geranyl phenyl ethers; Spectroscopic data; Anti-HBV activity
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Introduction

The genus *Illicium* , the sole genus of the family Illiciacae [1], contains about 50 species mainly distributed in East and Southeast Asia. Amongst, the fruit of *I. verum*, normally called as Chinese star anise, is not only one of traditional Chinese medicines but also one of the most popular cooking seasonings in China and Southeast Asia [1]. Interestingly, most of other *Illicium* species are considered to be poisonous [2] , resulting in limits of use for medicinal purposes, such as *I. difengpi* [3] listed in Chinese Pharmacopeia and *I. oligandrum* for treating rheumatic arthritis; *I. simonsii* for treating cystic hernia, distending pain, scabies and vomiting [4-5]; and *I. lanceolatum* for treating bruises, internal injuries and back pain [6]. Plenty of phytochemical investigations on *Illicium* genus have been carried out in order to clarify the relationship between the plants, constituents, bioactivity and toxicity, contributing to the discovery of a large number of secondary metabolites such as monoterpenoids [7], sesquiterpenoids [8-14], diterpenoids [12,15-16], phenylpropanoids [17-18], lignans [19-20], neolignans [3, 21-22] and phytoquinoids. These metabolites exhibit a wide range of biological activities including antioxidant [3,23],antiinflammatory [3,5,24],antimicrobial [6],antiviral [12, 15-16, 25] , neurotoxic [4, 10, 22] , anti-HIV and anti-HBV activities [14], and cytotoxic activities [5, 15], which have attracted considerable attention for natural products, synthetic chemistry and pharmacology researches [26-27].

Illicium micranthum Dunn, an evergreen shrub or small tree native to South China [1], is also poisonous and used for the treatment of rheumatism [8, 17], traumatic injury [28], stomach vomiting and as a pesticide [17, 28-29]. Phytochemical studies on it have led to the report of several sesquiterpenoids [29], phenylpropanoids [17] , phytoquinoids [28] and monoterpene phenyl ethers [30]. In the current study, fourteen new geranyl phenyl ethers, including eight geranyl vanillin ethers illimicranins A–L (**1**–**8**), two dimethyl acetal derivatives of ger-

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anyl vanillin ethers (**9** and **10**), two geranyl isoeugenol ethers illimicranins I and J (**11** and **12**), one geranyl guaiacylacetone ether illimicranin K (**13**) and one geranyl zingerone ether illimicranin L (**14**), together with three known compounds (**15**–**17**), were isolated from the leaves and twigs of *I. micranthum* (Fig. 1). The anti-HBV (hepatitis B virus) activity was evaluated for selected isolates on HepG2.2.15 cell line. The isolation, structural elucidation and biological evaluation were herein presented.

Results and Discussion

Compound **1** was assigned the molecular formula $C_{18}H_{22}O_4$ with eight degrees of unsaturation (DOUs) by the HR-ESI-MS *m/z* 325.1410 $[M + Na]^+$ (Calcd. for $C_{18}H_{22}NaO_4$, 325.1410). The ^{1}H NMR spectrum (Table 1) revealed the presence of one 1,3,4-trisubstituted aromatic ring [δ_H 7.44 (dd, J = 8.1, 1.6 Hz, H-6′), 7.41 (d, J = 1.6 Hz, H-2′) and 6.97 (d, J = 8.1 Hz, H-5′)], four methyls [three allylic at δ_H 2.24 (s, Me-10), 2.17 (s, Me-9), 1.90 (s, Me-8), and one oxygenated at δ_H 3.92 (s)], two methylenes [one at δ_H 2.70 (t, J = 7.0 Hz, H_2-2) and one oxygenated at δ_H 4.24 (t, J = 7.0 Hz, H_2-1)] and three methines [one aldehydic at δ_H 9.85 (s, H-7′), and two olefinic at δ_H 6.14 (s, H-4) and 6.07 (s, H-6)]. The ^{13}C NMR (Table 2) and HSQC spectra resolved 18 carbons classified as one ketone carbonyl carbon (δ_C 191.4, C-5), one aldehyde carbonyl carbon (δ_C 191.0, C-7′), five sp^2 quaternary carbons, five sp^2 methines, two sp^3 methylenes (including one oxygenated at δ_C 67.2), and four methyls (including one oxygenated at δ_C 56.2). The ^{1}H–^{1}H COSY correlation of H_2-1/H_2-2 and the HMBC correlations of H_2-1/C-3, H_2-2/C-3 and C-4, H-4/C-2, Me-10/C-2, C-3 and C-4, Me-8/C-6 and C-7, Me-9/C-6 and C-7 permitted the assignments of two fragments C-1/C-2/C-3/C-4/Me-10 and C-6/C-7/Me-8/Me-9 as shown in Fig. 2, respectively, which were then connected through C-5 by the HMBC correlations from H-4 and H-6 to C-5. The 1,3,4-trisubstituted aromatic ring was connected to C-1 through the ether bond by the chemical shifts of C-1 (δ_C 67.2) and C-4′ (δ_C 153.8), and the HMBC correlation of H_2-1/C-4′. Furthermore, the HMBC correlations of H-7′/C-1′, C-2′ and C-6′, H-2′ and H-6′/C-7′, and -OMe/C-3′ assigned the locations of the formyl and methoxy groups at C-1′ and C-3′, respectively. Thus, its planar structure was confirmed as a geranyl vanillin ether with similar structure as micranthumnin F (**15**) [29], which was also obtained in this study. The 3*E* geometry was assigned by comparison of the NMR data of **1** with micranthumnins D and E [30]; methyl 4-[[(3*E*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [31], methyl 4-[[(3*Z*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [31], methyl 4-[[(3*E*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-hydroxybenzoate [32] and methyl 4-[[(3*Z*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [32]. Finally, the structure of **1** was established and named as illimicranin A.

Compound **2** possessed the same molecular formula $C_{18}H_{22}O_4$ as **1** by the HR-ESI-MS data. The 1D and 2D NMR spectral analyses indicated that **2** had the same planar structure as **1** (Fig. 2). **2** differed from **1** mainly as the chemical shifts of CH_2-2 [δ_H 3.11 (t, J = 6.7 Hz), δ_C 33.7] and Me-10 [δ_H 2.04 (s), δ_C 27.2] (Tables 1 and 2), due to the *Z*-geometry of the Δ^3 double bond at **2**, which was identified by directly comparing the NMR data of **2** with micranthumnins D and E [30], methyl 4-[[(3*E*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [31], methyl 4-[[(3*Z*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [31], methyl 4-[[(3*E*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-hydroxybenzoate [32] and methyl 4-[[(3*Z*)-3,7-dimethyl-5-oxo-3,6-octadienyl]oxy]-3-methoxybenzoate [32], and confirmed by detailed 2D NMR analysis (Fig. 2). Therefore, **2** was elucidated and named as illimicranin B.

The molecular formula of compound **3** was determined as $C_{18}H_{24}O_4$ by its HR-ESI-MS *m/z* 327.1565 $[M + Na]^+$ (Calcd. for $C_{18}H_{24}NaO_4$, 327.1567) with 2 mass units more than that of **1**, suggesting that one double bond at **1** was hydrogenated at **3**. Direct comparison of their NMR data (Tables 1 and 2) showed the major differences due to the presence of one additional methylene [δ_H 2.30 (d, J = 7.0 Hz,

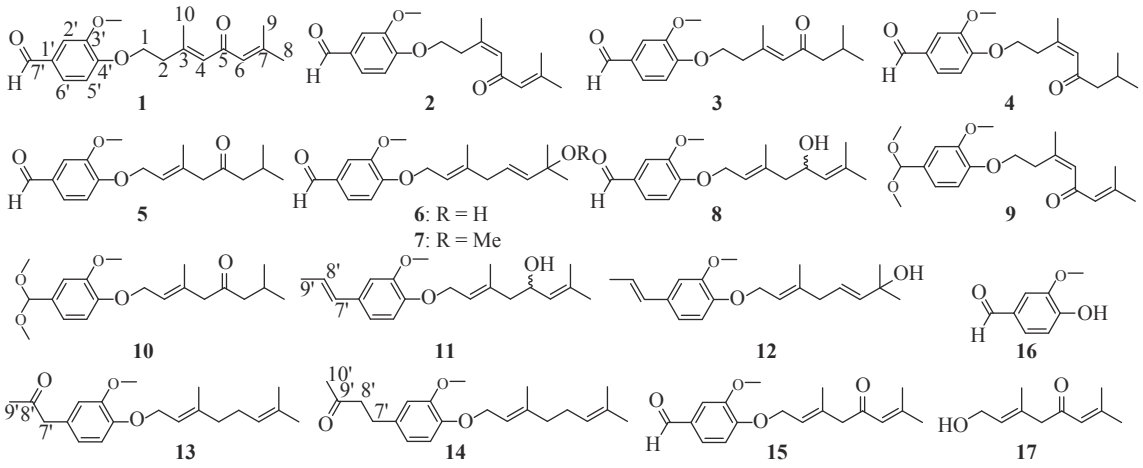

Fig. 1 Structures of isolates 1–17 from *I. micranthum*

Table 1 ^{1}H NMR data of **1**–**14** in $CDCl_3$ (δ in ppm and *J* values in Hz). [a]overlapped

No.	1	2	3	4	5	6	7
1	4.24 (t, 7.0, 2H)	4.33 (t, 6.7, 2H)	4.23 (t, 6.8, 2H)	4.30 (t, 6.7, 2H)	4.74 (d, 6.2, 2H)	4.71 (d, 6.4, 2H)	4.72 (d, 6.4, 2H)
2	2.70 (t, 7.0, 2H)	3.11 (t, 6.7, 2H)	2.69 (t, 6.8, 2H)	3.07 (t, 6.7, 2H)	5.59 (t, 6.2)	5.54 (t, 6.4)	5.55 (t, 6.4)
4	6.14 (s)	6.16 (s)	6.16 (s)	6.18 (s)	3.13 (s, 2H)	2.77 (d, 6.2, 2H)	2.80 (d, 6.4, 2H)
5						5.61 (dt, 15.8, 6.2)	5.53 (dt, 15.9, 6.4)
6	6.07 (s)	6.06 (s)	2.30 (d, 7.0, 2H)	2.30 (d, 7.0, 2H)	2.29 (d, 6.9, 2H)	5.66 (brd, 15.8)	5.48 (d, 15.9)
7			2.13 (m)	2.13 (m)	2.12 (m)		
8	1.90 (s, 3H)	1.89 (s, 3H)	0.92 (d, 6.6, 3H)	0.92 (d, 6.6, 3H)	0.89 (d, 6.6, 3H)	1.31 (s, 3H)	1.25 (s, 3H)
9	2.17 (s, 3H)	2.17 (s, 3H)	0.92 (d, 6.6, 3H)	0.92 (d, 6.6, 3H)	0.89 (d, 6.6, 3H)	1.31 (s, 3H)	1.25 (s, 3H)
10	2.24 (s, 3H)	2.04 (s, 3H)	2.21 (s, 3H)	2.04 (s, 3H)	1.77 (s, 3H)	1.74 (s, 3H)	1.75 (s, 3H)
2′	7.41 (d, 1.6)	7.39 (s)	7.42 (s)	7.39 (d, 1.4)	7.41 (s)	7.41 (s)	7.42 (s)
5′	6.97 (d, 8.1)	7.16 (d, 8.2)	6.97 (d, 8.1)	7.13 (d, 8.2)	6.96 (d, 8.1)	6.97 (d, 8.1)	6.97 (d, 8.1)
6′	7.44 (dd, 8.1, 1.6)	7.44 (d, 8.2)	7.44 (d, 8.1)	7.45 (dd, 8.2, 1.4)	7.43 (d, 8.1)	7.43 (d, 8.2)	7.43 (d, 8.1)
7′	9.85 (s)	9.83 (s)	9.86 (s)	9.84 (s)	9.84 (s)	9.85 (s)	9.85 (s)
7-OMe							3.14 (s, 3H)
3′-OMe	3.92 (s, 3H)	3.90 (s, 3H)	3.92 (s, 3H)	3.91 (s, 3H)	3.92 (s, 3H)	3.93 (s, 3H)	3.94 (s, 3H)
No.	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1	4.73 (d, 6.4, 2H)	4.24 (t, 6.6, 2H)	4.66 (d, 6.3, 2H)	4.62 (d, 6.2, 2H)	4.59 (d, 6.4, 2H)	4.60 (d, 6.0, 2H)	4.58 (d, 6.4, 2H)
2	5.66 (t, 6.4)	3.09 (t, 6.6, 2H)	5.62 (m)	5.59 (t, 6.2)	5.54 (t, 6.4)	5.51 (t, 6.0)	5.50 (t, 6.4)
4	a 2.29 (dd, 13.6, 8.3) b 2.22 (dd, 13.6, 4.6)	6.14 (s)	3.11 (s, 2H)	a 2.25 (dd, 13.5, 8.4) b 2.19 (dd, 13.5, 4.2)	2.74 (d, 5.8, 2H)	2.06 (t, 6.6, 2H)	2.06 (m, 2H)[a]
5	4.51 (ddd, 8.3, 8.3, 4.6)			4.48 (m)	5.61 (m)[a]	2.11 (brt, 6.6, 2H)	2.10 (m, 2H)[a]
6	5.16 (d, 8.3)	6.06 (s)	2.30 (d, 6.9, 2H)	5.16 (d, 8.4)	5.62 (m)[a]	5.08 (t, 6.1)	5.08 (t, 6.2)
7			2.12 (m)				
8	1.71 (s, 3H)	1.89 (s, 3H)	0.90 (d, 6.6, 3H)	1.71 (s, 3H)	1.31 (s, 3H)	1.67 (s, 3H)	1.67 (s, 3H)
9	1.69 (s, 3H)	2.16 (s, 3H)	0.90 (d, 6.6, 3H)	1.68 (s, 3H)	1.31 (s, 3H)	1.60 (s, 3H)	1.59 (s, 3H)
10	1.81 (s, 3H)	2.03 (s, 3H)	1.74 (s, 3H)	1.76 (s, 3H)	1.70 (s, 3H)	1.72 (s, 3H)	1.71 (s, 3H)
2′	7.41 (s)	6.98 (m)[a]	6.99 (d, 1.3)	6.88 (s)	6.88 (s)	6.70 (s)	6.70 (s)
5′	6.97 (d, 8.1)	6.98 (m)[a]	6.85 (d, 8.2)	6.79 (d, 8.1)	6.79 (d, 8.1)	6.83 (d, 8.1)	6.79 (d, 8.2)
6′	7.43 (d, 8.1)	6.98 (m)[a]	6.96 (dd, 8.2, 1.3)	6.82 (d, 8.1)	6.82 (d, 8.1)	6.72 (d, 8.1)	6.68 (d, 8.2)
7′	9.85 (s)	5.31 (s)	5.32 (s)	6.33 (d, 15.7)	6.33 (d, 15.7)	3.62 (s, 2H)	2.74 (t, 7.3, 2H)
8′				6.10 (m)	6.10 (m)		2.84 (t, 7.3, 2H)
9′				1.86 (d, 6.4, 3H)	1.86 (d, 6.4, 3H)	2.15 (s, 3H)	
10′							2.14 (s, 3H)
3′-OMe	3.93 (s, 3H)	3.86 (s, 3H)	3.88 (s, 3H)	3.87 (s, 3H)	3.87 (s, 3H)	3.85 (s, 3H)	3.85 (s, 3H)
7′-OMe		3.32 (s, 3H × 2)	3.33 (s, 3H × 2)				

2H), δ_C 53.7, CH_2-6], one additional methine [δ_H 2.13 (m), δ_C 25.2, CH-7] and two secondary methyls [δ_H 0.92 (d, *J* = 6.6 Hz, Me × 2), δ_C 22.8 (2C), Me-8, 9] at **3** and the absence of two allylic methyls and one double bond at **1**, which confirmed that the Δ^6 double bond was hydrogenated. Accordingly, the chemical shift of ketone carbonyl C-5 (δ_C 201.2) at **3** down-field shifted Δδ 9.8 ppm as compared with that of **1**. The planar structure of **3** was further determined by the detailed analysis of 2D NMR spectral data (Fig. 2).

Compound **4** had the same molecular formula and planar structure as **3** by the HR-ESI-MS data and detailed analysis of 2D NMR spectral data (Fig. S1). Same as **1** and **2**, the dir-

Table 2 ^{13}C NMR data of **1**–**8** and **11**–**13** in $CDCl_3$ at 150 MHz (δ in ppm)

No.	1	2	3	4	5	6	7	8	11	12	13
1	67.2	68.2	67.0	68.1	65.8	66.1	66.2	65.9	65.9	66.1	66.1
2	40.3	33.7	40.2	33.8	123.9	119.7	119.8	122.3	123.6	120.9	120.0
3	152.2	154.4	152.7	155.0	135.3	140.5	140.7	138.6	137.3	139.4	140.7
4	127.9	127.8	125.8	125.8	54.0	42.4	42.7	47.9	48.0	42.4	39.7
5	191.4	190.8	201.2	200.8	208.2	124.1	127.1	66.6	66.4	124.4	26.4
6	126.2	126.0	53.7	53.5	51.3	140.7	138.0	127.5	127.5	140.2	124.0
7	155.4	155.5	25.2	25.2	24.6	70.8	74.9	135.6	135.3	70.8	131.9
8	28.0	27.9	22.8	22.8	22.6	30.0	26.0	25.9	25.9	29.9	25.8
9	20.8	20.8	22.8	22.8	22.6	30.0	26.0	18.4	18.3	29.9	17.9
10	19.6	27.2	19.6	27.1	17.4	16.9	16.9	17.3	17.1	16.8	16.8
1′	130.5	130.0	130.5	130.1	130.3	130.2	130.2	130.2	131.6	131.5	126.9
2′	109.7	109.2	109.7	109.1	109.3	109.3	109.3	109.4	109.0	108.9	112.7
3′	150.1	149.9	150.1	149.9	150.1	150.1	150.1	150.1	149.7	149.6	149.8
4′	153.8	154.1	153.7	154.0	153.7	154.0	153.9	153.8	147.3	147.4	147.6
5′	111.9	111.8	111.9	111.7	111.9	111.9	111.9	111.9	113.8	113.5	113.6
6′	126.8	127.2	126.7	127.3	126.8	126.8	126.8	126.8	118.7	118.6	121.6
7′	191.0	191.1	191.0	191.1	191.0	191.1	191.0	191.0	130.7	130.7	50.8
8′									124.0	123.9	207.1
9′									18.5	18.5	29.2
7-OMe							50.4				
3′-OMe	56.2	56.1	56.2	56.1	56.2	56.2	56.2	56.2	55.9	55.9	56.1

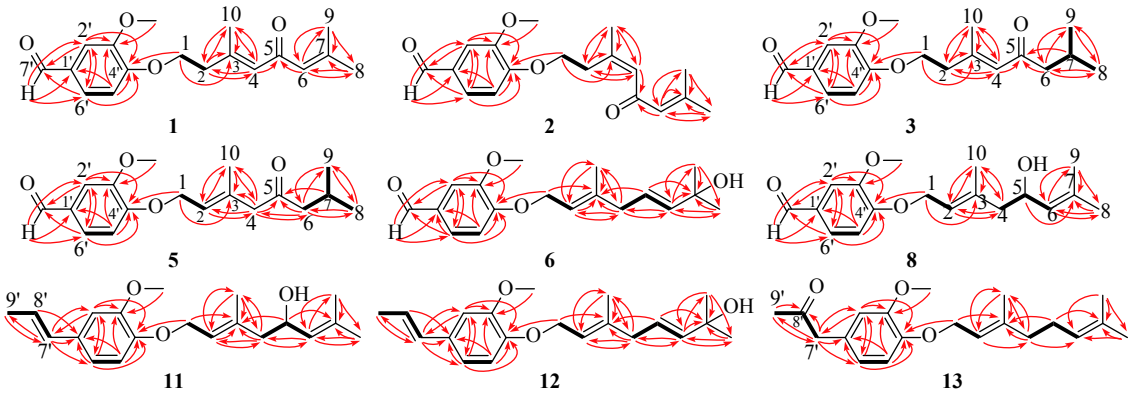

Fig. 2 ^{1}H–^{1}H COSY (—) and HMBC (→) correlations of selected compounds

ect comparison of the NMR data of **3** and **4** [CH_2-2: for **3**, δ_H 2.69 (t, J = 6.8 Hz), δ_C 40.2; for **4**, δ_H 3.07 (t, J = 6.7 Hz), δ_C 33.8 and Me-10: for **3**, δ_H 2.21 (s), δ_C 19.6; for **4**, δ_H 2.04 (s), δ_C 27.1] (Tables 1 and 2) assigned their structural differences as the *Z* (**3**) and *E* (**4**) geometry of the Δ^3 double bond. Consequently, the structures of **3** and **4** were established and named as illimicranins C and D, respectively.

Compound **5** was assigned the same molecular formula $C_{18}H_{24}O_4$ as **3** by the HR-ESI-MS ion peak at *m/z* 327.1569 $[M + Na]^+$ (Calcd. for $C_{18}H_{24}NaO_4$, 327.1567). The ^{1}H NMR data (Table 1) revealed that **5** had the same characteristic signals for one 1,3,4-trisubstituted aromatic ring, four methyls, three methylenes and three methines (including one aldehydic and one olefinic) as **3**, with different chemical shifts for the allylic methyl (Me-10), two methylenes (including the oxygenated one CH_2-1) and the olefinic methine, suggesting the migration of Δ^3 double bond at **3** to Δ^2 at **5.** The results were confirmed by the ^{1}H–^{1}H COSY correlation of H_2-

1/H-2 and the HMBC correlations of Me-10/C-2, C-3 and C-4, H_2-1 and H_2-4/C-3, and H-2/C-4. Its planar structure was further determined by detailed analysis of 2D NMR spectral data (Fig. 2). The *E*-geometry of the Δ^2 double bond was assigned by directly comparing the NMR data of **5** and micranthumnins A–C, F and G [30], methyl 4-[[(2*E*)-3,7-dimethyl-5-oxo-2,6-octadienyl]oxy]-3-methoxybenzoate and methyl 4-[[(2*E*)-3,7-dimethyl-5-oxo-2,6-octadienyl]oxy]-3-hydroxybenzoate [31]. **5** was then established and named as illimicranin E.

Compound **6** possessed the molecular formula $C_{18}H_{24}O_4$ by its HR-ESI-MS data. The planar structure of **6** was characterized by detailed analysis of 2D NMR spectral data (Fig. 2). Two spin systems were directly determined by the $^1H-^1H$ COSY correlations of H_2-1/H-2, H_2-4/H-5 and H-5/H-6, and then connected through C-3 by the HMBC correlations of H_2-1, H-2, H_2-4 and H-5/C-3, H-2/C-4 and H-4/C-2. The allylic methyl [δ_H 1.74 (s)] was linked with C-3 by the HMBC correlations from Me-10 to C-2, C-3 and C-4. One oxygenated isopropyl group was connected to C-6 by the HMBC correlations from Me-8 and Me-9 to C-6 and C-7 (δ_C 70.8), and from H-5 and H-6 to C-7. The vanillin moiety was assigned and connected to C-1 through the ether bond as compounds **1**–**5** by the HMBC correlations of H_2-1/C-4′, H-7′/C-1′, C-2′ and C-6′, H-2′ and H-6′/C-7′, and -OMe/C-3′. The 2*E* geometry was directly assigned by comparing the NMR data of **6** with **5**. Therefore, the structure of **6** was determined and named as illimicranin F.

Compounds **7** had the molecular formula $C_{19}H_{26}O_4$ by the HR-ESI-MS *m/z* 341.1722 $[M + Na]^+$ (Calcd. for $C_{19}H_{26}NaO_4$, 341.1723) with 14 mass units more than that of **6**. The NMR data of **7** (Tables 1 and 2) clearly showed the presence of one additional methoxy group [δ_H 3.14 (s), δ_C 50.4] than **6**, which was assigned as 7-OMe by the HMBC correlation of 7-OMe/C-7 (δ_C 74.9). The structure of **7** was further confirmed by the NMR spectral analyses (Tables 1 and 2, Fig. S2) and named as illimicranin G.

In addition to the isolation of **6** as a pure compound, a mixture containing compounds **6** and **8** in a ratio of 1 ∶ 2 as measured by ^1H NMR were also obtained. Compound **8** had the same molecular formula $C_{18}H_{24}O_4$ as **6** by the HR-ESI-MS data. The comprehensive analyses for the NMR data of the mixture showed that **8** differed from **6** mainly due to the presence of one additional oxygenated methine [δ_H 4.51 (ddd, *J* = 8.3, 8.3, 4.6 Hz), δ_C 66.6, CH-5], two more allylic methyls [δ_H 1.71 (s), Me-8; 1.69 (s), Me-9], one less olefinic methine and two less high-field tertiary methyls at **8** than **6** (Tables 1 and 2), implying the migration of 7-OH and Δ5 double bond at **6** to 5-OH and Δ^6 double bond at **8**. The results were confirmed by the $^1H-^1H$ COSY correlations of H_2-4/H-5 and H-5/H-6, and the HMBC correlations from Me-8 and Me-9 to C-6 and C-7, and from H-5 to C-7 (δ_C 135.6). Similarly, the 2*E* geometry was assigned by comparing the NMR data of **8** with **5**–**7**. Thus, the structure of **8** was established and named as illimicranin H. Unfortunately, the stereochemistry of C-5 was not elucidated currently due to the small amount of the mixture .

Comparing with the ^1H NMR data of **2** and **5**, compounds **9** and **10** (Table 1) clearly showed major difference due to the presence of one additional methine and two more methoxy groups at **9** and **10** and the absence of the aldehydic methine at **2** and **5**, respectively, suggesting that **9** and **10** were the aldehyde dimethyl acetal derivatives of **2** and **5**, respectively. Unfortunately, the ^{13}C and 2D NMR data of **9** and **10** were not successfully obtained as they were not stable and changed to **2** and **5** quickly. But still, their structures were assigned by comparing previous data for aldehyde dimethyl acetal moiety [33]. Accordingly, the chemical shifts of aromatic methines H-2′ and H-6′ of **9** and **10** up-field shifted Δδ 0.45 ppm as compared with those of **2** and **5**, respectively, due to the absence of conjugated formyl group. **9** and **10** might be the artificial products of **2** and **5** formed in methanol, and were named as illimicranin B dimethyl acetal and illimicranin E dimethyl acetal, respectively.

Compounds **11** and **12**, also obtained as a mixture in a ratio of 3 ∶ 2, possessed the same molecular formula $C_{20}H_{28}O_3$ by the HR-ESI-MS data. Comparing with the ^1H NMR data (Tables 1 and 2) of the mixture of **8** and **6**, the mixture of **11** and **12** showed obvious differences due to the presence of one additional allylic Me-9′ and two more olefinic methines as *E*-geometry double bond at **11** and **12** and the absence of the aldehydic methine at **8** and **6**, respectively, suggesting that **11** and **12** had one propenyl group replacing the formyl group at **8** and **6**, which was confirmed by the $^1H-^1H$ COSY correlations of H-7′/H-8′ and H-8′/Me-9′, and the HMBC correlations of H-8′/C-1′, and H-7′/C-1′, C-2′ and C-6′. Their structures were further confirmed as geranyl isoeugenol ethers by comprehensive analysis of the 2D NMR data (Fig. 2) and named as illimicranins I and J. Similarly, the stereochemistry of C-5 at **11** was not currently determined because of the small amout of the mixture.

Compound **13** was assigned the molecular formula $C_{20}H_{28}O_3$ by the HR-ESI-MS *m/z* 339.1930 $[M + Na]^+$ (Calcd. for $C_{20}H_{28}NaO_3$, 339.1931). Direct comparison of the NMR data of **13**, methyl 4-[(2*E*)-3,7-dimethyl-2,6-octadienyl)oxy]-3-methoxybenzoate [31] and methyl 4-[[(2*E*)-3,7-dimethyl-2,6-octadienyl]oxy]-3-hydroxybenzoate [32] clearly showed that they possessed the same geranyl moiety (Tables 1 and 2). In addition, the ^1H NMR of **13** showed the presence of one 1,3,4-trisubstituted aromatic ring, one methoxy, one methyl and one methylene, while the ^{13}C NMR disclosed one ketone carbonyl carbon (δ_C 207.1, C-8′). Thus, one vanillyl methyl ketone moiety was established by the HMBC correlations of Me-9′ and H_2-7′/C-8′, H_2-7′/C-1′, C-2′ and C-6′, and OMe/C-3′. Then the geranyl and vanillyl methyl ketone moieties were connected through the ether bond by the chemical shifts of C-1 and C-4′, and the HMBC correlations of H_2-1/C-4′. Thus, the structure of **13** was determined as a geranyl guaiacylacetone ether and name as illimicranin K.

Compound **14** had the molecular formula $C_{21}H_{30}O_3$ by

the HR-ESI-MS *m/z* 353.2086 $[M + Na]^+$ (Calcd. for $C_{21}H_{30}NaO_3$, 353.2087) with 14 mass unit more than that of **13**. The ^1H NMR revealed **14** and **13** with the same geranyl moiety and only difference in 1,3,4-trisubstituted aromatic ring moiety as two coupling methylenes [δ_H 2.84 (t, J = 7.3 Hz, H_2-8′) and 2.74 (t, J = 7.3 Hz, H_2-7′)] at **14** in place of one methylene at **13**. Although the ^{13}C and 2D NMR data of **14** were not currently measured due to its poor quantity of 0.2 mg, the structure of **14** was still determined as geranyl zingerone ether by comparing the reference data for zingerone moiety [34] and named as illimicranin L.

Three known compounds (**15**–**17**) were identified according to their spectroscopic data [7, 35-36]. Interestingly, micranthumnin F (**15**) [7] was considered as a complex structure formed by vanillin (**16**) [35] and 8-hydroxy-2,6-dimethyl-2,6-octadien-4-one (**17**) [36].

Eight pure isolates (**1**–**6**, **15** and **16**) with enough amounts were evaluated for anti-HBV activity on HepG2.2.15 cell line which can stably support HBsAg and HBeAg secretion, and HBV DNA replication [37]. First, the cytotoxicities of the tested compounds were determined through assessing the viability of HepG2.2.15 cells by MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide] assay in the presence of 0–200 μmol·L^{-1} concentrations. The results revealed that all the tested compounds displayed no significant cytotoxicity with the 50% cytotoxic concentrations (CC_{50}) value higher than 100 μmol·L^{-1}. Then, they were evaluated for the inhibitory effects against the secretion of HBsAg and HBeAg on HepG2.2.15 cells at concentrations of 0.39, 0.78, 1.56, 3.13, 6.25 and 12.5 μmol·L^{-1}. Amongst, compounds **1**, **2** and **15** inhibited HBsAg secretion with IC_{50} values of 6.32, 1.60 and 3.11 μmol·L^{-1}, respectively and HBeAg secretion with IC_{50} values of 15.90, 13.82 and 1.36 μmol·L^{-1}, respectively. Furthermore, to evaluate the inhibitory effects of **1**, **2** and **15** on HBV replication, HepG2.2.15 cells were treated with the above compounds at the same concentrations of 0.39–12.5 μmol·L^{-1} for 7 days with 25 nmol·L^{-1} ETV as a control. HBV DNA in the supernatants and cells were measured by real-time q-PCR. The results showed that compounds **1** and **15** strongly inhibited HBV DNA replication with IC_{50} values of 0.31 and 0.38 μmol·L^{-1}, respectively, while **2** displayed weaker inhibitory effect with an IC_{50} value > 25 μmol·L^{-1}. Therefore, the preliminary structure-activity relationship study revealed that the α,β-unsaturated ketone group (C5–C7 units) is necessary for their anti-HBV activity.

In summary, fourteen new (**1**–**14**) and one known (**15**) geranyl phenyl ethers were obtained from *I. micranthum*. Amongst, the geranyl moiety displayed as geranyl with or without a carbonyl at C-5 and various double bond arrangements, and the phenyl moiety showed as vanillin, isoeugenol, guaiacylacetone or zingerone. Both geranyl or its derivatives and those phenyl compounds, such as **16** and **17**, were widely distributed in plant resources, while their complexes were rare. To the best of our knowledge, there have been only two geranyl vanillin ethers reported, including **15** from the same plant as this study [30] and *O*-geranylvanillin from *Crithmum maritimum* [38] . As for the geranyl isoeugenol ethers, micranthumnin G obtained from the same plant as this study [30] and 2-methoxy-4-propenyl-1-(3,7,11-trimethyldodeca-2,6,10-trienyloxy) benzene as a synthesized compound [39] were the only two ones reported before. Moreover, illimicranins K and L (**13** and **14**) represented the first example of geranyl guaiacylacetone ether and geranyl zingerone ether, respectively. It' s worthy to note that geranyl phenyl ethers were discovered only from *I. micranthum* in the current and earlier [30] studies until now as for the *Illicium* genus. Moreover, two new (**1** and **2**) and one known isolates (**15**) showed good anti-HBV activity.

Experimental

General experimental procedures

IR spectra were measured on a Bruker TENSOR 27 spectrometer with KBr disks. UV spectra were obtained on an Agilent Cary60 spectrophotometer. Optical rotation values were measured by a Rudolph Autopol I automatic polarimeter. HR-ESI-MS spectra were obtained on a Bruker SolariX 7.0 T instrument. NMR spectra were performed on an Agilent DD2 600 MHz instrument. Semi-preparative HPLC was performed on a Waters 1525 pump equipped with a Waters 2489 detector and an YMC-pack ODS-A column (10 mm × 250 mm, 5 μm, 12 nm). Silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd.), MCI gel (CHP20P, 75–150 μm, Mitsubishi Chemical Industries Ltd.) and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for column chromatography (CC). Silica gel 60 GF_{254} plates (Qingdao Haiyang Chemical Co., Ltd.) were used for thin-layer chromatography (TLC). All solvents used were bought from Chengdu Chron Chemicals Co., Ltd..

Plant material

The leaves and twigs of *I. micranthum* were collected in August 2017 from Xishuangbanna Tropical Botanical Garden, Yunnan Province, China, and authenticated by Prof. XU You-Kai of Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences. A voucher specimen has been deposited at School of Pharmaceutical Sciences, Chongqing University (Accession number CRZ2017IMD).

Extraction and isolation

The air-dried leaves and twigs (6.5 kg) of *I. micranthum* were powdered and extracted with 95% ethanol (3 × 25 L, 3 d each time) at room temperature. After evaporation of solvent under reduced pressures, a crude extract (546.2 g) was suspended in distilled water (1.5 L) and sequentially partitioned with petroleum ether (PE), EtOAc and *n*-BuOH (each 4 × 1.0 L). The PE and EtOAc partitions were merged based on TLC profiles and the combination (111.8 g) was then applied to a MCI gel chromatography column (CC), eluted with MeOH/H_2O in gradient (7 ∶ 3, 8 ∶ 2, 9 ∶ 1, 10 ∶ 0, each 1 L, *V*/*V*), to afford three fractions (Fr. 1–Fr. 3). Fr. 1 (15.2 g) was fractionated by a silica gel CC eluted with PE/EtOAc (20 ∶ 1,

10 ∶ 1, 5 ∶ 1, 3 ∶ 1, 2 ∶ 1 and 1 ∶ 1, *V*/*V*) to get six fractions (Fr. 1A–Fr. 1F). Fr. 1B (1.5 g) was separated by a silica gel CC eluted with PE/acetone (20 ∶ 1, 10 ∶ 1, 5 ∶ 1, 3 ∶ 1, each 1 L, *V*/*V*) to provide five fractions (Fr. 1B1–Fr. 1B5). Fr. 1B2 was purified by semi-preparative HPLC with MeCN/H_2O (70 ∶ 30 to 100 ∶ 0, *V*/*V*) to yield **9** (5 mg, t_R 20.0 min) and **2** (8.8 mg, t_R 22.0 min). Fr. 1B3 was purified by Sephadex LH-20 with CH_2Cl_2/MeOH (1 ∶ 1, *V*/*V*) followed by semi-preparative HPLC with MeCN/H_2O (60 ∶ 40 to 80 ∶ 20, *V*/*V*) to obtain **1** (12.8 mg, t_R 25.0 min), **7** (1.7 mg, t_R 26.0 min) and **3** (3.8 mg, t_R 40.0 min). Fr. 1B4 was purified by semi-preparative HPLC with MeCN/H_2O (50 ∶ 50 to 90 ∶ 10, *V*/*V*) to give **4** (8.1 mg, t_R 34.0 min), **13** (1.4 mg, t_R 45.0 min) and **14** (0.4 mg, t_R 48.0 min). Fr. 1B5 was separated by a silica gel CC eluted with PE/acetone (20 ∶ 1, 15 ∶ 1, 10 ∶ 1, each 500 mL, *V*/*V*) to get **16** (15.0 mg). Fr. 1C (2.1 g) was separated by a silica gel CC with PE/acetone (20 ∶ 1, 10 ∶ 1, 5 ∶ 1, 3 ∶ 1, each 1 L, *V*/*V*) to get five fractions (Fr.1 C1–Fr. 1C5). Fr. 1C.3 was purified by Sephadex LH-20 with CH_2Cl_2/MeOH (1 ∶ 1, *V*/*V*) followed by semi-preparative HPLC with MeOH/H_2O (50 ∶ 50 to 90 ∶ 10, *V*/*V*) to afford **10** (0.8 mg, t_R 27.0 min), **15** (31.9 mg, t_R 39.0 min) and **5** (13.7 mg, t_R 42.0 min). Fr. 1C4 was purified by semi-preparative HPLC with MeCN/H_2O (60 ∶ 40 to 90 ∶ 10, *V*/*V*) to give a mixture of **11** and **12** (10.5 mg, t_R 45.0 min). Fr. 1D (2.4 g) was separated by a silica gel CC eluted with PE/acetone (10 ∶ 1, 5 ∶ 1, 3 ∶ 1, 2 ∶ 1, 1 ∶ 1, each 1 L, *V*/*V*) to afford five fractions (Fr. 1D1–Fr. 1D5). Fr. 1D5 was purified by Sephadex LH-20 with CH_2Cl_2/MeOH (1 ∶ 1, *V*/*V*) followed by semi-preparative HPLC with MeCN/H_2O (30 ∶ 70 to 70 ∶ 30, *V*/*V*) to obtain **17** (1.1 mg, t_R 11.0 min) and **6** (8.0 mg, t_R 35.0 min). Similarly, Fr. 1E (1.3 g) was separated by a silica gel CC eluted with PE/acetone (10 ∶ 1, 6 ∶ 1, 5 ∶ 1, 4 ∶ 1, 2 ∶ 1 to 1 ∶ 1, each 1 L, *V*/*V*) followed by semi-preparative HPLC with MeCN/H_2O (40 ∶ 60 to 90 ∶ 10, *V*/*V*) to afford a mixture of **6** and **8** (0.8 mg, t_R 27.0 min).

Illimicranin A (1) Colorless oil; $[\alpha]_D^{20}$ +3.5 (*c* 0.48, MeOH); UV (MeOH) λ_{max} (log ε) 231 (4.15), 271 (4.35) nm; IR (KBr) ν_{max} 2926, 2852, 2727, 1688, 1593, 1511, 1462, 1390, 1343, 1271, 1129, 1031, 870, 812, 775, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 325.1410 $[M + Na]^+$ (Calcd. for $C_{18}H_{22}NaO_4$, 325.1410).

Illimicranin B (2) Colorless oil; $[\alpha]_D^{24}$ −3.1 (*c* 0.49, MeOH); UV (MeOH) λ_{max} (log ε) 271 (4.33), 231 (4.16) nm; IR (KBr) ν_{max} 2928, 2852, 2725, 1686, 1627, 1594, 1511, 1459, 1388, 1343, 1271, 1128, 1128, 1031, 871, 813, 772, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 325.1410 $[M + Na]^+$ (Calcd. for $C_{18}H_{22}NaO_4$, 325.1410).

Illimicranin C (3) Colorless oil; $[\alpha]_D^{23}$ +2.7 (*c* 0.23, MeOH); UV (MeOH) λ_{max} (log ε) 308 (3.55), 271 (3.65), 231 (3.97) nm; IR (KBr) ν_{max} 2925, 2858, 2726, 1688, 1592, 1511, 1464, 1425, 1395, 1271, 1197, 1133, 1032, 866, 810, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 327.1565 $[M + Na]^+$ (Calcd. for $C_{18}H_{24}NaO_4$, 327.1567).

Illimicranin D (4) Colorless oil; $[\alpha]_D^{23}$ −1.6 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 308 (3.85), 275 (3.94), 229 (4.26) nm; IR (KBr) ν_{max} 2926, 2859, 1686, 1592, 1512, 1463, 1427, 1391, 1342, 1271, 1134, 1032, 865, 812, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 327.1566 $[M + Na]^+$ (Calcd. for $C_{18}H_{24}NaO_4$, 327.1567), 303.161 $[M - H]^-$ (Calcd. for $C_{18}H_{23}O_4$, 303.160).

Illimicranin E (5) Colorless oil; $[\alpha]_D^{24}$ −2.2 (*c* 0.56, MeOH); UV (MeOH) λ_{max} (log ε) 308 (3.92), 275 (4.00), 229 (4.15) nm; IR (KBr) ν_{max} 2957, 2869, 2727, 1686, 1591, 1509, 1462, 1422, 1395, 1341, 1269, 1133, 1063, 993, 866, 811, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 327.1569 $[M + Na]^+$ (Calcd. for $C_{18}H_{22}NaO_4$, 327.1567).

Illimicranin F (6) Colorless oil; $[\alpha]_D^{20}$−2.4 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 259 (4.98), 228 (5.39) nm; IR (KBr) ν_{max} 3361, 2925, 2855, 1683, 1590, 1509, 1462, 1425, 1390, 1346, 1268, 1133, 1030, 981, 809, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 327.1565 $[M + Na]^+$ (calcd for $C_{18}H_{24}NaO_4$, 327.1567).

Illimicranin G (7) Colorless oil; $[\alpha]_D^{24}$ −1.9 (*c* 0.09, MeOH); UV (MeOH) λ_{max} (log ε) 308 (4.13), 275 (3.21), 226 (5.35) nm; IR (KBr) ν_{max} 2924, 2854, 1732, 1661, 1634, 1592, 1509, 1463, 1422, 1267, 1133, 1077, 1030, 807, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 341.1722 $[M + Na]^+$ (Calcd. for $C_{19}H_{26}NaO_4$, 341.1723).

Mixture of illimicranins F (6) and H (8) Colorless oil; $[\alpha]_D^{30}$ −11.6 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 308 (4.28), 275 (4.35), 231 (4.48) nm; IR (KBr) ν_{max} 3362, 2924, 2854, 2729, 1682, 1635, 1590, 1510, 1463, 1452, 1392, 1342, 1267, 1196, 1133, 1031, 982, 866, 810, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 327.1555 $[M + Na]^+$ (Calcd. for $C_{18}H_{24}NaO_4$, 327.1567).

Illimicranin B dimethyl acetal (9) Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) see Table 1.

Illimicranin E dimethyl acetal (10) Colorless oil; $[\alpha]_D^{25}$ −5.4 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 275 (4.02), 228 (4.66) nm; IR (KBr) ν_{max} 2925, 2858, 1711, 1593, 1511, 1462, 1418, 1363, 1267, 1134, 1104, 1052, 998, 863, 805, 729 cm^{-1}; ^{1} H NMR ($CDCl_3$, 600 MHz) see Table 1; HRESIMS *m*/*z* 373.1984 $[M + Na]^+$ (Calcd. for $C_{20}H_{30}NaO_5$, 373.1986).

Mixture of illimicranins I and J (11 and 12) Colorless oil; $[\alpha]_D^{23}$ +53.8 (*c* 0.54, MeOH); UV (MeOH) λ_{max} (log ε) 259 (4.10), 204 (4.39) nm; IR (KBr) ν_{max} 3440, 2926, 1671, 1592, 1511, 1459, 1418, 1381, 1336, 1260, 1224, 1136, 968, 919, 855, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 339.1930 $[M + Na]^+$ (Calcd. for $C_{20}H_{28}NaO_3$, 339.1931),

315.1973 $[M-H]^-$ (Calcd. for $C_{20}H_{27}O_3$, 315.1966).

Illimicranin K (13) Colorless oil; $[\alpha]_D^{25}$ −5.8 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 279 (4.89), 231 (4.16) nm; IR (KBr) ν_{max} 2924, 2855, 1714, 1663, 1592, 1511, 1422, 1461, 1378, 1265, 1228, 1134, 1032, 807 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) see Table 1 and ^{13}C NMR ($CDCl_3$, 150 MHz) data see Table 2; HR-ESI-MS *m*/*z* 339.1930 $[M+Na]^+$ (Calcd. for $C_{20}H_{28}NaO_3$, 339.1931).

Illimicranin L (14) Colorless oil; $[\alpha]_D^{25}$ −6.7 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 275 (4.09), 228 (4.52) nm; IR (KBr) ν_{max} 2924, 2855, 1719, 1660, 1511, 1462, 1371, 1262, 1099, 1033, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) see Table 1; HR-ESI-MS *m*/*z* 353.2086 $[M+Na]^+$ (Calcd. for $C_{21}H_{30}NaO_3$, 353.2087).

Anti-hepatitis B virus activity

The selected isolates were measured for anti-hepatitis B virus activity on HepG2.2.15 cell line according to our previous report [37]. Each sample was tested in triplicate.

Supplementary Material

Supplementray information can be acquired by e-mail to corresponding author.

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