Monoamine Oxidase Inhibitory Coumarins from the Aerial Parts of *Dictamnus albus*

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The methanol extract from the aerial parts of *Dictamnus albus* was active in inhibiting monoamine oxidase (MAO) from the mouse brain. Activity-guided fractionation led to the isolation of four known coumarins, 7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin (**1**), auraptene (**2**), umbelliferone (**3**), and xanthotoxin (**4**), as active compounds along with an inactive alkaloid, skimmianine (**5**). Compounds **1** and **2** inhibited MAO activity in a concentration-dependent manner with IC_{50} values of 0.7 and 1.7 µM, respectively. Compounds **1** and **2** showed a slight and potently selective inhibitory effect against MAO-B (IC_{50} 0.5 and 0.6 µM, respectively) compared to MAO-A (IC_{50} 1.3 and 34.6 µM, respectively). According to kinetic analyses derived by Lineweaver-Burk reciprocal plots, compounds **1** and **2** exhibited a competitive inhibition to MAO-B.

Key words: *Dictamnus albus*, Rutaceae, Coumarin, Monoamine oxidase inhibitor

INTRODUCTION

Dictamnus albus (Rutaceae) is a perennial plant widely distributed in Korea, China, and Eastern Siberia. The root bark of *D. albus* has been used to treat jaundice, leprosy, cough, rheumatism, amenorrhea, and some skin diseases (Jung and Shin, 1990). Previous phytochemical studies with this plant have isolated and identified several dissimilar compounds including limonoids, furoquinoline alkaloids, flavonoids, coumarins, sesquiterpenes, and sesquiterpene glycosides (Chang *et al.*, 2001, 2002; Nam *et al.*, 2005; Souleles, 1989; Takeuchi *et al.*, 1993; Zhao *et al.*, 1998). It has been reported that fraxinellone exhibits antifertility activity while obacunone potentiates the cytotoxic effects of vinblastine against L1210 cells (Jung *et al.*, 2000; Woo *et al.*, 1987). There are no reports, however, describing monoamine oxidase (MAO) inhibitory effects of *D. albus* extracts or constituents.

MAO catalyzes the oxidative deamination of a number of neurotransmitters including dopamine (DA), norepinephrine (NE), and 5-hydroxytryptamine (5-HT) (Benedetti

and Dostert, 1992). MAO is classified into two forms, MAO-A and MAO-B, which differ in amino acid sequence, substrate specificity, susceptibility to specific inhibitors, and tissue distribution. MAO-A preferentially deaminates the neurotransmitters 5-HT, NE, and epinephrine and is irreversibly inhibited by low concentrations of clorgyline. MAO-B preferentially deaminates β-phenylethylamine and benzylamine and is irreversibly inhibited by *l*-deprenyl (Benedetti and Dostert, 1992; Youdim and Bakhle, 2006).

Selective MAO-A inhibitors are used in the treatment of neurological disorders such as depression, whereas the MAO-B inhibitors are useful for the treatment of Parkinson's disease and Alzheimer's disease (Yamada and Yasuhara, 2004; Youdim *et al.*, 2006; Youdim and Bakhle, 2006).

As a part of our ongoing research on MAO inhibitors of higher plant origin, the methanol extract from the aerial parts of *D. albus* was found to possess significant inhibitory effects on mouse brain MAO. We report herein the isolation and structural determination of MAO inhibitors in *D. albus*, together with MAO inhibitory activities of the isolated compounds.

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MATERIALS AND METHODS

General experimental procedures

The optical rotations were measured with a JASCO DIP-370 polarimeter. Melting points were measured on a Büchi model B-540 without correction. The UV and IR spectra were recorded on a JASCO UV-550 and Perkin Elmer model LE-599 spectrometer, respectively. The ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker AMX 500 MHz NMR spectrometer with tetramethylsilane (TMS) as an internal standard. The EI-MS was recorded on Hewlett-Packard MS 5988 mass spectrometer. Column chromatography was performed using silica gel (Kieselgel 60, 70-230 mesh and 230-400 mesh, Merck) and Diaion HP-20P, and thin layer chromatography (TLC) using pre-coated silica gel 60 F_{254} (0.2 mm, Merck). The fluorescence intensities were measured on a Perkin Elmer LS50B fluorescence spectrophotometer.

Kynuramine, clorgyline, *l*-deprenyl, 4-hydroxyquinoline, iproniazid, amitriptyline and bovine serum albumin (BSA) were purchased from the Sigma Chemical Co. (St. Louis, MO, U.S.A.).

Plant materials

The aerial parts of *D. albus* were collected at the herb garden of the Chungbuk National University, Cheongju, Korea, in September 2003 and identified by Emeritus Prof. Kyong Soon Lee, a plant taxonomist at Chungbuk National University. A voucher specimen (CBNU 00127) has been deposited at the Herbarium of College of Pharmacy, Chungbuk National University, Korea.

Activity-guided isolation

The dried aerial parts of *D. albus* (1 kg) were extracted three times with MeOH at room temperature. After filtration and evaporation of the solvent under reduced pressure, the combined methanol extract (150 g) was suspended in water (1.5 L), and then successively partitioned with hexane (3 × 1.5 L), CH_2Cl_2 (3 × 1.5 L), and EtOAc (3 × 1.5 L). The most active hexane extract (15 g) was subjected to silica gel column chromatography (5 × 30 cm), and eluted with hexane-acetone (50:1, 20:1, 10:1, 5:1, 2:1, 0:1), to give six fractions (DH-1 - DH-6). The active fraction (DH-3) was further fractionated using a silica gel column and eluted with hexane-EtOAc (50:1, 20:1, 10:1, 2:1, 0:1), to yield five subfractions (DH-31 - DH-35). The subfraction DH-34 was rechromatographed on Diaion HP-20P using acetonitrile-H_2O (30:70, 50:50, 75:25, 100:0), and afforded 7-(6'*R*-hydroxy-3', 7'-dimethyl-2'*E*, 7'-octadienyloxy) coumarin (1, 15 mg), auraptene (2, 22 mg), and umbelliferone (3, 25 mg).

The CH_2Cl_2-soluble extract (10 g) was also separated over a silica gel column (3 × 20 cm), and eluted with hexane-acetone (15:1, 10:1, 5:1, 2:1, 0:1), to provide five fractions (DC-1 - DC-5). The active fraction (DC-3) was further purified over a silica gel column (2 × 20 cm), eluted with CH_2Cl_2-acetone (50:1, 30:1, 20:1, 10:1, 5:1), and yielded auraptene (2, 5 mg) and xanthotoxin (4, 15 mg). Skimmianine (5, 11 mg) was obtained by recrystallization in a CH_2Cl_2-acetone mixture from fraction DC-4.

Characterization of 7-(6'*R*-hydroxy-3', 7'-dimethyl-2'*E*, 7'-octadienyloxy) coumarin (1)

Colorless prism; mp 72-75°C; UV (MeOH): λ_{max} nm (log ε): 320 (4.0); $[\alpha]_D^{25}$ +15 (c 0.1, MeOH); EI-MS *m/z* 314 [M]$^+$; ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 7.67 (1H, d, *J* = 9.5 Hz, H-4), 7.51 (1H, d, *J* = 8.6 Hz, H-5), 6.90 (1H, dd, *J* = 8.6, 2.4 Hz, H-6), 6.89 (1H, d, *J* = 2.4 Hz, H-8), 6.23 (1H, d, *J* = 9.5 Hz, H-3), 5.49 (1H, br t, *J* = 6.7 Hz, H-2'), 4.89 (1H, br s, H-8'), 4.80 (1H, br s, H-8'), 4.66 (2H, d, *J* = 6.7 Hz, H-1'), 3.97 (1H, br t, *J* = 6.4 Hz, H-6'), 2.09-2.12 (2H, m, H-4'), 1.78 (3H, s, 10'-CH$_3$), 1.70 (3H, s, 9'-CH$_3$), 1.60-1.67 (2H, m, H-5'); ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 163.8 (C-2), 163.4 (C-7), 157.1 (C-8a), 148.7 (C-7'), 145.8 (C-4), 142.9 (C-3'), 130.4 (C-5), 120.4 (C-2'), 114.5 (C-4a), 114.0 (C-3), 113.2 (C-6), 111.5 (C-8'), 102.5 (C-8), 76.0 (C-6'), 66.5 (C-1'), 36.6 (C-4'), 34.1 (C-5'), 17.6 (C-10'), 16.8 (C-9').

Characterization of auraptene (2)

Colorless needle crystal; mp 71-72°C; UV (MeOH): λ_{max} nm (log ε): 325 (4.2); EI-MS *m/z* 286 [M]$^+$; ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 7.86 (1H, d, *J* = 9.4 Hz, H-4), 7.51 (1H, d, *J* = 8.3 Hz, H-5), 6.90 (1H, dd, *J* = 8.3, 2.3 Hz, H-6), 6.88 (1H, d, *J* = 2.3 Hz, H-8), 6.22 (1H, d, *J* = 9.4 Hz, H-3), 5.46 (1H, br t, *J* = 6.6 Hz, H-2'), 5.07 (1H, m, H-6'), 4.65 (2H, d, *J* = 6.6 Hz, H-1'), 2.10 (4H, m, H-4', H-5'), 1.77 (3H, s, 9'-CH$_3$), 1.61 (3H, s, 8'-CH$_3$), 1.58 (3H, s, 10'-CH$_3$); ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 163.8 (C-2), 163.5 (C-7), 157.1 (C-8a), 145.8 (C-4), 143.0 (C-3'), 132.7 (C-7'), 130.4 (C-5), 124.9 (C-6'), 120.3 (C-2'), 114.6 (C-4a), 114.0 (C-3), 113.2 (C-6), 102.5 (C-8), 66.5 (C-1'), 40.5 (C-4'), 27.3 (C-8'), 25.8 (C-5'), 17.7 (C-10'), 16.7 (C-9').

Characterization of umbelliferone (3)

Pale yellow needle crystal; mp 200-201°C; UV (MeOH): λ_{max} nm (log ε): 321 (4.0); EI-MS *m/z* 162 [M]$^+$; ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 7.85 (1H, d, *J* = 9.5 Hz, H-4), 7.50 (1H, d, *J* = 8.4 Hz, H-5), 6.84 (1H, dd, *J* = 8.4, 2.2 Hz, H-6), 6.74 (1H, d, *J* = 2.2 Hz, H-8), 6.15 (1H, d, *J* = 9.5 Hz, H-3), 9.43 (1H, s, 7-OH); ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 161.9 (C-2), 161.0 (C-7), 157.0 (C-8a), 144.7 (C-4), 130.4 (C-5), 123.2 (C-4a), 113.7 (C-3), 112.8 (C-6), 103.3 (C-8).

Characterization of xanthotoxin (4)

Colorless needle; mp 146-148°C; UV (MeOH): λ_{max} nm (log ε): 305 (4.1); EI-MS *m/z* 216 [M]$^+$; ^{1}H-NMR (500 MHz,

CD$_3$OD) δ: 8.01 (1H, d, J = 9.6 Hz, H-4), 7.87 (1H, br s, H-2'), 7.54 (1H, s, H-5), 6.94 (1H, br s, H-3'), 6.37 (1H, d, J = 9.6 Hz, H-3), 4.24 (3H, s, 8-OCH$_3$); ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 162.7 (C-2), 149.1 (C-7), 148.5 (C-2'), 146.7 (C-4), 144.2 (C-8a), 133.9 (C-8), 128.0 (C-6), 118.0 (C-4a), 115.0 (C-3), 114.8 (C-5), 107.9 (C-3'), 61.8 (8-OCH$_3$).

Characterization of skimmianine (5)

Colorless needle; mp 177-178°C; UV (MeOH): λ$_{max}$ nm (log ε): 249 (4.6), 321 (3.9), 332 (3.8); EI-MS m/z 259 [M]$^+$; ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 8.01 (1H, d, J = 9.4 Hz, H-5), 7.58 (1H, d, J = 2.7 Hz, H-2), 7.23 (1H, d, J = 9.4 Hz, H-6), 7.04 (1H, d, J = 2.7 Hz, H-3), 4.42 (3H, s, 7-OCH$_3$), 4.12 (3H, s, 8-OCH$_3$), 4.03 (3H, s, 4-OCH$_3$); ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 164.4 (C-9a), 157.2 (C-7), 152.2 (C-4), 143.0 (C-2), 142.1 (C-8), 141.5 (C-8a), 118.2 (C-5), 114.9 (C-4a), 112.1 (C-6), 104.7 (C-3), 102.1 (C-3a), 61.7 (8-OCH$_3$), 59.0 (7-OCH$_3$), 56.8 (4-OCH$_3$).

MAO preparation and measurement of MAO activity

A mouse brain mitochondrial fraction was prepared as a source of MAO activity following the procedure described previously (Naoi *et al.*, 1989; Ro *et al.*, 2001). MAO activity was measured fluorometrically using kynuramine as a substrate according to the method of Kraml (Kraml, 1965; Ro *et al.*, 2001). In brief, the samples (50 μL) were added to 0.2 M potassium phosphate buffer (750 μL, pH 7.4), which contained 30 μL of mouse brain mitochondrial suspension. The reaction was initiated by the addition of 200 μL of 500 mM kynuramine. After incubation of 37°C for 30 min, the reaction was terminated by the addition of 250 μL of 10% ZnSO$_4$ and 50 μL of 1 N NaOH, and the reaction mixture was centrifuged at 3,000 × g for 5 min. 1.4 μL of 1 N NaOH was added in 700 μL of assay mixture taken from the supernatant, then the mixture was transferred into a fluoro 96-well plate. The fluorescence intensity of 4-hydroxyquinoline, which was formed from kynuramine by MAO, was measured at an emission wavelength of 380 nm and an excitation wavelength of 315 nm using a Perkin Elmer LS50B fluorescence spectrometer. Clorgyline (1 μM) or *l*-deprenyl (1 μM) was preincubated with the suspension for 15 min to measure MAO-B and MAO-A activity, respectively. A Lineweaver-Burk plot on MAO-B was obtained from incubations at five substrate concentrations. The inverse values of the reaction velocities were then represented as a function of the inverse value of the substrate concentration.

RESULTS AND DISCUSSION

The MeOH extract of the aerial parts of *D. albus* showed significant inhibitory effects on mouse brain MAO activity

(62.3% inhibition at 250 μg/mL). The MeOH extract was consecutively fractionated with hexane, CH$_2$Cl$_2$, EtOAc, and water. Of these fractions, the hexane and CH$_2$Cl$_2$ fractions exhibited 71.2% and 50.2% inhibition of MAO activity at a concentration of 200 μg/mL, respectively. Further activity-guided chromatographic purification of these two fractions led to the isolation of four known coumarins, 7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin (1), auraptene (2), umbelliferone (3), and xanthotoxin (4), as active compounds along with an inactive alkaloid, skimmianine (5). The structures of these isolates were identified by physical and spectroscopic measurement (mp, UV, MS, ^{1}H-NMR, ^{13}C-NMR, 2D NMR) and by comparing the data obtained with published values (Chakravarty *et al.*, 1999; Ishii *et al.*, 1983; Kanamori *et al.*, 1986; Masuda *et al.*, 1992; Stevenson *et al.*, 2003; Thanh *et al.*, 2004; Woo and Kang, 1985).

The compounds 1-5 were tested for their MAO inhibitory activity (Table I). Compounds 1 and 2 inhibited MAO activity in a dose-dependent manner with IC$_{50}$ values of 0.7 and 1.7 μM, respectively, which were stronger than that of iproniazid used as positive control (IC$_{50}$: 20.8 μM).

Table I. Inhibitory effects of compounds 1-5 from *D. albus* on MAO activity

	Concentration (μM)	MAO activity (% of control) (nmol/min/mg protein)	IC$_{50}$ (μM)
Control		0.835 ± 0.006 (100.0)	
Iproniazid	20	0.422 ± 0.008 (50.5)	20.8
Compound 1	0.1	0.593 ± 0.006 (71.0)	0.7
	1	0.385 ± 0.017 (46.1)**	
	5	0.271 ± 0.005 (32.5)***	
	10	0.204 ± 0.004 (24.4)**	
Compound 2	0.1	0.637 ± 0.014 (76.3)	1.7
	1	0.458 ± 0.004 (54.8)**	
	5	0.331 ± 0.006 (39.6)***	
	10	0.278 ± 0.004 (33.3)***	
Compound 3	10	0.787 ± 0.010 (94.2)	87.5
	50	0.557 ± 0.002 (66.7)*	
	100	0.389 ± 0.005 (46.6)**	
	200	0.260 ± 0.009 (31.1)***	
Compound 4	10	0.704 ± 0.012 (84.3)	64.6
	50	0.456 ± 0.008 (54.7)**	
	200	0.252 ± 0.009 (30.2)**	
	400	0.128 ± 0.007 (15.4)***	
Compound 5	100	0.768 ± 0.009 (92.0)	>400
	300	0.577 ± 0.012 (69.1)	
	400	0.575 ± 0.006 (68.9)*	

The data represent the mean ± S.E.M. of three independent experiments performed in triplicate. Significantly different from control values: * P<0.05; ** P<0.01; *** P<0.001 (Student's *t*-test).

Compounds **3** and **4** exhibited moderate MAO inhibitory activity with the IC_{50} values of 87.5 and 64.6 μM, respectively, while compound **5** was inactive (IC_{50}: >400 μM). These results indicate that the presence of a geranyl moiety at the C-7 position of coumarin could improve the potency of MAO inhibitory activity.

To confirm MAO-A and MAO-B selectivity's, *l*-deprenyl and clorgyline pretreated MAO preparations were used for the measurement of MAO-A and MAO-B activity, respectively. Compound **1** showed a slight selective inhibitory effects against MAO-B (IC_{50}: 0.5 μM) compared to MAO-A (IC_{50}: 1.3 μM) (Table II). However, compound **2** was shown to be potently selective against MAO-B compared to MAO-A, and in a concentration dependent manner with the IC_{50} values of 0.6 μM and 34.6 μM, respectively (Table III). As a positive control, amitriptyline inhibited the MAO-A and MAO-B activities with IC_{50} values of 302.5 and 25.7 μM, respectively.

Kinetic analyses using Lineweaver-Burk plots were performed to elucidate the inhibition modes of compounds **1-2** given their strong inhibitory activity against MAO-B. Reaction mixtures consisting of five different concentrations of kynuramine was used as a MAO-B substrate in the absence or presence of compounds. As shown in Fig. 2, compounds **1-2** inhibited mouse brain MAO-B in a competitive manner with K_i values of 0.46 μM and 0.83 μM, respectively (n=5).

Some coumarin derivatives of natural and synthetic origin have been characterized as MAO inhibitors (Bruhlmann et

al., 2001; Jo et al., 2002). Further, it has been reported that simple coumarins have a low MAO inhibitory potency, whereas properly modified natural coumarins have been characterized as potent and selective MAO inhibitors

Table III. Inhibitory effects of compound **2** on MAO-A and MAO-B activities

	Concentration (μM)	MAO activity (% of control) (nmol/min/mg protein)	IC_{50} (μM)
Control		0.835 ± 0.012	
MAO-A (Deprenyl-treated)			
Control + Deprenyl		0.432 ± 0.007 (100.0)	
Compound 2	10	0.293 ± 0.013 (67.8)*	34.6
	20	0.252 ± 0.013 (58.4)*	
	50	0.192 ± 0.006 (44.4)**	
	100	0.151 ± 0.004 (34.9)***	
MAO-B (Clorgyline-treated)			
Control + Clorgyline		0.608 ± 0.030 (100.0)	
Compound 2	0.1	0.454 ± 0.001 (74.6)	0.6
	0.5	0.345 ± 0.006 (56.7)*	
	1	0.264 ± 0.012 (43.4)**	
	2	0.193 ± 0.004 (31.8)***	

The activities of MAO-A and MAO-B in mouse brain extracts were measured in the presence of 1 μM *l*-deprenyl or clorgyline, respectively. The data represent the mean ± S.E.M. of three independent experiments performed in triplicate. Significantly different from control values: * $P<0.05$; ** $P<0.01$; *** $P<0.001$ (Student's *t*-test).

Table II. Inhibitory effects of compound **1** on MAO-A and MAO-B activities

	Concentration (μM)	MAO activity (% of control) (nmol/min/mg protein)	IC_{50} (μM)
Control		0.835 ± 0.013	
MAO-A (Deprenyl-treated)			
Control + Deprenyl		0.381 ± 0.009 (100.0)	
Compound 1	0.1 ·	0.286 ± 0.003 (75.1)	1.3
	0.5	0.220 ± 0.006 (57.7)**	
	2	0.175 ± 0.006 (46.0)**	
	10	0.120 ± 0.009 (31.6)***	
MAO-B (Clorgyline-treated)			
Control + Clorgyline		0.543 ± 0.002 (100.0)	
Compound 1	0.1	0.418 ± 0.009 (77.0)	0.5
	0.5	0.271 ± 0.002 (49.9)*	
	2	0.156 ± 0.006 (28.7)***	
	10	0.046 ± 0.002 (8.4)***	

The activities of MAO-A and MAO-B in mouse brain extracts were measured in the presence of 1 μM *l*-deprenyl or clorgyline, respectively. The data represent the mean ± S.E.M. of three independent experiments performed in triplicate. Significantly different from control values: * $P<0.05$; ** $P<0.01$; *** $P<0.001$ (Student's *t*-test).

7-(6'R-Hydroxy-3',7'-dimethyl-2'E,7'-octadienyloxy)coumarin (1)

Auraptene (2)

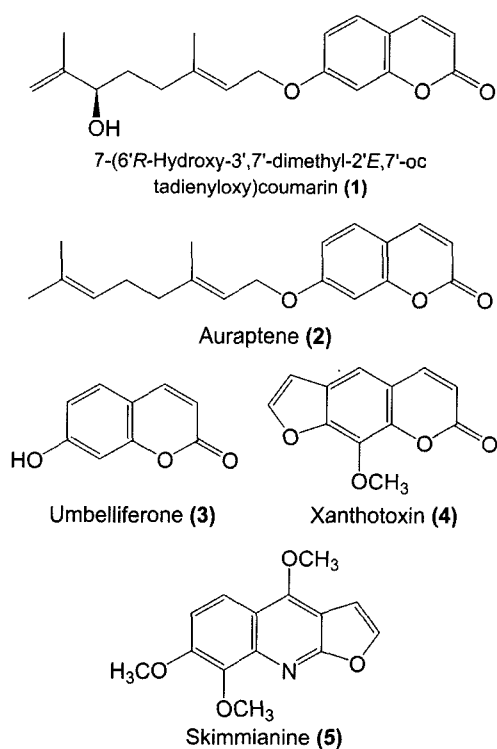Umbelliferone (3)   Xanthotoxin (4)

Skimmianine (5)

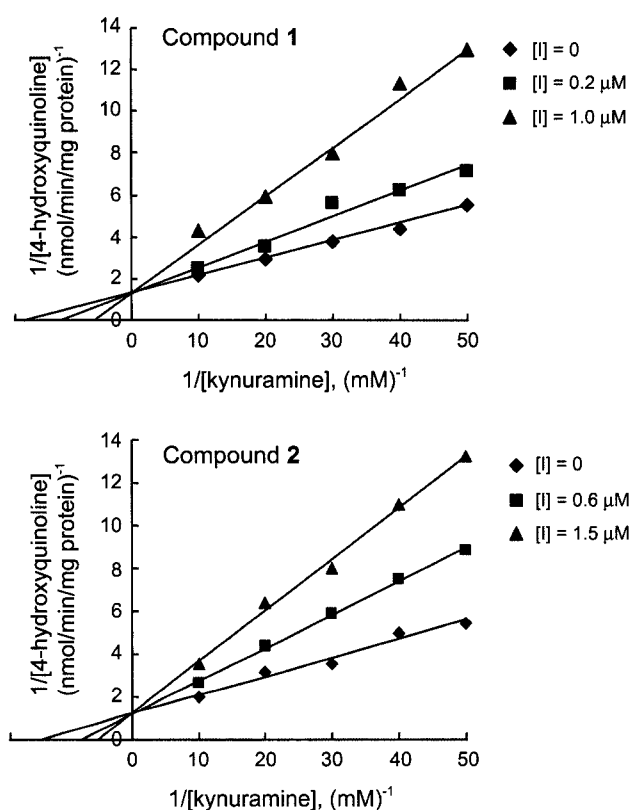**Fig. 1.** Structures of compounds **1-5** from *Dictamnus albus*

Fig. 2. Lineweaver-Burk plots for compounds 1-2 against MAO-B. The reciprocal of MAO-B activities was plotted against the reciprocal of substrate concentrations (n=5).

(Catto *et al.*, 2006; Gnerre *et al.*, 2000; Huong *et al.*, 1999). Geiparvarin, a natural 7-substituted coumarin from the leaves of *Geijera parviflora*, and desmethylgeiparvarin also showed potent and selective MAO-B inhibition (Carotti *et al.*, 2002). In our findings, introducing a lipophilic 7-substituent of the coumarin nucleus enhance the inhibition potency of MAO activity. Moreover, geranylated coumarin auraptene showed the potent and selective MAO-B inhibitory activity.

The selective inhibitors of MAO-B have been suggested for the treatment of Parkinson's disease and Alzheimer's disease (Youdim *et al.*, 2006). Indeed, low dose selegiline, a selective MAO-B inhibitor, has recently been approved for use as adjunctive treatment in Parkinson's disease (Patkar *et al.*, 2006). Accordingly, we suggest that *D. albus*, containing potent MAO-B inhibitory 7-substituent coumarins, could be a possible new therapeutic candidate for the threatment of Parkinson's and Alzheimer's disease. Additional pharmacological investigations and *in vivo* physiological functional studies, however, remain to be conducted.

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