Bioorganic & Medicinal Chemistry Letters 19 (2009) 3521–3524

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Repenins A–D, four new antioxidative coumarinolignoids from *Duranta repens* Linn.

Nisar Ahmad [a], Fozia Zeb [b], Ijaz Ahmad [c,*], Fanghai Wang [d]

[a] Department of Plant Sciences, Kohat University of Science and Technology, Kohat-26000, N.W.F.P., Pakistan
[b] Kohat Institute of Medical Sciences, Kohat University of Science and Technology, Kohat-26000, N.W.F.P., Pakistan
[c] Department of Chemistry, Kohat University of Science and Technology, Kohat-26000, N.W.F.P., Pakistan
[d] Department of Biological Sciences, University of Zhongshan, Guangzhou-510275, China

ARTICLE INFO

Article history:
Received 20 October 2008
Revised 22 April 2009
Accepted 2 May 2009
Available online 7 May 2009

Keywords:
Duranta repens
Verbenaceae
Coumarinolignoids
Antioxidant

ABSTRACT

Phytochemical investigations on the $CHCl_3$-soluble fraction of the whole plant of *Duranta repens* Linn. led to the isolation of four new coumarinolignoids, Repenins A–D (**1–4**), along with the known coumarinolignoids, cleomiscosin A (**5**) and durantin A (**6**). Their structures were determined by modern spectroscopic analysis including 1D and 2D NMR techniques and chemical studies. The compounds (**1–6**) showed potent antioxidative scavenging activity against DPPH radicals, with IC_{50} values in the range 0.420–0.625 mM. Repenin B (**2**) displayed the strongest scavenging potential with IC_{50} values of (0.420 mM).

The genus *Duranta* (Verbenaceae) comprises about 35 species which mainly occur in West Indies, Tropical and South America. It is represented in Pakistan by the two species namely *Duranta repens* and *Duranta stenostachya*.[1]

Duranta repens Linn. (syn. *D. erecta, D. microphylla, D. plumieri* common name Sky Flower, Golden Dew Drop, Pigeon Berry) is a large sub-tropical shrubs to small tree up to 18 feet in height. It is commonly grown as a hedge plant and when trimmed, forms a strong compact hedge almost impenetrable to cattle.[2] *Duranta repens* is widely distributed in the Northern Area of Pakistan. Medicinally the fruit of this plant is used for the treatment of malaria.[3] The MeOH extract also shows insecticidal and antifeedant properties against *Aedes aegypti* and *Attagenus piceus*, respectively.[4]

Previous studies on the genus *Duranta* have resulted in the isolation of various compounds including coumarinolignoids,[5] (*E*)-cinnamic acid, (*E*)-*p*-methoxycinnamic acid,[6] diterpenoids,[7,8] flavonoids,[7,8] steroids,[9] glycosides of phenylpropanoids,[10,11] triterpenes,[12] and iridoids.[6,13,14]

Antioxidants, which scavenge active oxygen species (free radicals), were found in a variety of foodstuffs and are commonly referred to as scavengers.[15,16] Many oxidants are plant based and play an important role in protecting plants that are exposed to sunlight and live under severe oxygen stress. Antioxidants also play an important role in human health because the biologic defense mechanism cannot operate under severe oxygen stress. According to recent research, activated oxygen is thought to be major factor in aging, hardening of the arteries, diabetes, cancer and tissue in injury skin.[17,18] Indeed approximately 90% of age related diseases are linked to activated oxygen.

Free radicals have significant relevance in the inflammation process, cardiovascular disease,[19–21] arteriosclerosis, malaria, rheumatoid arthritis, neurodegenerative disease and aging process.[22,23] $CHCl_3$ soluble fraction of the title plant was found to be the most promising for the said activity and is therefore selected for further Phytochemical investigation.

Herein in this Letter we report the isolation and characterization of four new coumarinolignoids, Repenins A–D (**1–4**), along with the known coumarinolignoids, cleomiscosin A (**5**)[24] and durantin A (**6**)[5] from $CHCl_3$ soluble fraction of the plant. All the coumarinolignoids (**1–6**) showed potent antioxidant scavenging activity against DPPH radicals with IC_{50} values ranging from 0.420 to 0.625 mM.

Repenin A (**1**) was isolated as a light yellow amorphous powder. The positive-ion high resolution FAB-MS of **1** established the molecular formula $C_{29}H_{24}O_{10}$ showing a $[M+H]^+$ peak at *m/z* 533.1444 (calcd for $C_{29}H_{25}O_{10}$, 533.1447). The IR spectrum revealed the presence of the aromatic group (1590 cm^{-1}), α,β-unsaturated carbonyls (1720, 1715 cm^{-1}), a methoxyl (2930 cm^{-1}) and hydroxyl groups (3430 cm^{-1}). The UV maxima at 286 and 328 nm and the IR absorption at 1720 cm^{-1} along with the presence of two characteristic doublets of the methine protons in the

* Corresponding author. Tel.: +92 922 554565; fax: +92 922 554556.
E-mail address: drijaz_chem@yahoo.com (I. Ahmad).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.05.006

^{1}H NMR spectrum H-3 at δ 6.33 and H-4 at δ 7.81 with a coupling constant of 9.5 Hz suggested that **1** was a coumarin derivative.[25]

The ^{1}H NMR of **1** showed some downfield signals attributable to a phenolic proton at δ 6.78 (1H, s), three aromatic methines displaying an ABX pattern in which hydrogen at δ 7.10 appeared as a doublet (J = 1.9 Hz), another methine proton appeared as double doublet at δ 6.97 (J = 8.0, 1.9 Hz) while the remaining hydrogen of an ABX system appeared at δ 6.83 giving a doublet (J = 8.0 Hz). The ^{1}H NMR spectrum further showed two aromatic methoxyl groups at δ 3.89 and 3.83 (each 3H, s) and the propanoid moiety attached to aromatic ring and dioxane at δ 5.09 (1H, d, J = 8.1 Hz), 4.21 (1H, ddd, J = 8.1, 2.5, 1.7 Hz), 3.90 (1H, dd, J = 12.5, 2.5 Hz) and 4.13 (1H, dd, J = 12.5, 1.7 Hz)] for H-7′, H-8′, H-9′b and H-9′a, respectively.[26] The above spectral data were closely related to a coumarinolignoid, cleomiscosin A,[24] differing in having additional characteristic signals for *p*-hydroxycinnemoyl moiety [aromatic protons showing AA′, BB′ pattern with δ 7.40 (2H, d, J = 8.0 Hz) and δ 6.89 (2H, d, J = 8.0 Hz); trans olefinic protons at δ 7.51 (1H, d, J = 15.9 Hz) and δ 6.41 (1H, d, J = 15.9 Hz)] and was further confirmed by electron impact mass spectrum (EI-MS) showing intense peaks at *m/z* 147.

The fragmentation pattern in the electron impact mass spectrometry (EI-MS) was also similar to a coumarinolignan, cleomiscosin A,[24] showing strong peak at *m/z* 386 due to the loss of $C_9H_7O_2$ moiety. Further diagnostic fragments a, b and c (Fig. 1) at *m/z* 208, 180 and 137 originated from the ion at *m/z* 386 (link scan measurements) confirmed the presence of a methoxyl group in the coumarin moiety while another methoxyl and a phenolic groups in the phenyl ring.

The ^{13}C NMR spectra (BB and DEPT) of **1** showed the signals of 29 carbon atoms in agreement with the molecular formula. These included two methyl, one methylene, 14 methine and 12 quaternary carbons. The downfield signals at δ 165.7 and 160.5 could be assigned to carbonyl carbon of the coumarin and cinnamoyl carbonyl groups, respectively. The signal at δ 62.5 was assigned to the oxygenated methylene while the resonances at δ 159.3, 149.8, 148.5, 146.0, 140.8, 137.1, 132.2, 130.9, 130.2 × 2, 125.9, 121.9, 116.5, 116.0 × 2, 112.0, 111.7 and 100.6 were assigned to the aromatic rings. Further the signals at δ 144.7, 144.3, 117.0 and 114.7 showed the presence of two olefinic bonds (Table 1).

All the assignments were further confirmed by ^{1}H–^{13}C multiple bond interaction in HMBC spectrum of **1** (Fig. 2). The proton at δ 5.09 (H-7′) showed ^2J interactions with C-8′ (δ 75.8) and C-1′ (δ 130.9) and ^3J correlations with C-9′ (δ 62.5), C-2′ (δ 111.7) and C-6′ (δ 121.9). The oxymethine proton at δ 4.21 (H-8′) showed ^2J and ^3J correlations with C-9′ (δ 62.5), C-7′ (δ 76.9) and C-1′ (δ 130.9) whereas the H-9′ protons at δ 4.13 and 3.96 correlated with C-8′ (δ 75.8), C-7′ (δ 76.9) and carbonyl carbon of cinnamoyl moiety (δ 165.7) and olefinic proton (H-2″) at δ 6.41 showed cross peak with carbonyl carbon (δ 165.7). These correlations of HMBC spectrum confirmed the attachment of cinnamoyloxy methylene at C-8′ and that of trisubstituted phenyl at C-7′. The presence of methoxyl groups at C-6 and C-3′ and phenolic group at C-4′ could also be inferred through HMBC correlations. The methoxyl group at δ 3.83 correlated with C-6 (δ 137.1) and other methoxyl group at δ 3.89 showed interaction with C-3′ (δ 149.8). The proton of the phenyl ring at δ 7.10 (H-2′) correlated with C-7′ (δ 76.9), C-6′ (δ 121.9) and C-4′ (δ 148.5) and another aromatic proton resonating at δ 6.97 (H-6′) coupled with C-7′ (δ 76.9), C-4′ (δ 148.5) and C-2′ (δ 111.7). The proton at δ 6.83 (H-5′) showed interactions with C-4′ (δ 148.5), C-3′ (δ 149.8) and C-1′ (δ 130.9). These results confirmed the 1,3,4 trisubstituted pattern of phenyl ring. These interactions were in suggestive of presence of feruloyl like substitution pattern.

The coumarinolignans occur naturally as regioisomeric pairs due to the linkage of benzodioxan moiety to the coumarin core. The structure was finally assigned by the selective heteronuclear decoupling experiments.[27] When the C-7′ and C-8′ hydrogen signals at δ 5.09 and 4.21 were irradiated, the carbon signals for C-7 (δ 132.2) and C-8 (δ 140.8), respectively showed significant sharpening. The coupling constant (J = 8.1 Hz) between the two vicinal oxymethine protons of C-7′ and C-8′ indicated that the phenyl group and the cinnamoyloxymethylene were *trans* oriented.[28] Hence the relative stereochemistry of **1** was deduced. However in viewing the optical inactivity, the ($[\alpha]_D^{25}$ = ±0), the compound was concluded to be a racemic.[25,27] All these evidences were in

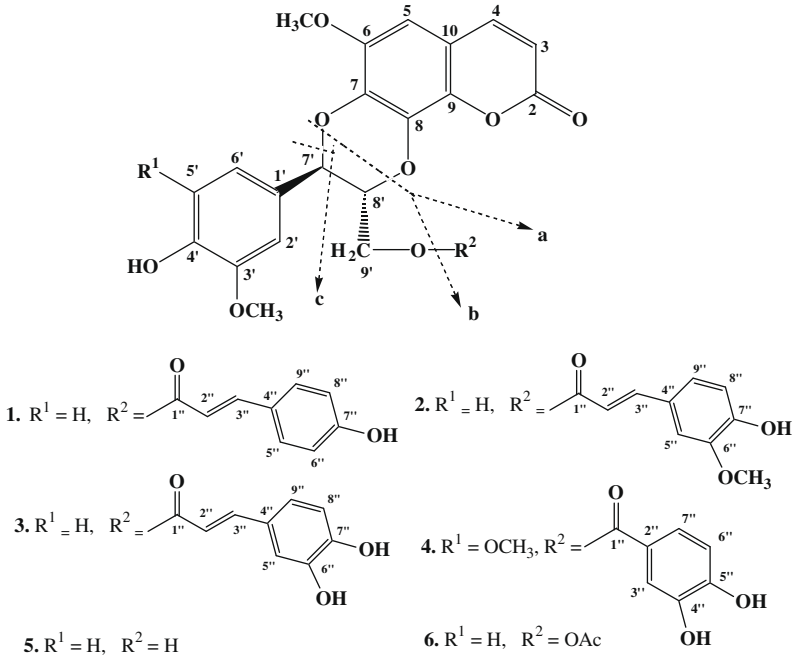

Figure 1. Structures and important mass fragmentation pattern of coumarinolignoids (**1**–**6**).

Table 1
^{1}H (400 MHz) and ^{13}C NMR (100 MHz) assignments (δ/ppm) of Repenins (**1**–**4**) in $CDCl_3$

Position	1		2		3		4	
	δ (^{1}H)	δ (^{13}C)	δ (^{1}H)	δ (^{13}C)	δ (^{1}H)	δ (^{13}C)	δ (^{1}H)	δ (^{13}C)
2	—	160.5	—	160.3	—	160.4	—	160.2
3	6.33 (d, 9.5)	114.7	6.31 (d, 9.5)	114.2	6.30 (d, 9.5)	113.9	6.32 (d, 9.5)	114.4
4	7.81 (d, 9.5)	144.3	7.83 (d, 9.5)	144.0	7.85 (d, 9.5)	144.2	7.83 (d, 9.5)	144.0
5	6.78 (s)	100.6	6.80 (s)	100.8	6.80 (s)	100.6	6.79 (s)	100.5
6	—	137.1	—	137.3	—	137.0	—	137.3
7	—	132.2	—	132.5	—	132.3	—	132.4
8	—	140.8	—	140.9	—	140.7	—	140.6
9	—	146.0	—	146.3	—	146.2	—	146.3
10	—	112.0	—	111.8	—	111.9	—	112.0
1′	—	130.9	—	130.6	—	130.7	—	130.6
2′	7.10 (d, 1.9)	111.7	7.07 (d, 1.8)	111.8	7.05 (d, 1.9)	111.7	6.89 (s)	111.6
3′	—	149.8	—	149.9	—	149.7	—	149.9
4′	—	148.5	—	148.7	—	148.4	—	148.6
5′	6.83 (d, 8.0)	116.5	6.84 (d, 8.2)	116.3	6.81 (d, 8.1)	116.1	—	116.4
6′	6.97 (dd, 8.0, 1.9)	121.9	6.95 (dd, 8.2, 1.8)	121.7	6.94 (dd, 8.1, 1.9)	121.8	6.89 (s)	122.3
7′	5.09 (d, 8.1)	76.9	5.07 (d, 8.1)	77.2	5.06 (d, 8.1)	77.3	5.03 (d, 8.1)	77.0
8′	4.21 (ddd, 8.1, 2.5, 1.7)	75.8	4.20 (ddd, 8.1, 2.6, 1.7)	76.1	4.19 (ddd, 8.1, 2.7, 1.9)	76.0	4.25 (ddd, 8.1, 2.6, 1.8)	75.9
9′	3.90 (dd, 12.5, 2.5) 4.13 (dd, 12.5, 1.7)	62.5	3.90 (dd, 12.6, 2.6) 4.10 (dd, 12.6, 1.7)	62.3	3.89 (dd, 12.6, 2.7) 4.15 (dd, 12.6, 1.9)	62.4	3.93 (dd, 12.5, 1.8) 4.13 (dd, 12.5, 2.6)	62.7
1″	—	165.7	—	165.5	—	165.3	—	163.0
2″	6.41 (d, 15.9)	117.0	6.45 (d, 16.0)	117.3	6.38 (d, 16.2)	117.5	—	124.2
3″	7.51 (d, 15.9)	144.7	7.55 (d, 16.0)	144.9	7.47 (d, 16.2)	144.8	7.50 (d, 2.0)	115.7
4″	—	125.9	—	126.4	—	126.3	—	144.1
5″	7.40 (d, 8.0)	130.2	7.10 (d, 2.1)	112.9	7.08 (d, 2.2)	113.5	—	145.6
6″	6.89 (d, 8.0)	116.0	—	148.2	—	144.7	6.96 (d, 8.3)	116.2
7″	—	159.3	—	150.3	—	147.3	7.46 (dd, 8.3, 2.0)	127.9
8″	6.89 (d, 8.0)	116.0	6.70 (d, 8.0)	116.0	6.90 (d, 8.0)	116.0	—	—
9″	7.40 (d, 8.0)	130.2	7.02 (dd, 8.0, 2.1)	124.1	6.95 (dd, 8.0, 2.2)	123.9	—	—
OCH_3-6	3.83 (s)	56.4	3.80 (s)	56.3	3.81 (s)	56.5	3.79 (s)	56.2
OCH_3-3′	3.89 (s)	56.0	3.85 (s)	55.9	3.86 (s)	56.0	3.85 (s)	56.6
OCH_3-6″	—	—	3.77 (s)	56.1	—	—	—	—
OCH_3-5′	—	—	—	—	—	—	3.85 (s)	56.6

Multiplicities and coupling constants (J = Hz) are given in parenthesis. δ in ppm from TMS.

accordance to the assigned structure of coumarinolignan as Repenin A (**1**).

Repenin B **(2)** was obtained as a light yellow amorphous solid, molecular formula $C_{30}H_{26}O_{11}$ by $[M+H]^+$ peak at *m/z* 563.1550 in HR-FAB-MS spectrometry (calcd for $C_{30}H_{27}O_{11}$; 563.1553).

The IR, ^{1}H and ^{13}C NMR spectra of **2** were almost identical to those of **1** except the difference due to 6″,7″-dioxigenated cinnamoyl moiety. The substitution pattern was confirmed by ^{1}H NMR which showed further ABX system at δ 7.10 (1H, d, J = 2.1 Hz, H-5″), 7.02 (1H, dd, J = 8.0, 2.1 Hz, H-9″) and 6.70 (1H, d, J = 8.0 Hz, H-8″).[29]

The ^{13}C NMR spectra of **2** also confirmed the 6″,7″-dioxigenated cinnamoyl group showing downfield signals at 150.3 (C-7″) and 148.2 (C-6″).[29] The additional aryl methoxyl group was also evident both from ^{1}H and ^{13}C NMR showing signals at δ 3.77 and δ 56.1, respectively. This was further confirmed by electron impact mass spectrum (EI-MS) showing intense peaks at *m/z* 177. The position of the additional methoxyl group was further confirmed by HMBC correlations in which the methoxy protons at δ 3.77 showed correlation with C-6″ (δ 148.2).

Repenin C **(3)** was isolated as a light yellow amorphous powder. The molecular formula was shown to be $C_{29}H_{24}O_{11}$ by $[M+H]^+$ peak at *m/z* 549.1395 in HR-FAB-MS (calcd for $C_{29}H_{25}O_{11}$; 549.1397).

The UV, IR, MS and NMR data of compound **3** suggested that **3** had the same skeleton as that of **1**, except the difference due to 6″,7″-dihydroxylcinnamoyl moiety, which was confirmed by ^{1}H NMR [ABX system at δ 7.08 (1H, d, J = 2.2 Hz, H-5″), 6.95 (1H, dd, J = 2.2, 8.0 Hz, H-9″) and 6.90 (1H, d, J = 8.0 Hz, H-8″)].[29]

The ^{13}C NMR spectra of **3** also confirmed the 6″,7″-dihydroxylcinnamoyl group showing downfield signals at 147.3 (C-7″) and 144.7 (C-6″)[29] and was further confirmed by electron impact mass spectrum (EI-MS) showing intense peaks at *m/z* 163.

Repenin D **(4)** was obtained as a light yellow amorphous solid, molecular formula $C_{28}H_{24}O_{12}$ by $[M+H]^+$ peak at *m/z* 553.1344 in HR-FAB-MS spectrometry (calcd for $C_{28}H_{25}O_{12}$; 553.1346).

The UV, IR, MS and NMR spectra of compound **4** closely resembled to those of **1**. The EI-MS spectrum gave diagnostic fragments a, b and c (Fig. 1) at *m/z* 208, 210 and 167. The fragments at *m/z* 208 ($C_{10}H_8O_5$) indicated the presence of one methoxyl group in the coumarin nucleus and the fragments b and c at *m/z* 210 ($C_{11}H_{14}O_4$) and 167 ($C_9H_{11}O_3$) indicated the presence of two methoxyls and one phenolic functionalities in the phenyl propanoid moiety.[30,31]

The assignment of protons in the ^{1}H NMR spectrum was made by the combination of their spin pattern analysis, HMQC and by the spectral comparison with that of **1**. The difference in the ^{1}H NMR spectrum of **4** with that of **1** was the substitution pattern of phenyl ring in which two aromatic methines at δ 6.89 (2H, s) and two aryl methoxyls at δ 3.85 (6H, s) were shown to be chemically equivalent confirming the symmetrical substitution pattern of the aromatic ring.[25] The other difference in the ^{1}H NMR spectrum of **4** with that of **1** was due to 4″,5″-dihydroxylbenzoyl moiety, instead of cinnamoyl group. The substitution pattern was confirmed by ^{1}H NMR which showed an ABX system at δ 7.50 (d, 2.0 Hz, H-3″), 7.46 (1H, dd, J = 2.0, 8.3 Hz, H-7″) and 6.96 (1H, d, J = 8.3 Hz, H-6″).[29]

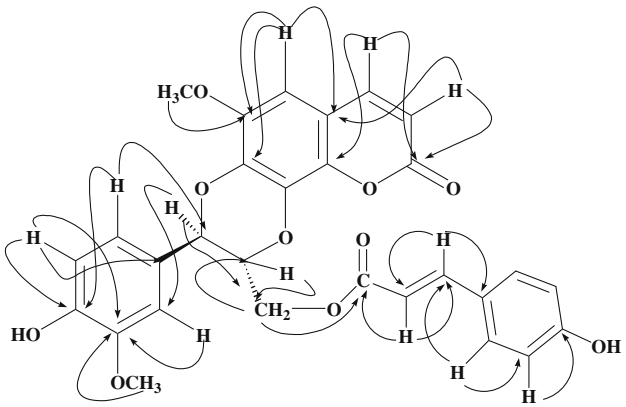

Figure 2. Important HMBC correlations of **1.**

Table 2
Antioxidant activities of coumarinolignoids (**1**–**6**)

S. No.	Name of compounds	Antioxidant activity IC_{50} ± SEM[a] (mM)
1	Repenin A	0.530 ± 0.08
2	Repenin B	0.420 ± 0.09
3	Repenin C	0.450 ± 0.10
4	Repenin D	0.510 ± 0.07
5	Cleomiscosin A	0.612 ± 0.10
6	Durantin A	0.625 ± 0.09
7	3-*t*-Butyl-4-hydroxyanisole (BHA)[b]	0.043 ± 0.07

[a] Standard error of mean of three determinations.
[b] Positive control used in antioxidant assays.

The ^{13}C NMR spectra of **4** also confirmed the 4″,5″-dihydroxybenzoyl group showing downfield signals at 145.6 (C-5″) and 144.1 (C-4″).[29] This was further confirmed by electron impact mass spectrum (EI-MS) showing intense peaks at *m/z* 137.

Alkaline hydrolysis of **1–4** provided *p*-hydroxy cinnamic acid, 3-methoxy,4-hydroxy cinnamic acid, 3,4-dihydroxy cinnamic acid and 3,4-dihydroxy benzoic acid, respectively (characterized through m.m.p., Co-TLC, superimposable IR), providing conclusive evidence for the presence of these moieties in the respective compounds. The important HMBC correlations were in complete agreement to the assigned structures (**1–4**). Surprisingly the Repenins A–D (**1–4**) showed no optical activity and were therefore recemic.[25,27]

We investigated the general antioxidative effects of the compounds to inhibit DPPH radicals for BHA and the coumarinolignoids (**1**–**6**) at a concentration of 1 mM, respectively with the IC_{50} values ranging between 0.420 and 0.625 mM, indicating a potent activity (Table 2). Compounds **2**, with 4-hydroxy-3-methoxyphenyl and 4-hydroxy-3-methoxycinnamoyl moieties and **4,** with 4-hydroxy-3,5-dimethoxyphenyl and 3,4-dihydroxybenzoyl moieties, showed greater potential to scavenge the DPPH radicals with the IC_{50} values (0.420 and 0.450 mM), respectively. Among these active substances, the known compounds cleomiscosin A (**5**) and durantin A (**6**), with one 4-hydroxy-3-methoxyphenyl moiety (each), showed less strong activity (IC_{50} values 0.610 and 0.625 mM), respectively, than all the tested compounds, but still significant activities in the test. BHA was used as a standard (IC_{50} = 0.043 mM).

The antioxidative activity was also examined in term of the chemical structures including those of functional radical and its orientation. Hydroxy and methoxy groups in the 1,4- and 1,3-orienntation at phenyl/cinnamoyle are mainly involved in the scavenging of coumarinolignoids (**1**-**6**). The *ortho* substitution with electron donor methoxy group in 1,4-oriennted phenyl/cinnamoyle hydroxyl compounds slightly increase the scavenging activity. This was observed in compounds **2** and **3**. Based on these results, a benzene ring where the hydroxyl radical is in 1,4-orienntation allow the oxygen atom to share a positive charge, thereby causing stabilization through delocalization. Because of the electron donating effect of the methoxy group in 1,3-orienntation, it helps to stabilize positive charge and this is taught to influence the scavenging ability. The substitution radical of 1,2- or 1,4-orienntation generally donate an electron to the aromatic ring to activate it, either by the resonance effect or inductive effect. This tendency was also found in the all scavenging tests against the coumarinolignoids (**1**–**6**).

The compounds **1–6** could be lead compounds in treatment of oxidative-stress related human diseases. However, further in vivo study would help in exploring the pharmacological properties of these compounds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.05.006.

References and notes

1. Nasir, E.; Ali, S. I.. In *Flora of West Pakistan*; Department of Botany, University of Karachi, 1974; 77. 18.
2. Sastri, B. N.. In *The Wealth of India*'; Publication and Information Directorate CSIR: New Delhi, India, 1952; III. 117.
3. Perry, L. M.; Metzger, J. *Medicinal Plants of East and Southeast Asia*; The MIT press: Cambridge, England, 1980.
4. Grainge, M.; Ahmad, S. *Hand Book of Plants with Pest-Control Properties*; J. Wiley & Sons: New York, 1998.
5. Iqbal, K.; Anis, I.; Muhktar, N.; Malik, A. *Heterocycles* **2003**, *60*, 151.
6. Kuo, Y. H.; Chen, Z. S.; Lin, Y. L. *Chem. Pharm. Bull.* **1996**, *44*, 429.
7. Anis, I.; Anis, E.; Ahmed, S.; Mustafa, G.; Malik, A.; Amtul, Z.; Rahman, A.-U. *Helv. Chim. Acta* **2001**, *84*, 649.
8. Inis, I.; Ahmed, S.; Malik, A.; Yasin, A.; Choudhary, M. I. *Chem. Pharm. Bull.* **2002**, *50*, 515.
9. Ahmed, S.; Nizami, T. A.; Nawaz, H. R.; Malik, A. *Fitoterapia* **1998**, *LXIX*, 448.
10. Lin, Y. L.; Kuo, Y. H. *Chem. Pharm. Bull.* **1992**, *40*, 1928.
11. Yoshio, T.; Youko, M.; Takashi, M.; Choei, O.; Eiji, H.; Anki, T.; Hideaki, O. *Phytochemistry* **1995**, *39*, 829.
12. Hiradate, S.; Yada, H.; Ishii, T.; Nakajima, N.; Ohnishi-Kameyama, M.; Sugie, H.; Zungsontiporn, S.; Fuji, Y. *Phytochemistry* **1999**, *52*, 1223.
13. Rimpler, H.; Timm, H. *Z. Naturforsch.* **1974**, *29c*, 111.
14. Rao, C. B.; Vijay Kumar, E. K. S. *Indian J. Chem., Sect. B* **1978**, *16*, 844.
15. Beckman, J. S.; Beckman, T. W.; Chen, J.; Marshall, P. A.; Freeman, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1620.
16. Bohme, G. A.; Bon, C.; Lemaire, M.; Reibaud, M.; Piot, O.; Stutzmann, J. M.; Doble, A.; Blanchard, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 9191.
17. Ito, N.; Hirose, M. *Adv. Cancer Res.* **1989**, *53*, 247.
18. Beckman, J. S.; Ye, Y. Z.; Anderson, P. J.; Chen, J.; Accavitti, M. A.; Tarpey, M. M.; White, C. R. *Biol. Chem. Hoppe-Seyler* **1994**, *375*, 81.
19. Hertog, M. G.; Feskens, E. J.; Hollman, P. C.; Katan, M. B.; Kromhout, D. *Lancet* **1993**, *342*, 1007.
20. Moure, A.; Cruz, J.; Franco, D.; Dominguez, M.; Sineiro, J.; Dominguez, H.; Nunez, J. *Food Chem.* **2001**, *72*, 145.
21. Hollman, P. C.; Hertog, M. G.; Katan, M. *Food Chem.* **1996**, *57*, 43.
22. Hunt, E. J.; Lester, C. E.; Lester, P. A.; Tackett, R. L. *Life Sci.* **2001**, *69*, 181.
23. Meyer, A. S.; Heiononen, M.; Frankel, E. N. *Food Chem.* **1998**, *61*, 71.
24. Ray, A. B.; Chattopadhyay, S. K.; Kumar, S. *Tetrahedron* **1985**, *41*, 209.
25. Yon, B. S.; Lee, I. K.; Ryoo, I. J.; Yoo, I. D. *J. Nat. Prod.* **2001**, *64*, 1238.
26. Arnoldi, A.; Aronona, A.; Merlini, L. *Heterocycles* **1984**, *22*, 1537.
27. Ray, A. B.; Chattopadhyay, S. K. *Heterocycles* **1982**, *19*, 19.
28. Kumar, S.; Ray, A. B.; Konno, C.; Dshima, Y.; Hikino, H. *Phytochemistry* **1988**, *27*, 636.
29. Ono, M.; Ito, Y.; Kubo, S.; Nohara, T. *Chem. Pharm. Bull.* **1997**, *45*, 1094.
30. Lin-Gen, Z.; Seligmann, O.; Wagner, H. *Phytochemistry* **1983**, *22*, 617.
31. Bhandari, P.; Pant, P.; Rastogi, R. P. *Phytochemistry* **1982**, *21*, 2147.