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Noncyanogenic Cyanoglucoside Cyclooxygenase Inhibitors from *Simmondsia chinensis*

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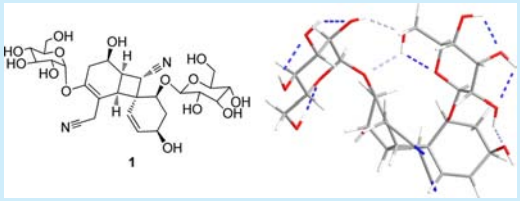
Supporting Information

ABSTRACT: Two new noncyanogenic cyanoglucoside dimers, simmonosides A and B (**1** and **2**), were identified from the aqueous extract of jojoba (*Simmondsia chinensis*) leaves. Compounds **1** and **2** are the first examples of noncyanogenic cyanoglucoside dimers containing a unique four-membered ring, representing novel dimerization patterns at α,β-unsaturated carbons of a nitrile group in **1** and γ,δ-unsaturated carbons in **2**. Their structures were elucidated based on spectroscopic evidence and electronic circular dichroism (ECD) calculations. Compounds **1** and **2** exhibit promising COX-2 inhibition activity, with IC_{50} values of 13.5 and 11.4 μM, respectively.



Jojoba (*Simmondsia chinensis* (Link) C. Schneider, family Simmondsiaceae) is a woody evergreen perennial shrub known as coffee berry, wild hazel, and goat nut.[1] The plant is a dioecious plant that grows in desert and semidesert areas and is native to the southwestern USA and northwestern Mexico.[1] Native Americans use jojoba as a folk remedy for cancer, cold, dysuria, obesity, parturition, sore throat, warts, and wounds.[1] Cultivation of jojoba has occurred predominantly in countries including Argentina, Peru, Australia, Israel, Palestinian Authority, and Egypt.[1,2] Jojoba is cultivated for its seed oil (liquid wax esters), which is composed mainly of extremely long, straight chain monoesters in the range of C_{40}–C_{44}, and it has many commercial industrial applications such as use in cosmetics.[3]

Simmondsins, as simmondsin and simmondsin 2′-ferulate, are cyanide-containing glycosides isolated mainly from the meal (plant material after wax extraction).[4] Simmondsins have insecticidal, antifeedant, and antifungal activities.[5] Long-term administration of lower doses of simmondsins induces a sustained food intake inhibition of approximately 20% in rats without any toxic effects.[6] As a part of our continuing interest in searching for drug leads from natural sources, we had the opportunity to continue the work on jojoba leaf constituents to investigate its chemical constituents and their potential biological activities.[7]

A combination of medium-pressure liquid chromatography (MPLC), gel filtration, and high-performance liquid chromatography (HPLC) on the ethyl acetate and aqueous fractions obtained from the leaves of *S. chinensis* afforded six noncyanogenic cyanoglucosides (**1**–**6**) (Figure 1). Their structures were elucidated by extensive 1D and 2D NMR analysis, accurate mass measurements, and comparison with the reported data.

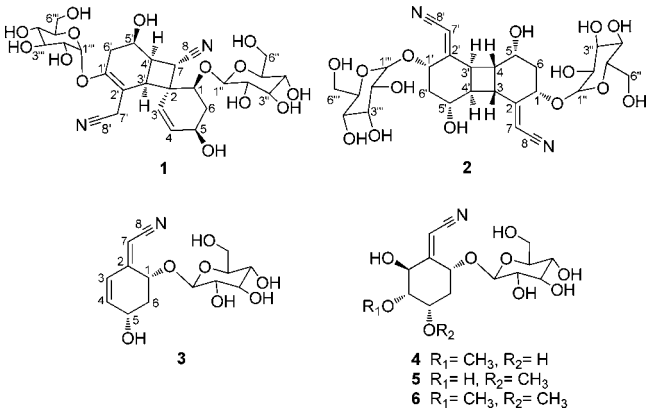


Figure 1. Structures of isolated compounds (**1**–**6**).

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Four known cyanogenetic glucosides (**3**–**6**) were identified as menisdaurin (**3**),[8] 5-demethyl simmondsin (**4**), 4-demethyl simmondsin (**5**), and simmondsin (**6**).[4c,9] All physical and spectral data of these compounds were in agreement with the respective published data (Table S1).

Compound **1** was isolated as a light yellow amorphous powder. HRESIMS showed a pseudomolecular ion peak at *m*/*z* 649.2215 $[M + Na]^+$ (calcd for $C_{28}H_{38}N_2O_{14}Na$, 649.2221), consistent with a molecular formula of $C_{28}H_{38}N_2O_{14}$, thus implying 11 degrees of unsaturation. The UV gave λ_{max}^{MeOH} 217, 246 nm, while the IR spectrum showed strong absorption bands attributed to hydroxyl (3454 cm^{-1}), nitrile (2247 cm^{-1}), and olefinic groups (1650 cm^{-1}).

The ^{13}C NMR spectrum in DMSO-d_6 (Table 1) of **1** showed 28 carbon signals, including two nitrile carbons [δ_C 120.8 (C-8) and 119.3 (C-8′)], indicating a dimer of two cyanoglucoside units.

The ^1H NMR spectrum exhibited two β-glucoside moieties, as proven by the presence of signals between δ_H 2.97 and 3.69, as well as two anomeric protons of glucose [δ_H 4.23 (d, J = 7.5 Hz, H-1″) and 4.45 (d, J = 7.5 Hz, H-1‴)], corresponding to two anomeric carbons at [δ_C 97.9 (C-1″) and 100.2 (C-1‴)] in the ^{13}C NMR spectrum, respectively. The ^1H and ^{13}C NMR data also exhibited two olefinic systems at [δ_C 130.0 (C-3), δ_H 6.00 (d, J = 10.0 Hz, H-3) and δ_C 132.4 (C-4), δ_H 5.87 (dd, J = 3.3, 10.0 Hz, H-4)] of cis configuration, as well as one between [δ_C 148.7 (C-1′) and 104.4 (C-2′)]. Two hydroxyl groups at [δ_C 63.0 (C-5), δ_H 4.05 (m, H-5) and δ_C 64.3 (C-5′), δ_H 3.96 (m, H-5′)] and two methylenes at [δ_C 32.1 (C-6), δ_H 1.89 and 1.49 (m, H-6a/b) and δ_C 30.6 (C-6′), δ_H 2.63 and 2.30 (m, H-6′a/b)] were also observed. From the above data, it is obvious that the cyanoglucoside unit is closely similar to menisdaurin (**3**).

The connection of two menisdaurin subunits was identified using 2D NMR (^1H–^1H COSY, ^1H–^{13}C HSQC, and ^1H–^{13}C HMBC). The key HMBC correlations from H-3′ to C-3, C-2, and C-7; H-4′ to C-8 and C-7; and H-5′ to C-7, supported by the COSY correlation between H-4′ and H-7, confirmed the dimerization occurred at the α,β-unsaturated carbons (C-2 and C-7) of the nitrile group. Further correlations observed from H-1″ to C-1 as well as from H-1‴ to C-1′ confirmed the glucoside linkages at C-1 and C-1′ (Figure 2A, Table S2).

The relative configuration depicted in **1** was deduced from 2D NOESY spectral data. The NOESY spectrum of **1** showed that protons H-5 and H-1 were oriented *syn* with regard to H-6a based on mutual NOE correlations (Figure 2B). In a similar manner, H-3′, H-4′, and H-5′ were found to be oriented *syn* with regard to H6′b, leaving the 5′-OH in the *anti*-position. Moreover, H-3 showed strong NOE correlations to both H-3′ and H-4′. The relative stereochemistry in the bridged four-membered ring was more difficult to define, and two possible diastereomers were modeled (Figure 3).

The absolute configuration of **1** was determined by quantum chemical ECD calculations. The preliminary conformational distribution search was performed using the MOE software package using the MMFF94 force field with default parameters.[10] The corresponding minimum geometries were fully optimized at the B3LYP/6-31G(d) level using the time-dependent density functional theory (TDDFT) method, as implemented in the Gaussian 09 program package. The stable conformers obtained were then submitted to ECD calculations at the B3LYP/6-31G(d) basis set level. The overall predicted ECD spectra of the **1a** and **1b** conformations by quantum chemical calculations were subsequently compared with the experimental data. This comparison revealed good agreement between the calculated **1b** spectrum and the measured CD curve (Figure 3), whereas the diastereomer **1a** showed the opposite result, confirming the absolute configuration of compound **1** as 1*S*, 2*S*, 3*Z*, 5*R*, 7*S*, 1′*E*, 3′*S*, 4′*R*, and 5′*R*. Thus, **1** is identified as a new natural product for which the name simmonoside A is proposed.

Compound **2** was obtained as a light yellow amorphous powder. HRESIMS showed a pseudomolecular ion peak at *m*/*z*

Table 1. ^1H (600 MHz) and ^{13}C NMR (150 MHz) Data (in DMSO-d_6) for 1 and 2

	1		2	
no.	δ_C, mult.	δ_H, mult (J in Hz)	δ_C, mult.	δ_H, mult (J in Hz)
1	70.6, CH	3.87, dd (2.1, 8.4)	74.7, CH	4.63, m
2	49.0, C		163.9, C	
3	130.0, CH	6.00, d (10.0)	43.3, CH	3.70, d (6.4)
4	132.4, CH	5.87, dd (3.3, 10.0)	45.8, CH	2.02, m
5	63.0, CH	4.05, m	68.8, CH	4.02, m
6	32.0, CH_2	a. 1.89, m	39.1, CH_2	a. 2.25, m
		b. 1.49, m		b. 1.27, m
7	28.1, CH	3.40, m	93.9, CH	5.79, d (2.2)
8	120.8, C		117.0, C	
sugar I	*glucose*	*glucose*	*glucose*	*glucose*
1″	97.9, CH	4.23, d (7.5)	101.7, CH	4.32, d (7.9)
2″	73.0, CH	2.97, m	73.4, CH	3.00, m
3″	76.1, CH	3.13, m	76.6, CH	3.14, m
4″	70.0, CH	3.03, m	69.8, CH	3.09, m
5″	76.8, CH	3.07, m	76.9, CH	3.09, m
6″	61.4, CH_2	a. 3.69, m	61.0, CH_2	a. 3.63, dd (7.0, 11.6)
		b. 3.46, m		b. 3.44, m
OH-5		4.80, brs		4.99, brs
OH-2″		4.99, brs		5.11, brs
OH-3″		5.02, brs		4.99, brs
OH-4″		4.94, brs		4.93, brs
OH-6″		4.39, brs		4.07, brs
1′	148.7, C		74.7, CH	4.63, m
2′	104.4, C		163.9, C	
3′	42.1, CH	2.83, m	43.3, CH	3.70, d (6.4)
4′	36.5, CH	2.84, m	45.8, CH	2.02, m
5′	64.3, CH	3.96, m	68.8, CH	4.02, m
6′	30.6, CH_2	a. 2.63, m	39.1, CH_2	a. 2.25, m
		b. 2.30, m		b. 1.27, m
7′	17.8, CH_2	a. 3.92, d (18.0)	93.9, CH	5.79, d (2.2)
		b. 3.05, d (18.0)		
8′	119.3, C		117.0, C	
sugar II	*glucose*	*glucose*	*glucose*	*glucose*
1‴	100.2, CH	4.45, d (7.5)	101.7, CH	4.32, d (7.9)
2‴	73.3, CH	3.09, m	73.4, CH	3.00, m
3‴	76.6, CH	3.17, m	76.6, CH	3.14, m
4‴	69.8, CH	3.11, m	69.8, CH	3.09, m
5‴	77.0, CH	3.11, m	76.9, CH	3.09, m
6‴	61.0, CH_2	a. 3.66, m	61.0, CH_2	a. 3.63, dd (7.0, 11.6)
		b. 3.52, m		b. 3.44, m
OH-5′		4.82, brs		4.99, brs
OH-2‴		5.25, brs		5.11, brs
OH-3‴		5.05, brs		4.99, brs
OH-4‴		4.98, brs		4.93, brs
OH-6‴		4.51, brs		4.07, brs

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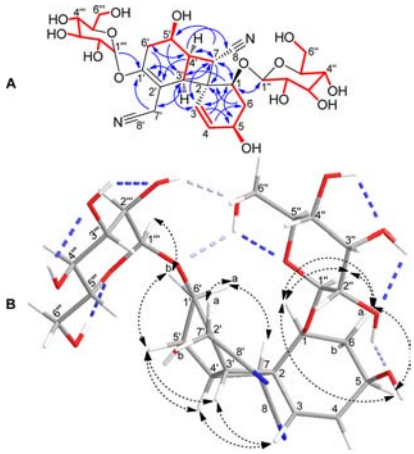

Figure 2. (A) Observed COSY (red bold bonds) and HMBC (H → C, blue) correlations of **1**. (B) Key NOESY (→, black) correlations and global energy minimum of **1**.

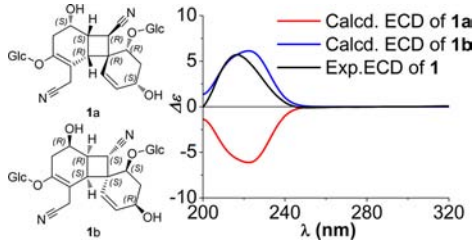

Figure 3. Attribution of the absolute configuration of **1** by comparison of the calculated CD spectra with the experimental spectrum.

649.2227 $[M + Na]^+$, consistent with a molecular weight of 626 amu. The molecular formula was established as $C_{28}H_{38}N_2O_{14}$, implying 11 degrees of unsaturation. The UV gave λ_{max}^{MeOH} 220, 231 nm, while the IR spectrum showed strong absorption bands attributed to hydroxyl, nitrile, and olefinic groups at 3449, 2223, and 1641 cm^{-1}, respectively.

The ^{13}C NMR spectra in DMSO-d_6 (Table 1) of **2** represented 14 carbon signals, indicating the symmetric homodimeric structure of this compound. Analyses of the ^1H and ^{13}C NMR, COSY, and HSQC spectra revealed that half of the molecule, $C_{14}H_{19}O_7N$, possesses one nitrile carbon δ_C 117.0 (C-8); one β-glucoside moiety is proven by the presence of one equatorial anomeric proton of glucose δ_H 4.32 (d, J = 7.9 Hz, H-1″), corresponding to an anomeric carbon at δ_C 101.7 (C-1″) in ^{13}C NMR; one olefinic system [δ_C 163.9 (C-2) and δ_C 93.9 (C-7), δ_H 5.79 (d, J = 2.2 Hz, H-7)]; one hydroxylated carbon [δ_C 68.8 (C-5), δ_H 4.02 (m, H-5)]; one methylene [δ_C 39.1 (C-6), δ_H 2.25 and 1.27 (m, H-6a/b)] and two aliphatic methines [δ_C 43.3 (C-3), δ_H 3.70 (m, H-3) and δ_C 45.8 (C-4), δ_H 2.02 (m, H-4)] were also observed. From the above data accompanied by key $^1H-^{13}C$ HMBC correlations from H-3′, H-4′, and H-4 to C-3, C-2, and C-7 supported by COSY correlations between H4, H-4′ and H-3, H-3′ confirmed that the dimerization occurred at the γ,δ-unsaturated carbons (C-3 and C-4) of the nitrile group. Further correlations observed from H-1″ to C-1 confirmed the glucoside linkages at C-1 (Figure 4A, Table S3).

In compound **2**, the relative configuration was deduced from 2D NOESY spectral data, which displayed that protons H-5, H-4, H-3, and H-1 were oriented *syn* with regard to H-6a based on mutual NOE correlations (Figure 4B). The observed mutual key NOESY correlations in **2** did not allow the configurational

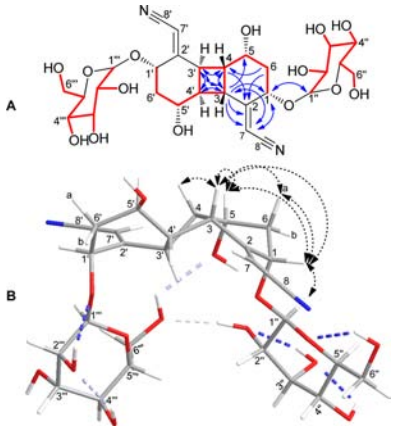

Figure 4. (A) Observed COSY (red bold bonds) and HMBC (H → C, blue) correlations of **2**. (B) Key NOESY (→, black) correlations and global energy minimum of **2**.

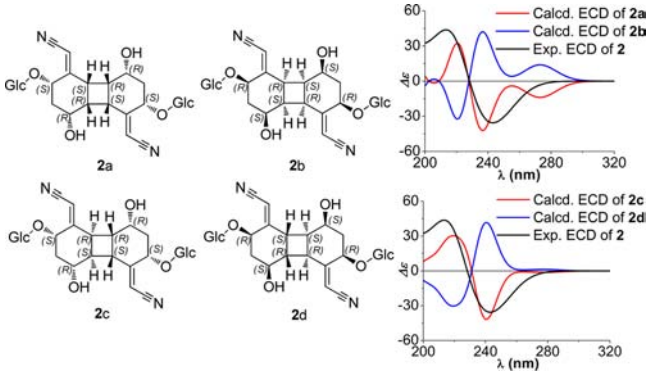

Figure 5. Attribution of the absolute configurations of **2** by comparison of the calculated CD spectra with the experimental spectrum.

analysis to be completed, in particular for the bridged four-membered ring. Therefore, to determine the absolute configuration of **2**, the quantum chemical calculation of the electronic circular dichroism (ECD) of all four possible stereoisomers of **2** (Figure 5) was performed utilizing time-dependent density functional theory (TDDFT).

Excellent agreement was found between the theoretical ECD curve for **2c**, 1*S*, 2*Z*, 3*S*, 4*R*, 5*R*, 1′*S*, 2′*Z*, 3′*R*, 4′*S*, 5′*R*, and the experimental CD curve (Figure 5). Thus, **2** is identified as a new natural product for which the name simmonoside B is proposed.

To date, the biosynthesis of nitrile glucosides has not been deeply studied. As outlined in Scheme S1, the nitrile glucosides with a cyclohexenylcyanomethylene structure are derived from (α-amino acid) tyrosine.[11] Tyrosine would undergo two initial hydroxylations to generate *N*,*N*-dihydroxytyrosine. Sequential dehydration and decarboxylation on this labile intermediate generate *p*-hydroxyphenylacetaldoxime, which subsequently undergoes dehydration and C-hydroxylation to produce *p*-hydroxymandelonitrile. *p*-Hydroxymandelonitrile would undergo allylic rearrangement, ketonization, and glucosylation to generate menisdaurin (**3**) (Scheme S1). The oxidation of menisdaurin leads to the production of simmondsin members (**4**–**6**), while a [2 + 2] cycloaddition between two molecules of menisdaurin leads to the formation of compounds **1** and **2**.

In the present study, the COX-2 inhibition and cytotoxic activities of pure compounds were evaluated using A-549 (human lung adenocarcinoma epithelial) and SGC-7901 (human gastric cancer) cell lines, as shown in Table 2. It is

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Table 2. Cytotoxic and COX-2 Inhibitory Activities for Isolated Compounds (1−6)

compd	IC_{50} (μM)		
	A-549	SGC-7901	COX-2
1	21.5	26.8	13.5
2	17.7	20.4	11.4
3	>100	>100	67.1
4	26.1	31.2	22.3
5	33.2	40.3	27.4
6	41.3	49.5	36.2
Cisplatin	11.6	7.5	
Indomethacin			1.6

obvious that the highest cytotoxic and COX-2 inhibition activities were observed with isolated dimers **1** and **2**. Compounds **1** and **2** exhibited moderate cytotoxic activity against A-549 (IC_{50s} 21.5 and 17.7 μM, respectively) and SGC-7901 (IC_{50s} 26.8 and 20.4 μM) cell lines. They also exhibited promising COX-2 inhibition activities (IC_{50} of 13.5 and 11.4 μM, respectively). Several studies have suggested that cyclooxygenase-2 (COX-2) expression is associated with the parameters of many aggressive cancers.[12] The contribution of COX-2 to carcinogenesis has been thought to be related to its abilities to (i) increase production of prostaglandins, (ii) inhibit apoptosis, (iii) convert procarcinogens to carcinogens, (iv) promote angiogenesis, (v) increase tumor cell invasiveness, and (vi) modulate inflammation and immune function.[12] Thus, COX-2 inhibitors exhibit anticancer activity by inducing apoptosis, reducing angiogenesis, suppressing proliferation, and weakening invasiveness, which make it a good target in cancer therapy.[12] It is noteworthy that simmondsin derivatives (**4**−**6**) exhibited an excellent reported angiogenesis-inhibiting activity, which make them a promising target for cancer therapy research.[13] Simmondsin derivatives are able to inhibit the angiogenic proteins vascular endothelial growth factor (VEGF) and β-fibroblast growth factor (βFGF), which stimulate endothelial cell proliferation. Angiogenic inhibitors could remarkably suppress melanoma, which implies anticancer and antimetastatic activities.[14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00206.

Experimental section, 1D NMR, 2D NMR, and HRESIMS (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Phillips, S. J.; Comus, P. W. A Natural History of the Sonoran Desert. University of California Press: Los Angeles, CA, 2000; pp 256−257. (b) Ranzato, E.; Martinotti, S.; Burlando, B. *J. Ethnopharmacol.* **2011**, *134*, 443. (c) Yaron, A.; Samoiloff, V.; Benzioni, A. *Lipids* **1982**, *17*, 169.

(2) El-Baz, E. E. T.; El-Dengawy, E. F.; El-Shahat, S. E. S.; El-Hassan, El. M. *J. Agric. Sci. Mansoura Univ.* **2009**, *34*, 10575.

(3) (a) Vrkoslav, V.; Urbanova, R.; Cvacka, K. J. *J. Chromatogr. A* **2010**, *1217*, 4184. (b) Wisniak, J. *Ind. Crops Prod.* **1994**, *3*, 43. (c) Habashy, R. R.; Abdel-Naim, A. B.; Khalifa, A. E.; Al-Azizi, M. M. *Pharmacol. Res.* **2005**, *51*, 95. (d) Ibrahim, H. M.; Abou-Arab, A. A.; Abu Salem, F. M. *Grasas Aceites* **2011**, *62*, 139.

(4) (a) Bellirou, A.; Bouali, A.; Bouammali, B.; Boukhatem, N.; Elmtili, B. N.; Hamal, A.; El-Mourabit, M. *Ind. Crops Prod.* **2005**, *21*, 229. (b) Lein, S.; Van Boven, M.; Holser, R.; Decuypere, E.; Flo, G.; Lievens, S.; Cokelaere, M. *J. Chromatogr. A* **2002**, *977*, 257. (c) Van Boven, M.; Busson, R.; Cokelaere, M.; Flo, G.; Decuypere, E. *Ind. Crops Prod.* **2000**, *12*, 203. (d) Van Boven, M.; Leyssen, T.; Busson, R.; Holser, R.; Cokelaere, M.; Flo, G.; Decuypere, E. *J. Agric. Food Chem.* **2001**, *49*, 4278.

(5) Abbassy, M. A.; Abdelgaleil, S. A. M.; Belal, A. S.; Rasoul, M. A. A. *Ind. Crops Prod.* **2007**, *26*, 345.

(6) (a) Cokelaere, M.; Buyse, J.; Daenens, P.; Decuypere, E.; Kühn, E. R.; Van Boven, M. *J. Agric. Food Chem.* **1993**, *41*, 1444. (b) Cokelaere, M.; Buyse, J.; Daenens, P.; Decuypere, E.; Kühn, E. R.; Van Boven, M. *J. Agric. Food Chem.* **1993**, *41*, 1449.

(7) Abdel-Mageed, W. M.; Bayoumi, S. A. H.; Radwan, A. A.; Salem-Bekhit, M. M.; Abd-Alrahman, S. H.; Basudan, O. A.; Sayed, H. M. *Ind. Crops Prod.* **2014**, *60*, 99.

(8) (a) Ueda, K.; Yasutomi, K.; Mori, I. *Chem. Lett.* **1983**, *1*, 149. (b) Yi, X. X.; Deng, J. G.; Gao, C. H.; Hou, X. T.; Li, F.; Wang, Z. P.; Hao, E. W.; Xie, Y.; Du, Z. C.; Huang, H. X.; Huang, R. M. *Molecules* **2015**, *20*, 14565.

(9) (a) Van Boven, M.; Daenens, P.; Cokelaere, M. M.; Janssen, G. *J. Agric. Food Chem.* **1994**, *42*, 2684. (b) Van Boven, M.; Blaton, N.; Cokelaere, M.; Daenens, P. *J. Agric. Food Chem.* **1993**, *41*, 1605.

(10) *MOE2009.10*, Chemical Computing Group Inc. www.chemcomp.com.

(11) (a) Nielsen, J. S. *Plant Physiol.* **2000**, *122*, 1311. (b) Celenza, J. L. *Curr. Opin. Plant Biol.* **2001**, *4*, 234. (c) Seigler, D. S.; Pauli, G. F.; Fröhlich, R.; Wegelius, E.; Nahrstedt, A.; Glander, K. E.; Ebinger, J. E. *Phytochemistry* **2005**, *66*, 1567. (d) Zintchem, A. A. À.; Ndongo, J. T.; Bikobo, S. D. N.; Nkot, J. L. *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 252. (e) Yamamoto, J.; Nishiguchi, K.; Manabe, K.; Masutani, C.; Hanaoka, F.; Iwai, S. *Nucleic Acids Res.* **2011**, *39*, 1165.

(12) (a) Fu, S. L.; Wu, Y. L.; Zhang, Y. P.; Qiao, M. M.; Chen, Y. *World J. Gastroenterol.* **2004**, *10*, 1971. (b) Xu, X. C. *Anti-Cancer Drugs* **2002**, *13*, 127.

(13) Oosterlynck, A. D.; Raes, S. US20060088613 A1 2006.

(14) Saharinen, P.; Eklund, L.; Pulkki, K.; Bono, P.; Alitalo, K. *Trends Mol. Med.* **2011**, *17*, 347.

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