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Monoamine Oxidase Inhibitory Components from the Roots of *Sophora flavescens*

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In our search for monoamine oxidase (MAO) inhibitors from natural resources, we found that the methanol extract of the roots of *Sophora flavescens* showed an inhibitory effect on mouse brain monoamine oxidase (MAO). Bioactivity-guided isolation of the extract yielded two known flavonoids, formononetin (**1**) and kushenol F (**2**), as active compounds along with three inactive compounds, oxymatrine (**3**), trifolirhizin (**4**), and β-sitosterol (**5**). Formononetin (**1**) and kushenol F (**2**) showed significant inhibitory effects on MAO in a dose-dependent manner with IC_{50} values of 13.2 and 69.9 μM, respectively. Formononetin (**1**) showed a slightly more potent inhibitory effect against MAO-B (IC_{50}: 11.0 μM) than MAO-A (IC_{50}: 21.2 μM). Kushenol F (**2**) also preferentially inhibited the MAO-B activity than MAO-A activity with the IC_{50} values of 63.1 and 103.7 μM, respectively.

Key words: *Sophora flavescens*, Leguminosae, Formononetin, Kushenol F, Monoamine oxidase inhibitor

INTRODUCTION

Monoamine oxidase (MAO, EC 1.4.3.4) is a FAD-containing enzyme located in the outer mitochondrial membrane of neuronal, glial, and other cells. MAO catalyzes the oxidative deamination of a number of neurotransmitters, such as norepinephrine, dopamine, and serotonin, as well as exogenous and endogenous amines to their corresponding aldehydes (Bach *et al.*, 1988; Benedetti and Dostert, 1992). Two different subtypes, MAO-A and MAO-B, have been identified based on their substrate selectivity, inhibitor sensitivity, and amino acid sequence (Abell and Kwan, 2001; Shih *et al.*, 1999). MAO-A preferentially oxidizes norepinephrine and serotonin, and is selectively inhibited by clorgyline. However, MAO-B preferentially deaminates β-phenylethylamine and benzylamine, and is selectively inhibited by *l*-deprenyl and pargyline (Kalgutkar *et al.*, 1995).

Due to the key role played by the two MAO forms in the metabolism of monoamine neurotransmitters, inhibitors of MAO are of considerable pharmacological and therapeutic interest in the area of several neurological diseases. MAO-A inhibitors are useful in the therapy of mental disorders, mainly as antidepressants, whereas MAO-B inhibitors expected to be useful in the therapy of Parkinson's and Alzheimer's disease (Thomas, 2000; Yamada and Yasuhara, 2004). A number of MAO inhibitors such as coumarins (Jo *et al.*, 2002), xanthones (Suzuki *et al.*, 1981; Thull *et al.*, 1993), and alkaloids (Lee *et al.*, 2003; Naoi and Nagatsu, 1987), have been isolated from natural products or synthesized for the development of medicines.

As a part of our ongoing research for MAO inhibitors from botanical resources, it was found that the methanol extract from the roots of *Sophora flavescens* significantly inhibited the mouse brain MAO activity. *S. flavescens* Ait. (Leguminosae) is a perennial herb and is widely distributed in Korea, Chinese, and Japan. Sophorae Radix, the dried root of *S. flavescens* has been used in traditional medicine as antibacterial, anti-inflammatory, antipyretic, antiasthmatic, and anthelmintic (Jung and Shin, 1989). Phytochemical studies of *S. flavescens* have been reported the isolation of quinolizidine alkaloids, triterpenoids, and flavonoids (Tang and Eisenbrand, 1992).

In this study, we identified MAO inhibitors in the dried root of *S. flavescens* and characterized their inhibitory

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activities on MAO-A and MAO-B.

MATERIALS AND METHODS

General experimental procedures

Melting points were measured on a Büchi model B-540 without correction. Optical rotations were determined on JASCO DIP-370 polarimeter at 25 °C. UV and IR spectra were obtained on a JASCO UV-550 and Perkin-Elmer model LE599 spectrometer, respectively. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded using a Bruker DRX 300 MHz NMR spectrometers using $CDCl_3$ or DMSO-d_6 as a solvent. EI-MS was recorded on Hewlett-Packard MS 5988 mass spectrometer. Open column chromatography was performed using a silica gel (Kieselgel 60, 70-230 mesh and 230-400 mesh, Merck), and thin layer chromatography (TLC) using a pre-coated silica gel 60 F_{254} (0.25 mm, Merck).

Kynuramine, clorgyline, *l*-depreyl, 4-hydroxyquinoline, and iproniazid were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Plant materials

The dried roots of *S. flavescens* were collected from the herb garden at Chungbuk National University, Cheongju, Korea, in October, 2001 and identified by Prof. K. S. Lee, a plant taxonomist at Chungbuk National University. A voucher specimen (CBNU 01020) has been deposited at the Herbarium of College of Pharmacy, Chungbuk National University, Korea.

Animals

The ICR male mice were purchased from Samyook Animal Center (Soowon, Korea) and maintained in accordance with the guidelines for animal care and use of laboratory animals, Chungbuk National University, Korea.

Extraction and activity-guided isolation

The dried roots of *S. flavescens* (3 kg) were extracted with 80% MeOH three times at room temperature to yield a dark-brown residue (450 g, 78.3% MAO inhibitory activity at the concentration of 250 μg/mL). The methanol extract suspended in water, and then partitioned in turn with CH_2Cl_2, EtOAc, BuOH, and water. When evaluated at 200 μg/mL, the MAO inhibitory activities for these four extracts were 82.9, 76.2, 14.0, and 9.2%, respectively. The most active CH_2Cl_2 extract (78 g) was chromatographed over silica gel column with a gradient of MeOH in CH_2Cl_2 (1, 2, 5, 10, 20, 50, 100%, 1 L each) as the solvent system, and afforded seven combined fractions (SR1-SR7). SR-2 fraction (5.6 g, 90.5% MAO inhibitory activity at the concentration of 150 μg/mL) was further purified over silica gel column with CH_2Cl_2-MeOH (20:1) gave formononetin (**1**) (25 mg) and β-sitosterol (**5**) (150 mg). Repeated silica gel column chromatography of SR-5 fraction (7.2 g, 85.0% MAO inhibitory activity at the concentration of 150 μg/mL) using CH_2Cl_2-MeOH (15:1, 10:1, 5:1) gave kushenol F (**2**) (12 mg), oxymatrine (**3**) (21 mg), and trifolirhizin (**4**) (9 mg).

Formononetin (1)

Colorless crystal; mp 260 °C; EI-MS *m/z* 268 $[M]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.07 (1H, d, *J* = 8.8 Hz, H-5), 7.94 (1H, s, H-2), 7.44 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 6.95 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 6.92 (1H, dd, *J* = 8.8, 2.1 Hz, H-6), 6.83 (1H, d, *J* = 2.1 Hz, H-8), 3.83 (3H, s, 4'-OCH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 55.7 (4'-OCH_3), 102.6 (C-8), 114.4 (C-3' and C-5'), 115.7 (C-6), 117.3 (C-4a), 124.5 (C-1'), 124.8 (C-3), 127.8 (C-5), 130.6 (C-2' and C-6'), 153.7 (C-2), 158.0 (C-8a), 159.5 (C-4), 163.1 (C-7), 177.1 (C-4).

Kushenol F (2)

Yellow pale powder; $[\alpha]_D^{25}$ 65° (c, 0.2 in MeOH); EI-MS *m/z* 424 $[M]^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.37 (1H, d, *J* = 8.3 Hz, H-6'), 6.41 (1H, dd, *J* = 8.3, 2.4 Hz, H-5'), 6.37 (1H, d, *J* = 2.4 Hz, H-3'), 6.15 (1H, s, H-8'), 5.60 (1H, dd, *J* = 11.1, 5.0 Hz, H-2), 5.05 (1H, t, *J* = 6.7 Hz, H-4"), 4.62 (1H, d, *J* = 2.1 Hz, H-9"a), 4.60 (1H, d, *J* = 2.1 Hz, H-9"b), 1.61 (3H, s, 10"-CH_3), 1.56 (3H, s, 6"-CH_3), 1.45 (3H, s, 7"-CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 17.8 (C-7"), 19.1 (C-10"), 25.8 (C-6"), 27.1 (C-1"), 31.9 (C-3"), 42.8 (C-3), 47.8 (C-2"), 75.3 (C-2), 95.1 (C-8), 102.7 (C-10), 103.4 (C-3'), 107.8 (C-5'), 108.2 (C-6), 111.2 (C-9"), 117.8 (C-1'), 124.4 (C-4"), 128.6 (C-6'), 131.6 (C-5"), 149.1 (C-8"), 156.1 (C-4'), 159.4 (C-2'), 162.1 (C-5), 163.0 (C-9), 165.3 (C-7), 197.8 (C-4).

Oxymatrin (3)

Colorless powder; mp 207°C; $[\alpha]_D^{25}$ +45° (c, 0.1 in MeOH); EI-MS *m/z* 264 $[M]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.32 (1H, m, H-11), 4.43 (1H, dd, *J* = 12.6, 5.1 Hz, H-17e), 4.21 (1H, t, *J* = 12.6 Hz, H-17a); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 17.9 (C-8), 18.0 (C-9), 19.4 (C-3), 25.5 (C-4), 26.9 (C-12), 29.3 (C-13), 33.7 (C-14), 35.3 (C-5), 42.4 (C-17), 43.5 (C-7), 53.7 (C-11), 67.9 (C-6), 69.9 (C-2), 70.4 (C-10), 170.8 (C-15).

Trifolirhizin (4)

Colorless powder; mp 142-144 °C; EI-MS *m/z* 446 $[M]^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.30 (1H, d, *J* = 8.5 Hz, H-1), 6.99 (1H, s, H-7), 6.70 (1H, dd, *J* = 8.5, 1.8 Hz, H-2), 6.50 (1H, d, *J* = 1.8 Hz, H-4), 6.49 (1H, s, H-10), 5.90 (2H, d, *J* = 12.8 Hz, -OCH_2O-), 5.52 (1H, d, *J* = 6.8 Hz, H-11a), 5.02 (1H, d, *J* = 7.2 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 41.3 (C-6a), 61.5 (C-6), 66.7 (C-6), 70.5 (C-4), 74.0 (C-2), 77.4 (C-5), 77.9 (C-3), 78.5 (C-11a), 94.1 (C-10), 101.1

(-OCH_2O-), 101.9 (C-1), 104.8 (C-4), 106.2 (C-7), 111.8 (C-2), 115.0 (C-11b), 119.1 (C-6b), 132.8 (C-1), 142.0 (C-8), 148.3 (C-9), 154.5 (C-10a), 157.0 (C-4a), 159.3 (C-3).

MAO preparation and assay for MAO activity

A crude mitochondrial fraction from mouse brain was isolated by the method of Naoi *et al.* with minor modification (Naoi and Nagatsu, 1987; Ro *et al.*, 2001). MAO activity was measured fluorometrically using kynuramine as a substrate according to the method of Kraml with a slight modification (Kraml, 1965; Ro *et al.*, 2001). 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 mL 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 LS 50B fluorescence spectrometer. The suspension was pre-incubated with either 1 μM of *l*-deprenyl (type-B inhibitor) or clorgyline (type-A inhibitor) for 15 min to measure MAO-A or MAO-B activity, respectively.

RESULTS AND DISCUSSION

In our ongoing search for naturally occurring MAO inhibitors, a methanol extract from the roots of *S. flavescens* exhibited strong inhibitory activity on mouse brain MAO. Activity-guided isolation of the methylenechloide-soluble fraction yielded two known flavonoids, formononetin (**1**) and kushenol F (**2**), as active compounds along with three inactive compounds, oxymatrine (**3**), trifolirhizin (**4**), and β-sitosterol (**5**) (Fig. 1). The structures were identified by physical and spectroscopic methods (mp, UV, IR, $[\alpha]_D$, MS, ^{1}H- and ^{13}C-NMR) and by comparing the data obtained with those of published values (Lee *et al.*, 2003; Park *et al.*, 2003; Ryu *et al.*, 1997; Sekine *et al.*, 1993; Wu *et al.*, 1985).

MAO activity in mouse brain mitochondria was measured using the non-selective substrate kynuramine, and clorgyline or *l*-deprenyl was added to define MAO-A or MAO-B activity, respectively.

As shown in Table I, Formononetin (**1**) and kushenol F (**2**) inhibited MAO activity in a concentration dependent manner and the IC_{50} values were 13.2 and 69.9 μM, respectively. Under the same experimental conditions, the IC_{50} value of iproniazid, a MAO inhibitor as a positive control, was 12.9 μM. In order to verify the selectivity of the MAO activity, *l*-deprenyl-pretreated MAO preparation was used for the measurement of MAO-A activity, and a clorgyline-pretreated one was for MAO-B. This result indicated that formononetin (**1**) showed a slightly potent inhibitory effect against MAO-B (IC_{50}: 11.0 μM) than MAO-A (IC_{50}: 21.2 μM) (Table II). Kushenol F (**2**) also preferentially inhibited the MAO-B activity than MAO-A activity in a concentration dependent manner with the IC_{50} values of 63.1 and 103.7 mM, respectively (Table III).

The regulation of the activity of MAO-B has been thought to be an effective approach for the prevention of

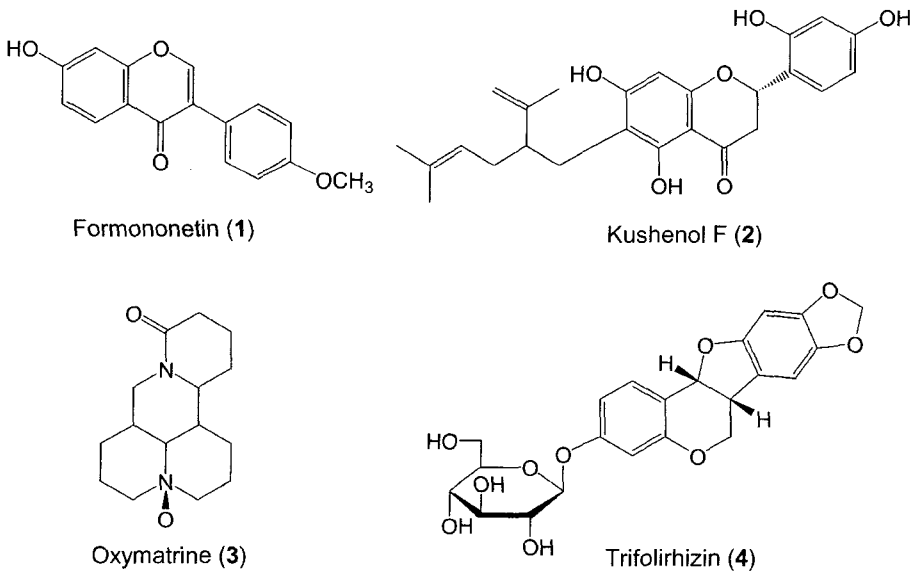

Fig. 1. Structures of isolated compounds from *S. flavescens*

Table I. Inhibitory effects of compounds **1-5** on MAO in mouse brain

Concentration (μM)		MAO activity (% of control) (nmol/min/mg protein)	IC_{50} (μM)
Control		1.259 ± 0.081 (100.0)	
Iproniazid	10	0.724 ± 0.020 (57.6)	12.9
Formononetin (**1**)	4	0.999 ± 0.021 (79.4)	13.2
	8	0.819 ± 0.051(65.1)**	
	16	0.541 ± 0.045(42.9)***	
	32	0.358 ± 0.031(28.5)***	
Kushenol F (**2**)	20	1.026 ± 0.031(81.5)	69.9
	40	0.843 ± 0.061(67.0)*	
	80	0.550 ± 0.042(43.7)***	
	160	0.262 ± 0.012(20.8)***	
Oxymatrine (**3**)	50	1.288 ± 0.101(102.3)	>100
	100	1.217 ± 0.048(96.7)	
Trifolirhizin (**4**)	50	1.192 ± 0.037(94.7)	>100
	100	1.024 ± 0.042(81.4)	
β-Sitosterol (**5**)	50	1.436 ± 0.053(102.4)	>100
	100	1.360 ± 0.075(105.7)	

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

Table II. Inhibitory effects of formononetin (1) on MAO-A and MAO-B in mouse brain

Concentration (μM)		MAO activity (% of control) (nmol/min/mg protein)	IC_{50} (μM)
Control		1.259 ± 0.131	
MAO-A (Deprenyl-treated)			21.2
Control + Deprenyl		0.469 ± 0.032(100.0)	
Formononetin (**1**)	8	0.361 ± 0.025(77.0)	
	16	0.278 ± 0.031(59.2)*	
	32	0.177 ± 0.023(37.7)**	
	64	0.090 ± 0.016(19.1)***	
MAO-B (Clorgyline-treated)			11.0
Control + Clorgyline		0.745 ± 0.082(100.0)	
Formononetin (**1**)	4	0.575 ± 0.021(77.1)	
	8	0.420 ± 0.035(56.3)*	
	16	0.294 ± 0.034(39.5)***	
	32	0.183 ± 0.021(24.5)***	

The activities of MAO-A and MAO-B in mouse brain 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 the control value: * P<0.05; ** P<0.01; *** P<0.001 (Student's *t*-test).

Parkinson's disease and adjunct treatment of Alzheimer's disease, while those of MAO-A expected to be useful for the treatment of depression and anxiety (Thomas, 2000; Yamada and Yasuhara, 2004). These results suggest that

Table III. Inhibitory effects of kushenol F (2) on MAO-A and MAO-B in mouse brain

Concentration (μM)		MAO activity (% of control) (nmol/min/mg protein)	IC_{50} (μM)
Control		1.259 ± 0.131	
MAO-A (Deprenyl-treated)			103.7
Control + Deprenyl		0.469 ± 0.032(100.0)	
Kushenol F (**2**)	20	0.396 ± 0.012(81.2)	
	40	0.321 ± 0.015(65.8)*	
	80	0.151 ± 0.024(30.9)**	
	160	0.071 ± 0.012(14.5)***	
MAO-B (Clorgyline-treated)			63.1
Control + Clorgyline		0.745 ± 0.082(100.0)	
Kushenol F (**2**)	20	0.559 ± 0.052(80.4)	
	40	0.444 ± 0.033(63.8)*	
	80	0.326 ± 0.024(46.8)**	
	160	0.206 ± 0.021(29.6)***	

The activities of MAO-A and MAO-B in mouse brain 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 the control value: *P<0.05; **P<0.01; ***P<0.001 (Student's *t*-test).

S. flavescens which contains compounds with slightly potent MAO-B inhibitory activity may be as a possible therapeutic candidate for the Parkinson's and Alzheimer's disease. However, further pharmacological investigations and *in vivo* physiological functions of *S. flavescens* remain to be elucidated.

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