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POLYOXYGENATED XANTHONES OF *CENTAURIUM LITTORALE**

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Key Word Index—*Centaurium littorale*; Gentianaceae; hexa-oxygenated xanthones; tetra-oxygenated xanthones; chemotaxonomy.

Abstract—Two apolar tetra-oxygenated xanthones (1,8-dihydroxy-3,5-dimethoxyxanthone and 1-hydroxy-3,5,8-trimethoxyxanthone) and two hexaoxygenated xanthones (1,8-dihydroxy-3,5,6,7-tetramethoxyxanthone and 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone) have been isolated from the root of *Centaurium littorale*. The isolation and structure of these xanthones are reported and details of the TLC analysis are given. The ^{13}C NMR and high resolution EIMS spectra of the two hexaoxygenated xanthones are reported. The xanthones found within the genus *Centaurium* Hill are reviewed.

INTRODUCTION

Centaurium littorale (D. Turner) Gilmour subsp. *littorale* (*C. vulgare* Rafn subsp. *vulgare*), a plant indigenous to the coasts of north-west Europe [2] is commonly used as a substitute for *C. erythraea* Rafn in the crude drug 'Centaurii herba'. The Gentianaceae is known to produce xanthone aglycones and glycosides with potential therapeutic effects [3]. Several xanthones have been isolated from the genera *Canscora, Eustoma, Frasera, Gentiana, Halenia, Macrocarpea* and *Swertia* [3, 4] and recently also from the genus *Centaurium* (Table 1).

Preliminary TLC examination of the methanolic extracts of the root and the aerial parts of *C. littorale* showed the presence of many phenolic aglycones and glycosides, which were probably xanthones. The aglycones are more abundant in the roots, whereas the glycosides are more abundant in the aerial parts. In this paper we report on the isolation and structure of some apolar xanthone aglycones from the root.

RESULTS AND DISCUSSION

After the extraction with chloroform of the milled root of *C. littorale* the part of the extract soluble in light petroleum was fractionated according to the acidity of the components. Two fractions were obtained consisting of strong acids (fractions B and K), one fraction consisting of weak acid components (fraction L), and two fractions with very weak acid and neutral components (fractions N_a and N_b).

From the N_a and N_b fractions the xanthones **7** and **2** respectively were obtained in pure form by crystallization. The two major components, **1** and **6** in the L-fraction, were purified by means of prep. TLC on silica gel thin-layers, using a solvent optimized for their separation and by crystallization.

Compound **1**, $C_{15}H_{12}O_6$ is a dihydroxy-dimethoxy-xanthone. Its spectral properties (mass, UV, IR and ^1H NMR) as well as its mp are in agreement with lit. data for 1,8-dihydroxy-3,5-dimethoxyxanthone [5–7].

Compound **6**, $C_{17}H_{16}O_8$ is 1,8-dihydroxy-3,5,6,7-tetramethoxyxanthone. Its spectral properties (mass, UV, IR and ^1H NMR) as well as its mp are in agreement with lit. data [8, 9]. The structure of **6** is also easily determined by ^{13}C NMR spectroscopy. The carbonyl carbon signal in the ^{13}C NMR spectrum at 184.0 ppm is characteristic for a doubly chelated carbonyl (1,8-di-OH) [10]. The ^{13}C NMR spectrum further reveals signals of four methoxyl carbons (δ55.9–61.2), two methine carbons (δ93.2 and 97.7), ten quaternary carbons, two of which have no oxygen substituent (δ102.2 and 103.6) and eight of which have an oxygen substituent (δ132.6–176.2). The long range multiplicity of the two methine carbons (*d* and *dd*) in the proton-coupled ^{13}C NMR spectrum is very characteristic for the 1,3-dioxygenated polyketide ring B with a hydroxyl group at C-1 [10, 11].

Compound **7**, $C_{18}H_{18}O_8$, is 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone. The oxygenation pattern is indicated by its ^1H NMR spectrum and its UV spectra. A methoxyl group at C-1 or C-8 is strongly indicated by the loss of significant fragment ion peaks in the mass spectrum due to the loss of hydroxyl and H_2O [12] and a hydroxyl group at C-1 or C-8 by the carbon signal in the ^{13}C NMR spectrum. The carbon signal at 180.4 is characteristic for a monochelated carbonyl carbon [10].

The attachment of the hydroxyl at C-1 is proved by the formation of its acetate (**7a**) and by ^{13}C NMR spectroscopy. The xanthone **7a** showed a downfield shift in the ^1H NMR signals of the *meta*-coupled aromatic protons (H-2; H-4), showing that the acetylated hydroxyl must be attached to the same ring. The attachment of the hydroxyl group at C-1 is also easily concluded from the long range

*Part 7 in the series "Secoiridoids and Xanthones in the genus *Centaurium*." For part 6 see: *Planta Med.* (1983) **49** 211–215. Parts of this work were presented at the 23rd annual meeting of the 'Gesellschaft für Arzneipflanzenforschung', held in May 1975 in Groningen and at the second 'Symposium voor Farmacognosie en Natuurstofchemie', held in Sept. 1975 in Utrecht. For summary see ref. [1].

Table 1. Distribution of xanthones within the genus *Centaurium*

SECTION species	Plant part*	detected via*	Oxygenation pattern 1,3,5,8	1,3,7,8	1,3,5,6,7,8	misc.	Ref.
CENTAURIUM							
C. erythraea	wh	is	**1**	**3**	**6**	**5**	[7]
					6		[9]
					8		
						11	[18]
						12	[19]
	rt	TLC	**1, 2**		**6, 7**		[22]
	ae	TLC			**6**		[22]
C. majus	ae	TLC			**6**		[22]
C. littorale	rt	is	**1, 2**		**6, 7**		[1]
	ae	TLC			**6**		[22]
C. linariifolium	ae	is			**6, 8**	**10**	[16]
				3	**9**	**5, 13, 14**	[20]
C. chloodes	ae	TLC	**1**	**3**	**6**		[22]
	rt	TLC	**1, 2**		**6, 7**		[22]
C. scilloides	ae	TLC	**1**	**3**	**6**		[22]
PARVIFLORA							[22]
C. pulchellum	wh	is	**1**	**3, 4**			[21]
	ae	TLC	**1**	**3**	**6**		[22]
			1-β-mono-glucoside		**6-β-mono-glucoside**		[22]
C. tenuiflorum	ae	TLC	**1**	**3**	**6**		[22]
			1-β-mono-glucoside		**6-β-mono-glucoside**		[22]
SPICARIA							
C. spicatum	rt	TLC	**1, 2**		**6, 7**		[22]
	ae	TLC	**1**		**6**		[22]
AMERICAN SPECIES							
C. cachanlahuen	wh	is	**1**	**3, 4**	**6**		[8]
C. quitense	ae	TLC			**6**		[22]

*ae, Aerial part; rt, root; wh, whole plant; is, isolation.

multiplicity of the C-2 and C-hydroxyl carbon signal in the proton-coupled ^{13}C NMR spectrum of **7**. The long range multiplicity of the C-2 signal is a double doublet because of the coupling to the C-1 hydroxyl proton and the C-4 proton, and is the same as the C-2 signal in the ^1H coupled spectrum of **6**. The C-1 hydroxyl signal appears as a triplet, due to coupling to the C-1 hydroxyl proton and the C-2 proton and is identical to the C-1 hydroxyl signal in the spectrum of compound **6** (Table 2).

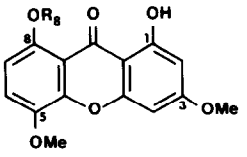
The mp and some spectral data of this compound differ somewhat from data reported for eustomin with the same postulated structure and isolated from *Eustoma grandiflorum* (Gentianaceae) [13]. Its mp is about 10 degrees higher and most of the ^1H NMR signals are about 0.8 ppm at higher field than reported by Sullivan *et al.* [13].

Compound **2**, $C_{16}H_{14}O_6$, is 1-hydroxy-3,5,8-trimethoxy-xanthone. Its spectral properties (mass, UV, IR and ^1H NMR) as well as its mp are in agreement with lit. data [14, 15].

Impurities of related xanthones in the above xanthone samples were detected in mass spectra; the impurities of xanthones with a higher mass are more easily detected than those with a lower mass. Very small amounts of a dihydroxy-trimethoxyxanthone (mass fragment ions of 318.0753 and 303.0505 with low intensities), and a dihydroxy-tetramethoxyxanthone (mass fragment ions of 348.0849 and 333.0605 with low intensities) were detected in the mass spectrum of xanthone **1**, most probably originating from xanthone **5** and **6** respectively. These fragment ions are not included in the mass spectrum of **1** (Table 3). In the mass spectrum of compound **6**, Parra *et al.* [16] reported fragment ions of mass 318 (31.2%) and 303 (52.8%) and of mass 288 (49.8%) and 273 (31.2%), all with high intensities. In the spectrum of **6** these fragment ions are only present with low intensities and other authors [8] do not mention these fragment ions in the xanthone **6**. Most probably these fragment ions are due to impurities of the xanthones **5** and **1** respectively in the samples of xanthone **6**.

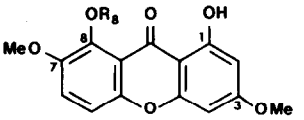
If low resolution mass spectra are being interpreted, one must be cautious about assigning some of the mass fragments; e.g. the fragment $[M-30]^+$ may be due to the loss of C_2H_6 or of CH_2O (or to an impurity). Both fragments can be seen in the spectrum of **6** (Table 3), the fragment due to the loss of C_2H_6 being the most abundant. Parra *et al.* [16], however, reported only the fragment due to the loss of CH_2O in the same component.

Further extraction of the milled roots with methanol yielded a considerable amount of brown gum after



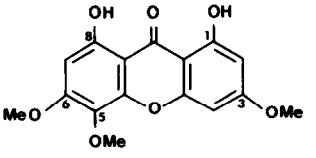
1 R_8 = H

2 R_8 = Me

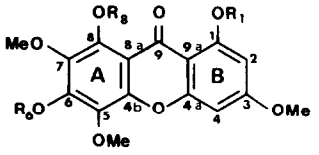


3 R_8 = H

4 R_8 = Me



5



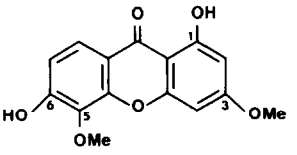
6 R_6 = Me; R_1 = R_8 = H

7 R_6 = R_8 = Me; R_1 = H

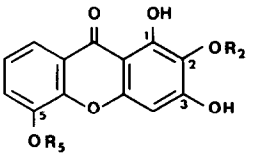
7a (7-acetyl) R_6 = R_8 = Me; R_1 = COMe

8 R_1 = R_6 = H; R_8 = Me

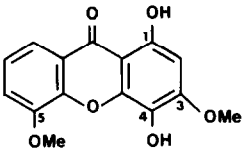
9 R_1 = R_6 = R_8 = H



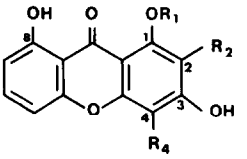
10



11 R_2 = H, R_5 = Me



12



13 R_1 = H; R_2 or R_4 = OMe

14 R_1 = Me; R_2 or R_4 = OMe

Table 2. ^{13}C NMR data for compounds **6** and **7** (25.2 MHz, $CDCl_3$)

Carbon numbering				6			7		
					multiplicity coupled spectrum			multiplicity coupled spectrum	
[11]	[10]	[23]	[24]		short range	long range		short range	long range
1				162.9		*t*	163.8		*t*
2				97.7	*d*	*dd*	97.4	*d*	*dd*
3				167.2		*br m*	166.3		*br m*
4				93.2	*d*	*d*	92.3	*d*	*d*
5				132.6		*m*	137.4		*m*
6				154.4		*m*	152.8		*m*
7				135.9		*m*	149.5		*m*
8				150.5		*d*	143.3		*m*
9a	(4b	9a	9)	103.6		*d*	103.9		*d*
4a	(4a	4a	10)	157.6		*d*	156.8		*d*
4b	(8b	10a	11)	145.6		*s*	147.5		*s*
8*a*	(8*a*	8*a*	12)	102.2		*d*	111.3		*s*
9	(C=O	9	13)	184.0		*s*	180.4		*s*
OMe (3)				55.9			55.8		
OMe (5)				61.2†			61.6†		
OMe (6)				61.7†			61.8†		
OMe (7)				62.1†			62.0†		
OMe (8)							62.2†		

*The quaternary xanthone carbons do not always have the same numbers in literature. In this paper the numbering is according to Sundholm [11]. Some other carbon numberings are given too for comparison reasons.

†Assignments bearing the same superscript in the same column may be reversed.

Signals were assigned by means of comparison with reported spectra of xanthones [24] and by proton-coupled ^{13}C-spectra. The assignments have been confirmed by reported spectra of Gentianaceae xanthones [10, 23] and of lichexanthones [11].

Table 3. High resolution mass measurements of the isolated xanthones **1**, **2**, **6** and **7** (mass tolerance: 0.004)

Mol formulae		**7** $C_{16}H_{18}O_8$ mass	%	**2** $C_{16}H_{14}O_6$ mass	%	**1** $C_{15}H_{12}O_6$ mass	%	**6** $C_{17}H_{16}O_8$ mass	%
$[M]^+$		362.1015	(79)	302.0793	(100)	288.0620	(53)	348.0840	(90)
$-H$	−1	361.0936	(2)	301.0735	(4)	287.0533	(1)		
$-Me$	−15	347.0734	(100)	287.0553	(40)	273.0408	(100)	333.0609	(100)
$-OH$	−17	345.0953	(2)						
$-H_2O$	−18	344.0888	(7)	284.0691	(40)				
$-CHO$	−29	333.0976	(6)	273.0762	(31)				
$-CH_2O$*	−30	332.0913	(2)					318.0729	(1)
$-C_2H_6$ (Me·Me)	−30							318.0374	(2)
$-CH_5O$ (Me·H_2O)	−33	329.0676	(2)	269.0471	(9)				
$-C_2H_3O$ (Me·CO)	−43	319.0803	(8)	259.0579	(9)	245.0448	(1)	305.0657	(6)
$-C_2H_4O$ (Me·CHO)	−44			258.0517	(22)				
$-C_2H_5O$*	−45							303.0502	(4)
$-CH_2O_2$ (H_2O·CO)	−46			256.0737	(7)				
$-CH_3O_2$ (H_2O·CHO)	−47			255.0668	(7)				
$-C_3H_6O$ (Me·Me·CO)	−58	304.0561	(9)			230.0216	(6)	290.0403	(3)
$-C_3H_7O$ (Me·Me·CHO)	−59	303.0483	(5)					289.0357	(2)
$-C_2H_4O_2$*	−60							288.0644	(2)

*Fragments most probably due to impurities of other xanthones.

evaporation of the methanol. When dilute HCl was added to the dried methanol fraction and the solution extracted before and after heating (hydrolysing) with chloroform, the chloroform fraction after hydrolysis yielded a yellow solution, and showed the xanthones **1** and **6** on TLC. This indicates that these xanthones also occur as glycosides in the plant material.

The 1,3,5,8-tetraoxygenated xanthones which were isolated are among the most common xanthones accumulating in members of the Gentianaceae [3]. The 1,3,5,6,7,8 hexaoxygenated xanthones, however, have only been reported in *Canscora decussata* [15] and *Eustoma grandiflora* [13] and from the genus *Centaurium*.

When we published our preliminary reports [1], no xanthones had been reported before in *Centaurium* species and the two hexaoxygenated xanthones **6** and **7** were new natural products. Later, however, generally without reference to this preliminary paper, other workers reported the isolation of xanthones with varying oxygenation patterns including **1** and **6** but not **2** and **7**, from *C. erythraea* [7, 9, 17–19], *C. cachanlahuen* [8], *C. linariifolium* [16, 20] and *C. pulchellum* [21] (Table 1). The xanthones **2** and **7** were not isolated from these plants, most probably because of the plant part that was used. Whereas we used roots for the isolation, all other investigators extracted the xanthones from the aerial parts or from whole plants. Even in the aerial parts of *C. littorale* the xanthone **7** was not detected on TLC (system A), although it is the main xanthone in the roots.

Recently we reported the results of screening for the 1,8-dihydroxyxanthones **1**, **3** and **6** and their β-monoglucosides in the aerial parts of no less than 99 populations of nine European and two American *Centaurium* species using TLC system B [22]. Only the xanthones that accumulate in major amounts were detected (detection limit: about 0.2%). A summary of these results is included in Table 1.

EXPERIMENTAL

General. Mps are uncorr. ^1H NMR spectra are recorded at 60 or 100 MHz and ^{13}C NMR spectra at 25.2 MHz, both in $CDCl_3$ using TMS as internal standard. MS spectra were recorded by direct inlet at 70 eV.

TLC. The following TLC systems were used; A, toluene–petrol (bp 40–60°)–HCO_2Et–HCO_2H (21:21:7:1) as solvent in combination with precoated silica gel plates. B, Toluene satd with H_2O as solvent in combination with precoated silanized silica gel plates. The plates were developed in unsaturated chambers over a distance of 15 cm. The xanthones were detected in UV-254 and 366 and in daylight, before and after spraying successively with 5% KOH in MeOH and fast blue salt B reagent.

Plant material. Flowering plants of *Centaurium littorale* subsp. *littorale* (2n = 40) (coll. no.: F-749VI6) were collected in August, 1974 in the Bijlmermeer near Amsterdam. The plant was identified via the treatment used by Melderis (1972) in Flora Europaea. Voucher specimens are kept at the Farmaceutisch Laboratorium, Utrecht and will be deposited later in the Herbarium Utrecht (U). The chromosomes were counted by Drs. J. van Loon, Populatie- en Evolutiebiologie, Rijksuniversiteit Utrecht.

Isolation. Air-dried and milled root of *C. littorale* (1.0 kg) was extracted successively in a Soxhlet with $CHCl_3$ and MeOH. The $CHCl_3$ extract was evapd and the portion soluble in petrol (bp 40–60°) was fractionated by successive extraction with 5% $NaHCO_3$ (B-fraction), 5% Na_2CO_3 (K-fraction) and 1% NaOH. The remaining organic solvent layer (N_a-fraction) was washed, dried and evapd to give a yellow solid from which the compound **7** was obtained in a pure form by crystallization. The aq. NaOH layer was extracted with $CHCl_3$ (3 × 50 ml). The combined $CHCl_3$ extracts (N_b-fraction) were washed, dried and evapd to yield a yellow solid, from which the xanthone **2** was crystallized. The remaining aq. NaOH layer was made acid and extracted with EtOAc. The combined extracts (L-fraction) were washed, dried and evapd to yield a yellow solid. On TLC the L-fraction showed

two major spots of the two components **1** and **6** in almost equal amounts. These xanthones were obtained in a pure form by means of prep TLC (system A) with 1.0 mm thick silica gel layers and by crystallization.

The $CHCl_3$ extract was evapd under red. pres. and the residue dissolved in 2 N HCl. The aq. solution was extracted successively with $CHCl_3$ (1 × 50 ml) before (M-fraction) and after boiling for 30 min (Mh-fraction). The Mh-fraction was washed with H_2O, dried and evapd to give a yellow solid.

Compound **1**. 1,8-Dihydroxy-3,5-dimethoxyxanthone, $C_{15}H_{12}O_6$, mp 185–187° (yellow needles, hexane p.a.) 90 mg. TLC: R_f in system A 0.50, B 0.73, KOH (UV366): brown. UV λ_{max}^{EtOH} nm (log ε): 235 (4.30), 255 (4.43), 279 (4.27), 300 sh (3.86), 335 (4.10), ca 384 sh (3.56); UV $\lambda_{max}^{EtOH+NaOH}$ nm (log ε): 248 (4.41), 365 (4.05); UV $\lambda_{max}^{EtOH+AlCl_3}$ (log ε): 257 (4.30), 286 (4.33), 324 (3.91), 370 (4.00). ^{1}H NMR (60 MHz, $CDCl_3$): δ3.93 (3H, *s*, OMe), 3.99 (3H, *s*, OMe), 6.36 (H, *d*, J = 2.5 Hz, H-2), 6.55 (H, *d*, J = 2.5 Hz H-4), 6.72 (H, *d*, J = 9 Hz, H-7), 7.27 (H, *d*, J = 9 Hz, H-6), 11.43 (H, *s*, OH), 12.03 (H, *s*, OH). IR ν_{max}^{KBr} cm^{-1}: 1670, 1640, 1610, 1580. MS: see Table 3.

Compound **6**. 1,8-Dihydroxy-3,5,6,7-tetramethoxyxanthone, $C_{17}H_{16}O_8$, mp 173–177° (yellow prisms), 100 mg. TLC: R_f in system A 0.40, B 0.54; KOH (UV 366): brown. UV λ_{max}^{EtOH} nm (log ε): 236 (4.17), 259 (4.33), 335 (4.14), 380 sh (3.53) UV $\lambda_{max}^{EtOH+NaOH}$ nm (log ε): 254 (4.50), 360 (4.10); UV $\lambda_{max}^{EtOH+AlCl_3}$ (log ε): 260 sh (4.20), 278 (4.36), 327 (3.96), 366 (4.13). ^{1}H NMR (60 MHz, $CDCl_3$): δ3.95 (3H, *s*, OMe), 4.00 (6H, *s*, 2 × OMe), 4.17 (3H, *s*, OMe), 6.35 (H, *d*, J = 2 Hz, H-2), 6.52 (H, *d*, J = 2 Hz, H-4), 11.83 (H, *s*. OH), 11.93 (H, *s*, OH). ^{13}C NMR: see Table 2. IR ν_{max}^{KBr} cm^{-1}: 1662, 1620, 1600, 1565. MS: see Table 3.

Compound **7**. 1-Hydroxy-3,5,6,7,8-pentamethoxyxanthone, $C_{18}H_{18}O_8$, mp 119–120° (yellow needles), 300 mg. TLC: R_f in system A 0.28; B 0.27; KOH (UV 366): yellow fluorescence. UV λ_{max}^{EtOH} nm (log ε): 240 sh (4.21), 258 (4.36), 315 (4.07), 355 sh (3.56) UV $\lambda_{max}^{EtOH+NaOH}$ (log ε): 240 (4.25), 274 (4.12), 304 sh (3.73), 319 (3.89), 385 (3.62); UV $\lambda_{max}^{EtOH+AlCl_3}$ (log ε): 226 (4.19), 237 (4.17), 273 (4.27 ± 9), 347 (4.08), *ca* 406 (3.51). ^{1}H NMR (100 MHz, $CDCl_3$): δ3.88 (3H, *s*, OMe), 3.93 (3H, *s*, OMe), 4.00 (6H, *s*, 2 × OMe), 4.12 (3H, *s*, OMe), 6.31 (1H, *d*, J = 2 Hz, H-2), 6.43 (1H, *d*, J = 2 Hz, H-4), 13.40 (1H, *s*, OH). ^{13}C NMR: see Table 2. IR ν_{max}^{KBr} cm^{-1}: 1659, 1590, 1565. MS: see Table 3.

Acetate of **7** (**7a**). Acetylation of **7** with pyridine–Ac_2O overnight at room temp gave **7a**, mp 130.5–131.5 (white needles, EtOH); UV λ_{max}^{EtOH} nm (log ε): 245 (4.53), 280 (4.09), 304 (2.24), 334 sh (3.72) ^{1}H NMR (100 MHz, $CDCl_3$): δ2.48 (3H, *s*, 1-OAc), 3.92 (9H, *s*, 3 × OMe), 3.99 (3H, *s*, OMe), 4.11 (3H, *s*, OMe), 6.55 (1H, *d*, J = 2.5 Hz, H-2), 6.82 (1H, *d*, J = 2.5 Hz, H-4). IR ν_{max}^{KBr} cm^{-1}: 1760, 1665, 1635, 1598.

Compound **2**. 1-Hydroxy-3,5,8-trimethoxyxanthone, $C_{16}H_{14}O_6$, mp 214° (yellow crystals), 10 mg. TLC: R_f in system A 0.16; B 0.13; KOH (UV 366): yellow fluorescence. UV λ_{max}^{EtOH} nm (log ε): 220 (4.23), *ca* 240 sh (4.28), 252 (4.39), 275 (4.08), ca 300 sh (3.84), ca 370 sh (3.57); UV $\lambda_{max}^{EtOH+NaOH}$ nm (log ε): 244 (4.34), 264 (4.13), 274 (4.14), 331 (4.02), 380 sh (3.62); UV $\lambda_{max}^{EtOH+AlCl_3}$ (log ε): 258 (4.34), 268 (4.35), 283 (4.36), 321 (3.94), 363 (4.11). ^{1}H NMR (250 MHz, $CDCl_3$): δ3.86 (3H, *s*, OMe), 3.96 (3H, *s*, OMe), 3.97 (3H, *s*, OMe), 6.32 (H, *d*, J = 3 Hz, H-2), 6.49 (H, *d*, J = 3 Hz, H-4), 6.72 (H, *d*, J = 10 Hz, H-7), 7.19 (H, *d*, J = 10 Hz, H-6), 13.22 (H, *s*, OH), IR ν_{max}^{KBr} cm^{-1}: 1655, 1620, 1580. MS: see Table 3.

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