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SHORT COMMUNICATION

Synthesis of (–)-arctigenin derivatives and their anticancer activity

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The natural dibenzylbutyrolactone type lignanolide (–)-arctigenin, which was prepared from fructus arctii, showed obvious anticancer activity. The synthesis of four new (–)-arctigenin derivatives and their anticancer bioactivities were examined. The structures of the four new synthetic derivatives were elucidated.

Keywords: (–)-arctigenin; synthesis; synthetic derivatives; anticancer bioactivity

1. Introduction

The natural dibenzylbutyrolactone type lignanolide (–)-arctigenin exhibited stronger anticancer activity (Suresh, Jie, Surya, Yukiko, Yasuhiro, Shigetoshi, & Hiroyasu, 2006; Takasi, Konoshtma, Bardeesy, Sharpless, & Depinho, 2000) and could be used as a lead precursor for further structure modification. The observation led us to research the importance of lactone in anticancer activity and change the bioavailability of (–)-arctigenin to find more safe and effective molecules. Herein, (–)-arctigenin was used as a lead compound for further modification, we first synthesised four new derivatives of (–)-arctigenin with methylamine, ethylamine, butylamine and 2-chloro-ethylsulfonate sodium, and the reaction equations are shown in Figures 1 and 2. Second, we elucidated the structures of the four new derivatives and examined their anticancer bioactivity.

2. Results and discussion

Three new synthetic ammonoylsis derivatives of **1**–**3**, were prepared by (–)-arctigenin and three *N*-substituted primary amines stirred at room temperature (Figure 1). The reactions were completed within 2–3 h for the three ammonoylsis derivatives (Eckart et al., 1996). The new synthetic compounds were characterised by ^{1}H-NMR, ^{13}C-NMR and 2D-NMR spectra (Figure 3).

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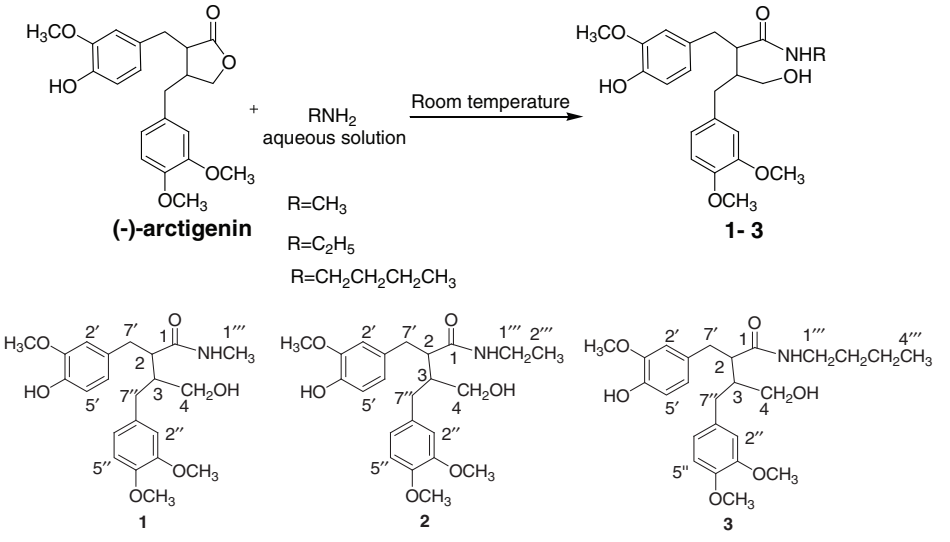

Figure 1. Synthetic route for *ammonoylsis* derivatives of **1**–**3**.

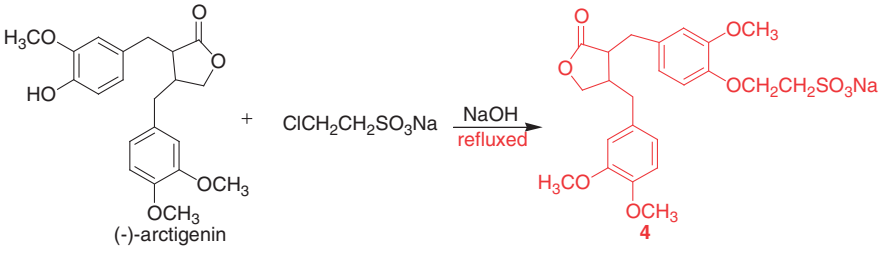

Figure 2. Synthetic route for alkylation derivative of **4.**

The new synthetic alkylation derivative of **4**, was synthesised with the treatment of (–)-arctigenin and 2-chloro-ethylsulfonate sodium (Figure 2). The reaction was completed in 2 h for the alkylation derivative **4**. Compound **4** was elucidated by ^{1}H-NMR, ^{13}C-NMR and 2D-NMR spectra (Figure 3).

All the synthetic derivatives were screened for anticancer activity by the five different human cancer cells, HCT116 (human colon), MGC-803 (human gaster), NCI-H460 (human lung), U251 (human astrocytes) and PANC-1 (human pancreas).

2.1. *The structure elucidation of the four new synthetic derivatives*

Compound **1** was obtained as white powder. The molecular formula of compound **1** was determined as $C_{22}H_{29}NO_6$ by the spectroscopic data. Compared with the molecular weight of (–)-arctigenin, the structure of **1** possesses an additional –$NHCH_3$ group. In the NMR spectra of **1**, three methoxyls were observed by the

signal at δ 3.80 (9H, s) in the ^{1}H-NMR spectrum and their corresponding carbon signals at δ 56.4, 56.5, 56.6, respectively in the ^{13}C-NMR spectrum according to the HSQC spectrum of **1**. Six aromatic protons emerged in the ^{1}H-NMR spectrum at δ 6.67 (1H, d, $J = 1.9$ Hz), 6.66 (1H, d, $J = 8.2$ Hz), 6.58 (1H, dd, $J = 1.9$, 8.2 Hz), 6.80 (1H, d, $J = 1.8$ Hz), 6.86 (1H, d, $J = 8.2$ Hz) and 6.77 (1H, dd, $J = 1.8$, 8.2 Hz), suggesting two ABX coupling systems in two phenyl groups. They coupled with the ^{13}C-NMR signals of **1** at low field, the structure of **1** was deduced to contain two 1,2,4-trisubstituted phenyl fragments. The carbon signal at δ 177.9 belonged to carboxyl group. With the aid of HSQC, the proton signals at δ 3.52 (1H, dd, $J = 11.3$, 4.5 Hz), 3.58 (1H, dd, $J = 11.3$, 5.0 Hz) correlated with the ^{13}C-NMR signal at δ 61.9, revealed the presence of one –CH_2OH group. The carbon signals at δ 35.5, 37.2, 52.0 and 45.6 in the ^{13}C-NMR spectrum and the proton signals at δ 2.75 (1H, dd, $J = 6.2$, 13.8 Hz), 2.70 (1H, dd, $J = 8.2$, 13.8 Hz), 2.86 (1H, dd, $J = 6.0$, 13.6 Hz), 2.82 (1H, dd, $J = 9.8$, 13.6 Hz), 2.56 (1H, m) and 1.98 (1H, m) in the ^{1}H-NMR belonged to two –CH_2– and two –CH– fragments. Furthermore, the signal at δ 2.59 (3H, s) due to methyl in –$NHCH_3$ showed long-range correlation with δ 177.9 due to the characteristic carbonyl carbon signal of C-1, suggesting that the –$NHCH_3$ linked to C-1. With the help of HMBC and HSQC spectra, the carbon and proton signals were attributable as shown in Supplementary Table S1 (online only). Thus, the structure was determined to be 2-(4′-hydroxyl-3′-methoxybenzyl)-3-(3″,4″-dimethoxy benzyl)-4-hydroxy-*N*-methylbutanamide, and the NMR spectral data are shown in Supplementary Table S1 (online only).

Compound **2** was afforded as white crystal. HR-ESI-MS gave its quasi molecular ion peak at m/z 418.2252 $[M + H]^+$ (calcd 418.2230), indicating that the molecular formula of **2** was confirmed as $C_{23}H_{31}NO_6$. Compared with the molecular weight of (–)-arctigenin, the structure of **2** contains an additional –$NHCH_2CH_3$ group. The proton signals at δ 3.06 (1H, qd, $J = 7.3$, 16.7 Hz), 3.09 (1H, qd, $J = 7.3$, 16.7 Hz) in the ^{1}H-NMR spectrum due to methylene in –$NHCH_2CH_3$ showed long-range correlation with δ 178.0 due to the characteristic carbonyl carbon signal of C-1, indicating the –$NHCH_2CH_3$ linked to C-1. By comparing the spectral data with those of **1**, the complete molecule of **2** was established by ^{1}H-NMR, ^{13}C-NMR, HSQC and HMBC experiments, whose structure was almost identical to that of **1**. Therefore, the structure of **2** was determined to be 2-(4′-Hydroxyl-3′-methoxy benzyl)-3-(3″, 4″-dimethoxy benzyl)-4-hydroxy-*N*-ethylbutanamide, and the NMR spectroscopic data are shown in Supplementary Table S1 (online only).

Compound **3** was afforded as white power. HR-ESI-MS gave its quasi molecular ion peak at m/z 446.2547 $[M + H]^+$, (calcd 446.2564), indicating that the molecular formula of **3** was confirmed as $C_{25}H_{35}NO_6$. The structure of **3** contains an additional –$NHCH_2CH_2CH_2CH_3$ group compared with the molecular weight of (–)-arctigenin, The proton signals at δ 2.98 (1H, m), 3.10 (1H, m) in the ^{1}H-NMR spectrum due to methylene in –$NHCH_2CH_2CH_2CH_3$ showed long-range correlation with δ 177.1 due to the characteristic carbonyl carbon signal of C-1, indicating that the –$NHCH_2CH_2CH_2CH_3$ linked to C-1. By comparing the spectroscopic data with that of **1** and **2**, the complete molecule of **3** was established by ^{1}H-NMR, ^{13}C-NMR, HSQC and HMBC experiments, whose structure was almost identical to those of **1** and **2**. Therefore, the structure of **3** was determined to be 2-(4′-Hydroxyl-3′-methoxybenzyl)-3-(3″, 4″-dimethoxy benzyl)-4-hydroxy-*N*-butylbutanamide, and the NMR spectroscopic data are shown in Supplementary Table S1 (online only).

Table 1. The IC_{50} of compound **1**, **2, 3, 4** and **(–)-arctigenin.**

Compounds	Unit	HCT116	MGC-802	NCI-H460	U251	PANC-1
(–)-arctigenin	$\mu mol\,L^{-1}$	4.99	>200	>200	>200	19.51
Compound **1**	$\mu mol\,L^{-1}$	>200	>200	>200	>200	>200
Compound **2**	$\mu mol\,L^{-1}$	100	200	>200	>200	>200
Compound **3**	$\mu mol\,L^{-1}$	>200	130.05	>200	>200	66.67
Compound **4**	$\mu mol\,L^{-1}$	39.1	>200	168.15	>200	60.24

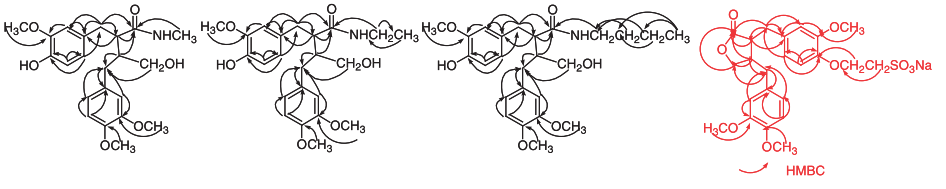

Figure 3. HMBC correlations of compounds **1**–**4**.

Compound **4** was afforded as yellow powder. ESI-MS gave its quasi molecular ion peak at $m/z + Na$ 547.1 $[m/z + Na]^+$, showing that the molecular weight is 502.1 (calcd 502.1). The molecular formula of compound **4** was determined as $C_{23}H_{27}NaO_9S$ by the quasi molecular ion peak at $m/z + Na$ 547.1 $[m/z + Na]^+$ in the ESI-MS, as well as from its NMR spectroscopic data. The structure of **4** possesses an additional $–CH_2CH_2SO_3Na$ group compared to the molecular weight of (–)-arctigenin. With the aid of HSQC, the proton signals at δ 4.37 (2H, t, $J = 7.3$ Hz), 3.31 (2H, t, $J = 7.3$ Hz) in the ^{1}H-NMR spectrum and the carbon signals at δ 66.3, 51.9 in the ^{13}C-NMR spectrum showed that the molecule of **4** contained $–OCH_2CH_2–$ group. With the help of HMBC, the proton signals at δ 4.37 (2H, t, $J = 7.3$ Hz) in the ^{1}H-NMR spectrum due to the methylene in $–OCH_2CH_2–$ showed long-range correlation with δ 148.1 due to the characteristic aromatic carbon signal of C-4′, indicating the $–OCH_2CH_2–$ linked to C-4′. The complete molecule of **4** was established by ^{1}H-NMR, ^{13}C-NMR, HSQC and HMBC experiments. Therefore, the structure of **4** was determined to be (3″, 4″-dimethoxybenzyl)-3-(4′-ethyl sulfonate sodium-3′-methoxybenzyl)-dihydrofuran-2(3*H*)-one, and the NMR spectral data are shown in Supplementary Table S1 (online only).

2.1.1. *The screen for anticancer bioactivity of (–)-arctigenin and new synthetic derivatives*

The anticancer bioactivities of **1**–**4** and (–)-arctigenin were determined **(**Qiu et al., 2009). Anticancer assay was performed by five different human cancer cells, HCT116 (human colon), MGC-803 (human gaster), NCI-H460 (human lung), U251 (human astrocytes) and PANC-1 (human pancreas). The IC_{50} of **1**–**4** and (–)-arctigenin ($200\,\mu mol\,L^{-1}$) for the five cell lines were described as Table 1. From the Table 1, results indicated that **1** and **2** showed weak cytotoxicity, **3** and **4** displayed moderate cytotoxicity.

3. Conclusion

As (–)-arctigenin showed strong anticancer activity, (–)-arctigenin was used to be a lead compound for further modification to find better anticancer bioactivity molecules. The synthetic derivatives of **1**–**4** were obtained with the treatment of amines and 2-chloro-ethylsulfonate sodium separately. **1**–**3** were ammonoylsis derivatives and **4** was alkylation derivative. With the aid of spectroscopic data, the structures of **1**–**4** were elucidated. The anticancer bioactivity of **1**–**4** and (–)-arctigenin were tested by five different human cancer cells. The results indicated that the anticancer bioactivity of **1**–**4** was weaker than that of (–)-arctigenin. It can come to the conclusion that the lactone ring and the phenolic hydroxyl affected the anticancer bioactivity.

Supplementary material

Experimental details relating to this paper are available online, alongside Table S1.

Acknowledgements

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