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Original Article

Chemical Constituents of *Caesalpinia bonduc*

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Abstract: This phytochemical investigation of *Caesalpinia bonduc* reported eight known compounds, namely *threo*-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-methoxy-propanol **(1)**, evofolin-B **(2)**, *trans*-Linalool-3,6-oxide-*β*-*D*-glucopyranoside **(3)**, 1-(2-methylbutyryl)phloroglucinol-glucopyranoside **(4)**, 1-(3-methylbutyryl)phloroglucinol-glucopyranoside **(5)**, (+)-isolariciresinol **(6)**, protocatechuic acid **(7)**, methyl gallate **(8)**. The structures of these compounds were identified by 1D- and 2D- nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) and by comparison with those reported in the literature. Compound **2** exhibited significant cytotoxic effects against the HepG2 cell line with an IC_{50} value of 48.37±3.18 μM.

Keywords: Caesalpinia bonduc, cytotoxic, HepG2 inhibitory.

1. Introduction

Caesalpinia is known as a genus of woody plants belonging to the Leguminosae family which were widely cultivated around tropical and subtropical areas of South East Asia with over 500 species [1-3]. Some species of *Caesalpinia* genus such as *C. bonduc*, *C. sappan* have been commonly used in traditional medicine for a long time as functional food, supporting the prevention of some diseases such as rheumatism, back pain, antipyretic around the world [1, 4, 5]. Previous studies showed that the chemical constituents of the *Caesalpinia* genus contained a diversity of secondary metabolites such as lignans, flavonoids, and terpenes [3, 6, 7]. They have a variety of characteristic biological activities like anti-inflammatory, anti-oxidant, anti-bacterial, and anti-diabetes [3, 4, 6-8]. In Vietnam, there have been only a few phytochemical investigations of *C. bonduc* [1]. As a continuation of our work on the bioactive constituents from *Caesalpinia* species, eight compounds (**1**–**8**) were isolated from the air-dried leaves of *C. bonduc*, collected from Vinh Phuc province of Vietnam. The cytotoxic activity of eight compounds (**1**–**8**) was screened on HepG2 human cancerous cells using the sulforhodamine B colorimetric assay.

2. Methodology

2.1. Plant Materials

The dried leaves of *Caesalpinia bonduc* were collected in Vinh Phuc, Vietnam, in November 2019 and were identified by

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Dr. Nguyen The Cuong at the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology (VAST). A voucher specimen (CB1-19) was deposited at the Lab of Pharmaceutical Chemistry, VNU University of Science, Hanoi.

2.2. General Experimental Procedures

Bruker AM500 FT-NMR spectrometer and TMS were used as internal standards. Optical rotations were determined on a Jasco DIP-370 automatic polarimeter. Column chromatography (CC) was performed using a silica gel (Kieselgel 60, 70-230, and 230-400 mesh, Merck) or RP-18 resins (30-50 µm, Fuji Silysia Chemical Ltd.). Thin layer chromatography (TLC) was done using pre-coated silica gel 60 F_{254} (0.25 mm, Merck) and RP-18 F_{254S} plates (0.25 mm, Merck).

2.3. Extraction and Isolation

The dried powders of *C. bonduc* leaves (5.0 kg) were sonicated with 15 liters of methanol (MeOH) at 50˚C for 30 minutes and repeated three times to obtain the MeOH extract. After removal of the solvent, this crude extract was suspended in 2 liters of hot water and partitioned first with dichloromethane (CH_2Cl_2) and then with ethyl acetate (EtOAc) to give the corresponding dichloromethane (**CBD**, 120 g), ethyl acetate (**CBE**, 50.2 g) and water (**CBW**) extracts after evaporation at reduced pressure. The **CBD** was separated on a silica gel CC and eluted with *n*-hexane–acetone (40:1 – 0:1, v/v) to give five fractions **CBD1-5**. The fraction **CBD5** was performed separation on an RP-18 CC eluting with MeOH–water (1:1, v/v) to obtain three fractions and compound **6** (10 mg). Compound **2** (6 mg) was obtained from the **CBD5C** using an RP-18 CC eluting with acetone-water (1:1, v/v). The **CBE** residue was subjected to an RP-18 CC eluting with MeOH – water (1:1.8, v/v) to give three fractions **CBE1-3**. The fraction **CBE2** was chromatographed on an RP-18 column eluting with a solvent system of acetone–water (1:2, v/v) to obtain three fractions: **CBE2A**, **CBE2B**, and **CBE2C**. Compound **8** (7 mg) was obtained from the **CBE2C** fraction on a silica gel CC eluting with CH_2Cl_2–EtOAc (2:1, v/v). The fraction CBE2A was separated on a silica gel CC eluting with CH_2Cl_2–acetone (6:1, v/v) to yield compounds **1** (12 mg) and **7** (5 mg). An aqueous residue (**CBW**) was performed on diaion CC and eluted with a solvent system of MeOH–water (stepwise 25:75, 50:50, 75:25, 100:0) to give four fractions **CBW1-4**. The fraction **CBW1** was subjected to an RP-18 CC and eluted with MeOH–water (1:1.2, v/v) to yield compound **3** (5 mg). The fraction **CBW2** was chromatographed on an RP-18 column eluting with MeOH–water (1:1, v/v) to yield compounds **4** (10 mg) and **5** (11 mg).

threo-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-methoxy-propanol (1)

Brown oil; $[\alpha]_D^{25}$: 0° (*c* 0.1, MeOH)
ESI-MS: *m/z* 335.16 $[M+H]^+$, $C_{18}H_{22}O_6$
^{1}H- and ^{13}C-NMR (CD_3OD) see Table 1.

Evofolin-B (2)

Pale-yellow oil; $[\alpha]_D^{25}$: -10.2° (*c* 0.1, $CHCl_3$)
ESI-MS: *m/z* 319.08 $[M+H]^+$, $C_{17}H_{18}O_6$
^{1}H- and ^{13}C-NMR (CD_3OD) see Table 1.

***trans*-linalool-3,6-oxide-*β*-D-glucopyranoside (3)** White amorphous powder; $[\alpha]_D^{25}$: +5.6 (*c* 0.4, MeOH)
ESI-MS: *m/z* 333.09 $[M+H]^+$, $C_{16}H_{28}O_7$
^{1}H- and ^{13}C-NMR (CD_3OD) see Table 2.

1-(2-methylbutyryl)phloroglucinol-glucopyranoside (4)

White amorphous powder; $[\alpha]_D^{25}$: -52.4° (*c* 0.1, MeOH)
ESI-MS: $[M+H]^+$ at *m/z* 373.22, $C_{17}H_{24}O_9$
^{1}H- and ^{13}C-NMR (CD_3OD) see Table 2.

1-(3-methylbutyryl)phloroglucinol-glucopyranoside (5)

White amorphous powder; $[\alpha]_D^{25}$: -54.8 (*c* 0.1, MeOH)
ESI-MS: *m/z* 373.19 $[M+H]^+$, $C_{17}H_{24}O_9$.
^{1}H- and ^{13}C-NMR (CD_3OD) see Table 2.

(+)-isolariciresinol (6)

White crystalline; $[\alpha]_D^{25}$: -110° (*c* 0.31, MeOH)
molecular formula $C_{20}H_{24}O_6$;
^{1}H-NMR (500 MHz, CD_3OD): 6.70 (d, 1.5, H-2), 6.76 (d, 8.0, H-5), 6.65 (dd, 1.5, 8.0,

H-6), 3.71 (d, 8.5, H-7), 1.79 (m, H-8), 3.42 (dd, 4.0. 11.0, H-9) and 3.72 (dd, 5.0, 11.0, H-9), 6.68 (s, H-2'), 6.21 (s, H-5'), 2.79 (d, 7.5, H-7'), 2.02 (m, H-8'), 3.69 (m, H-9'), 3.80 and 3.82 (6H, s, OCH_3)

^{13}C-NMR (125 MHz, CD_3OD): 138.6 (C-1), 113.9 (C-2), 149.0 (C-3), 145.9 (C-4), 116.0 (C-5), 123.2 (C-6), 48.1 (C-7), 48.0 (C-8), 62.3 (C-9), 129.0 (C-1'), 112.4 (C-2'), 147.2 (C-3'), 145.3 (C-4'), 117.4 (C-5'), 134.2 (C-6'), 33.6 (C-7'), 40.0 (C-8'), 66.0 (C-9'), 56.3 (3-OCH_3), 56.4 (3'-OCH_3).

protocatechuic acid (7)

Yellowish-white powder

molecular formula $C_7H_6O_4$

^{1}H-NMR (500 MHz, CD_3OD): 7.48 (d, 2.0, H-2), 6.83 (d, 8.0, H-5), 7.46 (dd, 2.0, 8.0, H-6).

methyl gallate (8)

molecular formula $C_8H_8O_5$

^{1}H-NMR (500 MHz, CD_3OD): 7.06 (2H, s, H-3, H-7), 3.82 (3H, s, OCH_3).

^{13}C-NMR (125 MHz, CD_3OD): 169.0 (C-1), 121.4 (C-2), 110.1 (C-3, C-7), 146.5 (C-4, C-6), 139.6 (C-5), 52.2 (OCH_3)

3. Results and Discussion

3.1. Structure Elucidation

Compound **1** was obtained as a brown oil. The ^{1}H-NMR spectrum of compound **1** showed proton signals of two ABX spin systems of two tri-substituted benzene rings at [δ_H 6.52 (d, J = 2.0 Hz), 6.61 (d, J = 8.0 Hz), 6.56 (dd, J = 2.0, 8.0 Hz)], and [δ_H 6.47 (d, J = 2.0 Hz), 6.51 (dd, J = 2.0, 8.0 Hz)]; singlet proton signals of three methoxy groups at δ_H 3.71 (6H, s) and δ_H 3.22 (3H, s); one oxygenated methylene group at δ_H 3.92 (dd, J = 6.5, 11.0 Hz) and 4.07 (dd, 6.0, 11.0 Hz); and two methine groups at δ_H 3.10 (m) and 4.32 (dd, J = 8.5 Hz). The ^{13}C-NMR and HSQC spectra of **1** showed the signals of 18 carbons including twelve aromatic carbons at δ_C 112.0 to 148.5; three methoxy groups at δ_C 56.3 and 56.8; two methine carbons at δ_C 56.0 and 87.4; one methylene at δ_C 65.0. Analysis of ^{1}H- and ^{13}C-NMR data combined with the literature suggested that **1** was a neolignan and similar to those of 4,4'-((1*R*,2*R*)-3-hydroxy-1-methoxypropane-1,2-diyl)bis(2-methoxyphenol) (Table 1) [9]. These were further supported by HMBC correlations analysis of **1** as shown in *Fig.2*. The HMBC correlations between two protons of two methoxy groups at δ_H 3.71 and C-3, C-3' (δ_C 56.3) indicated the position of two methoxy groups at C-3 and C-3'. The HMBC correlations from H-2 (δ_H 6.52) to C-4 (δ_C 147.0)/C-6 (δ_C 121.6)/C-γ (δ_C 87.4); from H-6 (δ_H 6.56) to C-2 (δ_C 112.0)/C-4 (δ_C 147.0)/C-γ (δ_C 87.4); from H-5 (δ_H 6.61) to C-4 (δ_C 147.0), and from proton of the methoxy group at δ_H 3.22 to C-γ (δ_C 87.4) suggested the presence of a [4-hydroxy-3-methoxyphenyl] ring and one methoxy group at C-γ. Moreover, the optical rotation of **1** was 0° (*c* 0.1, MeOH). Thus, the structure of compound **1** was elucidated to be *threo*-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-methoxypropanol.

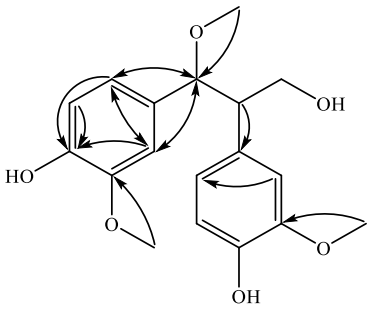

Figure 1. The key HMBC correlations of compound **1.**

Compound **2** was achieved as a pale-yellow oil. The ^{1}H-NMR spectrum of **2** revealed six protons of two ABX spin systems of the two aromatic rings and three protons directly bonded to sp^3 hybridized carbon atoms. The ^{13}C-NMR spectrum showed signals of 17 carbons consisting of one carbonyl, two methoxy groups, twelve olefinic carbons, one methylene, and one methine carbon. The ^{1}H- and ^{13}C-NMR data of compound **2** were very similar with **1** suggesting that **2** was also a neolignan. However, analysis of the ^{1}H-NMR spectroscopy indicated that one singlet proton

signal of a methoxy group at δ_H 3.22 in **1** was lost. Moreover, in the ^{13}C-NMR spectrum, there was no methoxy group at δ_C 56.8 (C-γ), instead of the appearance of carbonyl group at δ_C 199.7. These suggested that **2** had ketone at C-γ instead of the methoxy group as in **1**. Consequently, the structure of compound **2** was elucidated to be evofolin-B. These results match well with the literature [10].

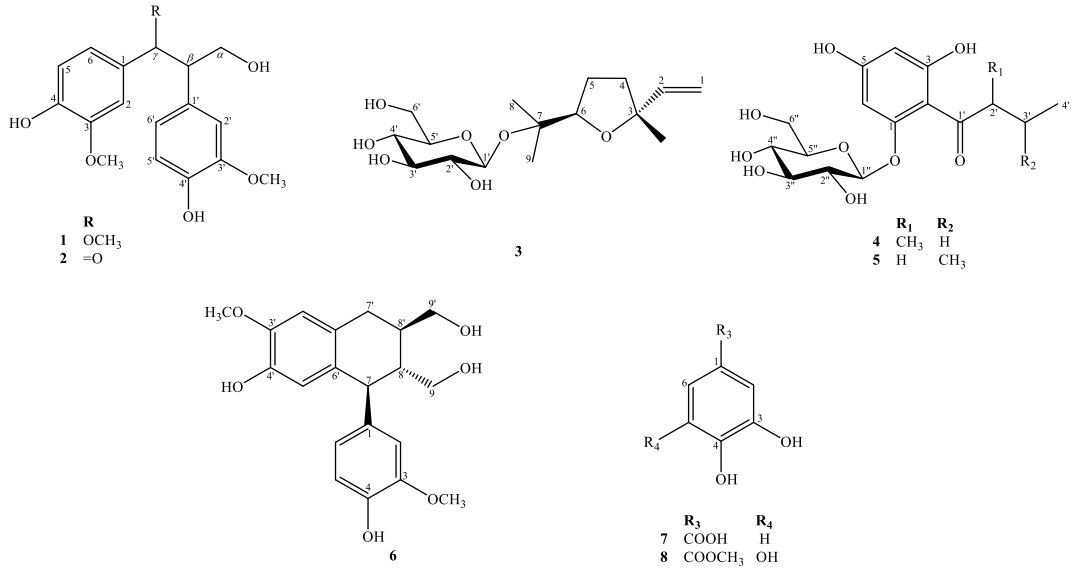

Figure 2. The chemical structures of compounds **1**-**8**.

Table 1. The ^{1}H- and ^{13}C-NMR data for compounds **1** and **2**

C	1			2		
	[#9]δ_C	[a,b]δ_C	[a,c]δ_H (mult., J = Hz)	[#10]δ_C	[a,b]δ_C	[a,c]δ_H (mult., J = Hz)
1	131.2	132.7	-	131.3	130.4	-
2	109.4	112.0	6.52 (d, 2.0)	112.3	112.8	7.58 (d, 2.0)
3	146.2	148.4	-	148.2	149.0	-
4	144.3	147.0	-	152.2	153.2	-
5	113.8	115.5	6.61 (d, 8.0)	115.3	115.7	6.82 (d, 8.0)
6	120.6	121.6	6.56 (dd, 2.0, 8.0)	124.5	125.1	7.63 (dd, 2.0, 8.0)
1'	131.8	132.7	-	129.9	129.9	-
2'	11.6	114.4	6.47 (d, 2.0)	112.3	112.7	6.91 (d, 2.0)
3'	146.3	148.5	-	148.5	149.3	-
4'	145.0	146.1	-	146.7	147.0	-
5'	114.2	115.7	6.61 (d, 8.0)	116.0	116.6	6.75 (d, 8.0)
6'	120.7	122.7	6.51 (dd, 2.0, 8.0)	121.9	122.2	6.78 (dd, 2.0. 8.0)
α	66.8	65.0	3.92 (dd, 6.5, 11.0) 4.07 (dd, 6.0, 11.0)	65.5	65.5	3.73 (dd, 5.0, 16.0) 4.77 (dd, 5.5, 14.0)
β	54.9	56.0	3.10 (m)	55.8	56.3	4.26 (dd, 2.0, 8.5)
γ	89.5	87.4	4.32 (d, 8.5)	198.0	199.7	-
3-OMe	55.9	56.3	3.71 (s)	56.2	56.4	3.84 (s)
3'-OMe	55.9	56.3	3.71 (s)	56.2	56.4	3.84 (s)
γ-OMe	56.6	56.8	3.22 (s)	-	-	-

Recorded in [a]CD_3OD, [b]125 MHz, [c]500 MHz.

Compound **3** was isolated as a white amorphous powder. The ^{1}H-NMR spectrum data indicated the singlet signals of three tertiary methyl groups at δ_H 1.24 (s), 1.27 (s), and 1.35 (s); three olefinic protons at δ_H 5.04 (dd, *J* = 1.5, 11.0 Hz), 5.25 (dd, *J* = 1.5, 17.5 Hz), and 5.94 (dd, *J* = 11.0, 17.5 Hz); and proton signals of two methylenes at δ_H 1.75 and 1.91, 1.86 and 1.96. The ^{13}C-NMR spectrum of **3** showed signals of 16 carbons consisting of three methyls, three methylenes, two olefinic carbons, two tertiary carbons, and six carbons of the sugar moiety. In addition, signals of glucopyranoside were proved based on the appearance of the characteristic signals on the ^{1}H-NMR spectrum at δ_H 4.53 (d, *J* = 7.5 Hz), 3.17 (dd, *J* = 7.5, 9.0 Hz), 3.37 (m), 3.32 (m), 3.29 (m), 3.84 (dd, *J* = 2.0, 11.5 Hz), 3.66 (dd, *J* = 5.5, 11.5 Hz) and the ^{13}C-NMR spectra at δ_C 98.8, 75.2, 78.0, 71.8, 77.6, and 62.9 ppm. The *β*-configuration for the anomeric carbon of glucose was suggested by the large coupling constant (7.5 Hz) of H-1' (δ_H 4.53). Thus, compound **3** was elucidated as *trans*-linalool-3,6-oxide-*β*-*D*-glucopyranoside. Its ^{1}H and ^{13}C NMR data were identical to those reported in the literature (Table 2) [11].

Table 2. The ^{1}H- and ^{13}C-NMR data for compound **3-5**

C	3			4			5		
	[#11]δ_C	[a,b]δ_C	[a,c]δ_H (mult., *J* = Hz)	[#12]δ_C	[a,b]δ_C	[a,c]δ_H (mult., *J* = Hz)	[#12]δ_C	[a,b]δ_C	[a,c]δ_H (mult., *J* = Hz)
1	112.2	112.1	5.04 (dd, 1.5, 11.0) 5.25 (dd, 1.5, 17.5)	161.8	161.8	-	162.2	162.2	-
2	145.2	144.9	5.94 (dd, 11.0, 17.5)	106.8	106.8	-	107.0	107.0	-
3	84.6	84.9	-	167.4	167.4	-	167.6	167.5	-
4	38.5	38.1	1.75 (m)/1.91 (m)	98.3	98.4	5.98 (d, 2.0)	98.3	98.4	5.98 (d, 2.0)
5	28.4	28.1	1.86 (m)/1.96 (m)	165.6	165.9	-	165.8	165.9	-
6	86.9	87.0	4.04 (t, 2.0)	95.3	95.7	6.20 (d, 2.0)	95.4	95.5	6.2 (d, 2.0)
7	80.6	80.6	-	-	-	-	-	-	-
8	24.0	23.8	1.24 (s)	-	-	-	-	-	-
9	20.8	20.9	1.27 (s)	-	-	-	-	-	-
10	26.2	27.0	1.35 (s)	-	-	-	-	-	-
1'	98.7	98.8	4.53 (d, 7.5)	211.8	211.8	-	207.2	207.2	-
2'	75.1	75.2	3.17 (dd, 7.5, 9.0)	47.0	47.0	3.93 (sept, 7.0)	54.2	54.2	2.91 (dd, 7.5, 16.0) 3.20 (dd, 6.5, 16.0)
3'	77.8	78.0	3.37 (m)	28.3	28.3	1.40 (m)/1.83 (m)	26.2	26.2	2.27 (m)
4'	71.7	71.8	3.32 (m)	12.0	12.1	0.91 (t, 7.0)	23.4	23.3	0.99 (d, 6.5)
5'	77.6	77.6	3.29 (m)	16.8	16.9	1.15 (d, 7.0)	22.9	22.9	0.95 (d, 6.5)
6'	62.7	62.9	3.84 (dd, 2.0, 11.5) 3.66 (dd. 5.5, 11.5)	-	-	-	-	-	-

1"				101.7	101.7	5.05 (t, 7.5)	101.9	101.9	5.04 (d, 7.5)
2"				74.8	74.8	3.54 (m)	74.8	74.8	3.56 (t, 9.0)
3"				78.7	78.7	3.49 (m)	78.6	78.6	3.48 (m)
4"				71.2	71.2	3.40 (m)	71.2	71.2	3.45 (t, 9.0)
5"				78.4	78.4	3.49 (m)	78.4	78.4	3.48 (m)
6"				62.5	62.5	3.90 (dd, 2.0, 12.0) 3.73 (dd, 5.5, 12.0)	62.5	62.5	3.74 (dd, 5.5, 12.0) 3.94 (dd, 2.0, 12.0)

Measured in [a] CD_3OD, [b] 125 MHz, [c] 500 MHz.

Compound **4** was obtained as a white amorphous powder. Its ^{1}H-NMR spectrum (Table 2) showed in the aliphatic region signals for a 2-methylbutyryl moiety at δ_H 3.93 (sept, J = 7.0 Hz), 1.15 (t, J = 7.0 Hz, 3H), and 0.91 (d, J = 7.0 Hz, 3H). Moreover, typical signals due to a glucosyl moiety were observed at δ_H 5.05 (1H, d, J = 7.5 Hz, H-1′), 3.90 (1H, dd, J = 2.0, 12.0 Hz, H_{glc}-6′a), and 3.73 (1H, dd, J = 5.5, 12.0 Hz, H_{glc}-6′b), of which the coupling constant of anomeric proton indicated the β-linkage with the aglycone. In the aromatic region of the spectrum, two *meta*-coupled doublets appeared at δ_H 5.98 and 6.20, indicating an asymmetrically substituted phloroglucinol moiety. Therefore, the sugar residue must be attached to C-1 of the phloroglucinol. Thus, compound **4** was confirmed as 1-(2-methylbutyryl)phloroglucinol-glucopyranoside, a compound previously isolated from the bark of *Acacia mearnsii* [12].

Compound **5** was obtained as a white amorphous powder. The NMR data of **5** was very similar to those of **4** except for the signals of the acyl moiety. In this case, NMR data were supportive of a 3-methylbutyryl moiety in **5** instead of a 2-methylbutyryl moiety in **4**. Thus, the structure of **5** was proposed as 1-(3-methylbutyryl)phloroglucinol-glucopyranoside. Furthermore, the NMR and ESI-MS data of **5** were compared and well agreed with those of 1-(3-methylbutyryl)phloroglucinol-glucopyranoside in the literature [12]. Consequently, compound **5** was established.

The known compounds **6-8** were identified as (+)-isolariciresinol (**6**), protocatechuic acid (**7**), and methyl gallate (**8**), respectively, by extensive analysis of their ESI-MS, ^{1}H- and ^{13}C-NMR data, as well as comparison with those reported [13-15].

3.2. Biological Activity

All compounds **1-8** were tested for cytotoxic activity against the human hepatocellular carcinoma HepG2 cell line, ellipticine was used as a positive control. As a result, compound **2** showed significant cytotoxic activity against the HepG2 cell line with an IC_{50} value of 48.37 ± 3.18 µM, while other compounds did not exhibit activity (Table 3).

Table 3. The cytoxic activity of compounds on HepG2 cell line

Compounds	Cell viability (% of control) at 100 µM	IC_{50} µM[a]
1	47.151.75	>100
2	63.76±4.31	48.37 ± 3.18
3	38.46±2.89	>100
4	27.29±1.63	>100

5	16.41±3.28	>100
6	41.89±4.12	>100
7	34.27±2.59	>100
8	29.08±2.68	>100
Ellipticine[b]	94.83±2.13	0.49±0.06

[a])The concentration that inhibits 50% of cell growth was calculated (IC_{50}).
Data are means of three experiments.
[b)] Ellipticine, an anticancer agent, was used as the reference compound.

4. Conclusion

Eight compounds *threo*-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-methoxy-propanol **(1)**, evofolin-B **(2)**, *trans*-linalool-3,6-oxide-*β*-*D*-glucopyranoside **(3)**, 1-(2-methylbutyryl)phloroglucinol- glucopyranoside**(4)**, 1-(3-methylbutyryl)phloroglucinol-glucopyranoside **(5)**, (+)-isolariciresinol **(6)**, protocatechuic acid **(7)** and methyl gallated **(8)** were isolated from the leaves of *C. bonduc* using combined chromatographic methods. Compound **2** showed a significant cytotoxic effect against the HepG2 human cancer cell line with the IC_{50} value of 48.37±3.18 μM, while the remaining compounds did not exhibit activity.

Acknowledgements

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