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Studies on the Monoamine Oxidase Inhibitors of Medicinal Plants I. Isolation of MAO-B inhibitors from *Chrysanthemum indicum*

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Abstract □ Fourteen kinds of medicinal plants were screened for determining inhibitory activities on monoamine oxidase B. The extracts of *Artemisia Messer-Schmidtiana* (herba), *Chrysanthemum indicum* (flos), *Ericibe obtusifolia* (radix et rhizoma) and *Sophora japonica* (flos) strongly inhibited the enzyme. Among them, Chrysanthemi flos was chosen for elucidating its active principles, and some flavonoids were isolated and identified as acacetin (I), 5,7-dihydroxy chromone (II), diosmetin (III), apigenin (IV), eriodictyol (V) and luteolin (VI). IC_{50} were determined as following: I, 2.46; II, 0.19; III, 2.11 mM, and the others showed weak inhibition.

Keywords □ Monoamine oxidase inhibitors, *Chrysanthemum indicum,* flavonoid, acacetin, 5,7-dihydroxy chromone, diosmetin, apigenin, eriodictyol, luteolin

Monoamine oxidase (EC 1.4.3.4) has been found to occur in two types of enzymes. One type, termed MAO-A, deaminates noradrenaline and serotonin much better than phenethylamine or benzylamine, and is preferentially inhibited by clorgyline, whereas the other, MAO-B, prefers phenethylamine and benzylamine as substrates and is preferentially inhibited by deprenyl.[1-3]

MAO inhibitors have been introduced into the treatment of depression[4,5] and Parkinson's disease,[6-8] as well as schizophrenia.[9] Their use has been limited, however, by the occurrence of severe and in some cases fatal hypertensive crisis following the ingestion of tyramine-containing food.[10] Another drawback of these drugs is the irreversibility of their interaction with the MAO enzyme, by so-called suicide reaction, since stable, steady-state inhibition of the enzymatic activity requires several days of treatment to be established.[11-13]

We attempted to obtain MAO inhibitors from medicinal plants using for anti-hypertensive and neurasthenia. Fourteen kinds of plants were screened for inhibitory activity on MAO-B, and *Artemisia Messer-Schmidtiana, Chrysanthemum indicum, Erycibe obtusifolia and Sophora japonica* strongly inhibited the enzyme. Among them, Chrysanthemi flos was chosen for elucidating its active principles. Earlier investigations on the constitutents of the plant showed the presence of some volatile oils and flavonoids.[14-17] We also isolated six flavonoids, which were identified as acacetin (I), 5,7-dihydroxy chromone (II), diosmetin (III), apigenin (IV), eriodictyol (V) and luteolin (VI). IC_{50} were determined as following: I, 2.46; II, 0.19; III, 2.11mM and the others showed weak inhibition on the enzyme. Compounds II, III and V were isolated for the first time from the plant.

EXPERIMENTAL METHODS

Instrumentals and reagents

Centrifugations were performed with a Sovall RT 6000 refrigerated centrifuge and a Sovall OTD 65B ultra centrifuge. The mps were taken on Mitamura-Riken apparatus and were uncorrected. The IR spectra were determined in KBr tablets on a Perkin Elmer Model 281B IR spectrophotometer. NMR spectra (80 MHz) were determined in $CDCl_3$ or DMSO-d_6 solution by a Varian Model FT 80A NMR spectrometer with TMS as an internal standard and chemical shifts are recorded in δ (ppm). A recording spectrophotometer, Gilford Type 2600 was used for the measurements of UV-visible absorption spectra. Mass spectra were obtained on a Hewlett Packard GC/MS spectrometer (Type 5985B) equipped with a direct inlet system and operating at 70eV.

Benzylamine hydrochloride and Sephadex

LH-20 were purchased from Tokyo Kasei Co. and Sigma Co., respectively. Norharman was an authentic reagent isolated or synthesized in our lab.[18,19] Medicinal plants except *Ilex pubescens* (Hong Kong) were purchased from a market in Chongno-5ka, Seoul. Kiesel-gel 60 for column chromatography and precoated Kiesel gel plate (60 F254) for TLC were purchased from E. Merck Co.

Preparation of test samples for MAO-B inhibition

Each five g of crude drug was refluxed with 70% methanol (50 m*l*) in a boiling water bath. After cooling, the methanolic solution was extracted with 50 m*l* of hexane, and then concentrated *in vacuo*. The residues were suspended in 45 m*l* of water, adjusted pH 1 with 1N HCl, and then extracted with ether (3 × 50 m*l*). The ethereal solutions were combined and concentrated to give fraction A. The aquous solution was alkalized with 5 m*l* of Na_2CO_3 solution, and then extracted with ether(3 × 50 m*l*). The combined ethereal solution was concentrated to yield fraction B. The aquous solution was extracted with 50 m*l* of n-butanol. The butanol solution was concentrated *in vacuo* to give fraction C. Each fraction was suspended in 50 m*l* of water to make the concentration of 10 m*l* per g crude drug.

MAO-B inhibition.

Rat liver mitochondrial monoamine oxidase was prepared by Zeller's method.[20] Activity of MAO-B was measured according to McEven *et al.*,[21] using benzylamine as a substrate. One m*l* of the enzyme source was mixed with 0.8 m*l* of 0.067M phosphate buffer (pH 7.1) and 1 m*l* of test solution or water. The mixture was preincubated at 37 °C for 30 min and then cooled in an ice bath. 0.2 m*l* of 12mM benzylamine HCl in the buffer was added to it. This mixture was further incubated at 37 °C for 90 min in a shaking water bath. The reaction stopped by addition of 0.3 m*l* of 60% perchloric acid. Affter extraction with 3 m*l* of cyclohexane (3 m*l*), the organic layer was taken and the absorbance of benzaldehyde produced was measured at 242 nm.

Purely isolated compounds were dissolved in ethanol and then were suspended in water for testing their inhibitory activities on MAO-B. Final concentration of ethanol in enzymatic reaction mixture was below 5%.

Isolation of compounds I to VI from Chrysanthemum indicum

Chrysanthemi flos (2.9Kg) was extracted with hot methanol (10*l* × 3 times). The methanol extract (870g) was partitioned with ether, and 145g of ethereal extract was obtained. The extract was subjected to chromatography on a silica gel column using the elution soluvent of benzene/acetone (3:1) to yield compounds I, III + IV, V and VI. And their Rf values were 0.58, 0.35, 0.22 and 0.15, respectively, on a TLC plate with the same solvent. The mixture of III plus IV was further chromatographed over silica gel using chloroform/methanol (10:1) as an eluent to separate each other. Compound II was isolated by combination with silica gel column (solvent, $CHCl_3$/MeOH = 10:1) and Sephadex LH-20 column (solvent, MeOH).

Compound I

Crystallized from acetone (yellowish needles). MP: 262-4 °C. UV (λ max in MeOH): 270, 296sh, 330nm; (λ max in MeOH + NaOH): 278, 295sh, 368. IR (cm^{-1}): 3400(OH), 1660,1610,1500. PMR (δ in DMSO-d_6): 3.82(3H,s,-OCH_3), 6.14(1H,d, J = 2Hz,C_6 – H), 6.37(1H,d, J = 2Hz, C_8 – H), 6.56 (1H,s, C_3 – H), 7.01(2H,d, J = 9Hz, $C_{3',5'}$ – H), 7.89 (2H,d, J = 9Hz, $C_{2',6'}$-H), 12.73(-OH). MS(%): *m/z* 284 (100, M^+), 256(11.3), 241(30.5), 152(23.7), 132(67.5).

Compounds III and IV

An eluate from a silica gel column using the eluting solvent of benzene/acetone (3:1), corresponding to Rf 0.35 on a TLC plate with the same solvent, was further chromatographed over silica gel eluting $CHCl_3$/MeOH (10:1) to give compounds III and IV. On TLC with this solvent system, Rf values of III and IV were 0.38 and 0.31, respectively. Each was crystallized from methanol.

Compound III (palely yellowish crystals)

MP: 258-9 °C. UV (λmax in MeOH): 240sh, 252, 267, 291 sh, 344nm; (λmax in MeOH + NaOH): 270, 303 sh, 386 nm. PMR (δ in DMSO-d_6): 3.86(3H,s,-OCH_3), 6.19 (1H,d, J = 2Hz, C_6-H), 6.45(1H,d, J = 2Hz, C_8-H), 6.72(1H,s, C_3-H), 7.08(1H,d, J = 9Hz, $C_{5'}$-H), 7.43(1H,d, J = 2Hz, $C_{2'}$-H), 7.54(1H,dd, J = 2.9Hz, $C_{6'}$-H), 12.91 (-OH). MS(%): *m/z* 300(100, M^+), 229(33.8), 178(49.8), 153(39.7), 152(19.9), 148(13.9).

Compound IV (palely yellowish crystalls)

MP: 245-250 °C. UV(λ max in MeOH): 267,296sh, 336 nm; (λ max in MeOH + NaOH): 276,296, 326nm. PMR(δ in DMSO-d_6): 6.18(1H,d, J = 2Hz, C_6-H), 6.46(1H,d, J = 2Hz, C_8-H), 6.73(1H,s, C_3-H), 6.91(2H,d, J = 9Hz, $C_{3',5'}$-H), 7.89(2H,d, J 9Hz, $C_{2',6'}$-H), 10.55, 12.94(OH)., MS(%): *m/z* 270(63.4, M^+), 253(3.4), 242(34.1), 229(3.0), 178(42.7), 153(96.6), 152(74.1), 121(88.1), 118(42.1), 108(100)

Compound V

Crystallized from acetone (palely yellowish crystals). MP: 265-8 °C. UV(λmax in MeOH): 289, 330sh nm; (λmax in MeOH + NaOH): 246,323nm. PMR (δin DMSO-d_6): 2.98(2H, qq, C_3-H), 5.35 (1H,q, J=3.5, 12Hz, C_2-H), 5.86(2H,s, $C_{6,8}$-H), 6.74, 6.87(3H, $C_{2'5'6'}$-H), 12.10(-OH). MS(%): *m/z* 288(15.6, M^+), 270(4.6), 260(3.2), 245(3.5), 179(28.2), 166(39.5), 153(100), 136(45.8).

A solution of V (5mg) in pyridine (0.2 m*l*) and acetic anhydride (0.2 m*l*) was kept at room temp. and treated as usual. Crystallization of the product with hexane gave its acetate (3 mg). MP: 138 °C. PMR (δin $CDCl_3$): 2.29(3 × 3H,s, 3 × $COCH_3$), 2.37(3H,s,$COCH_3$), 2.80(2H,m,C_3-H), 5.40 (1H,q, C_2-H), 6.54(1H,d, J=2Hz, C_6-H), 6.79(1H,d, J=2Hz, C_8-H), 7.29(3H,$C_{2'5'6'}$-H). MS (%): *m/z* 456(1, M^+), 414(100), 372(46), 330(65.7), 288(11.6).

Methylation of V with diazomethane yielded its methyl ether. PMR (δin $CDCl_3$): 2.80(3H,m, C_3-H), 3.28(2 × 3H,s, 2 × OCH_3), 3.78(2 × 3H,s, 2 × OCH_3), 5.35(1H,m,C_2-H), 6.07(2H,s, C_6-H & C_8-H), 6.28(3H,m, $C_{2'5'6'}$-H). MS(%): *m/z* 344(0.6, M^+), 330(6.2), 316(25.4), 302(5.9), 288(0.3), 193(31), 167(100)

Compound VI

Crystallized from acetone (yellowish needles). MP: 254-6 °C. UV(λmax in MeOH): 242sh, 253,267,291sh, 349nm; (λmax in MeOH + NaOH): 266sh, 329,401nm. PMR(δin DMSO-d_6): 6.17(1H,d, J=2Hz, C_6-H), 6.45(1H,d, J=2Hz, C_8-H), 6.59(1H,s, C_3-H), 6.87(1H,d,J=9Hz, $C_{5'}$-H), 7.37-7.47(2H, overlaps of $C_{2'}$-H and $C_{6'}$-H), 12.94(OH). MS(%): *m/z* 286(24.1, M^+), 258(7.8), 153(30.2), 135(10.3), 124(12.9), 111(13.8), 44(100).

Compound II

Crystallized from methanol (palely yellowish crystals). Rf 0.48(TLC solvent, $CHCl_3$/MeOH = 10:1). Ve/Vo 4.1 (in Sephadex LH column with methanol). MP: 194-5 °C, UV(λmax in MeOH): 224sh, 253sh, 258,296nm; (λmax in MeOH + NaOH): 220,268,323. PMR (δin DMSO-d_6): 4.10 (OH), 6.18(1H,d, J=2Hz, C_6-H), 6.24(1H,d, J=6Hz, C_3-H), 6.33(1H,d, J=2Hz, C_8-H), 8.14(1H,d, J=6Hz, C_2-H), 12.66(OH). MS(%): *m/z* 178(100,M^+), 152(8), 150(21.1), 124(10.3), 122(4.6), 96(5.3).

Acetylation of II (3 mg) with acetic anhydride (0.2 m*l*) and pyridine (0.2 m*l*) gave II-acetate. MP: 95-100 °C, PMR(δin $CDCl_3$): 2.31,2.40(2 × 3H, each s, $COCH_3$), 6.18(1H,d, J=6Hz, C_3-H), 6.83(1H,d, J=2Hz, C_6-H), 7.20(1H,d, J=2Hz, C_8-H), 7.72(1H,d, J=6Hz, C_2-H). MS(%): *m/z* 262(0.1, M^+), 220(35), 178(100).

Methylation of II in EtOH with diazomethane yielded its methyl ether. PMR (δ in $CDCl_3$): 3.82(2 × 3H,s, 2 × OCH_3), 6.29(1H,d, J=5Hz, C_3-H), 6.35(1H,d, J=3Hz, C_6-H), 6.55(1H,d, J=3Hz, C_8-H), 8.20(1H,d, J=5Hz). MS: *m/z* 206 (M^+).

RESULTS AND DISCUSSION

MAO-B inhibition of some medicinal plants

Methanol extracts of fourteen kinds of crude drugs were fractionated by solvents to divide into three groups; an ether soluble acidic/neutral fraction (fr.A), an ether soluble alkaloidal fraction (fr.B) and a buthanol soluble fraction (fr.C). Each fraction was examined for MAO-B inhibitory activity. As shown in Table I, the inhibition over 50% was found in fr.A of *Artemisia Messer-Schmidtiana, Inula britannica, Chrysanthemum indicum,*

Table I. MAO-B inhibition percent of fractionated crude drug

Botanical Origin	Part Used	Inhibition %		
		fr.A	fr.B	fr.C
Artemisia Messer -Schmidtiana	Herba	62.3	35.3	35.4
Inula britannica	Flow	58.5	12.2	51.2
Schizonepeta tenuifolia	Herba	22.9	7.9	28.2
Veratrum album	Rhizoma	46.2	-9.4	30.9
Chrysanthemum indicum	Flos	56.4	2.4	24.1
Erycibe obtusifolia	Radix	64.1	18.9	79.7
Ilex pubescens	Radix	21.6	-6.9	54.7
Chaenomeles sinensis	Fructus	1.1	1.2	19.3
Arisaema amurense	Rhizoma	12.9	6.4	-6.6
Smilax glabra	Rhizoma	6.6	14.7	-9.7
Sophora japonica	Flos	61.1	4.9	12.9
Lilium longiflorum	Bulbus	5.7	11.3	3.6
Sorghum vulgare	Radix	-6.2	17.6	4.1
Lycium chinensis	Fructus	-4.8	6 8	5.6

Erycibe obtusifolia and *Sophora japonica*, and in fr.C of *I. britanica*, *E. obtusifolia* and *Ilex pubescens*. Among them, *Chrysanthemum indicum* was chosen for elucidating its active principles.

Isolation of MAO-B inhibitors from Chrysanthemi flos

As shown in Table II, the ether extract of Chrysanthemi flos was divided into five fractions by silica gel column chromatography using the eluting solvent system of benzene/acetone (10:1 → 5:1 → 4:1 → 3:1 → 2:1). And MAO-B inhibitory activity of each fraction was measured. Major activities were found in fraction S2 and S3. Chromatography of the ether extract over silica gel column using the eluting solvent of benzene/acetone (3:1) gave compounds I, III + IV, V and VI. Compounds III and IV were separated by silica gel column chromatography using chloroform/methanol (10:1).

MAO-B inhibitory activities of the ether extract were re-examined after another fractionation by silica gel column chromatography using chloroform /methanol (10:1) and by Sephadex LH-20 column chromatography using methanol. The ether extract (70g) was firstly chromatographed over silica gel column with the eluting solvent to give three fractions. Fractions 2 (12g) and 3 (15g) showing the inhibitory activities were combined, concentrated and dissolved in methanol. And methanol-soluble part (9g) was subjected to Sephadex LH-20 column chromatography to yield 13 subfractions. An aliquot (about 1/300) of each fraction was taken for MAO-B inhibition.

As shown in Table III, L2 to L6, L9, and L11 to L14 exhibited the inhibition. The fractions of L2 to L6 discarded because of high UV absorption at 242nm of cyclohexane layer in the enzymatic inhibition test. Compound II was isolated from L10

Table II. MAO-B inhibition percent of fractions from Chrysanthemi flos

Fraction No.	Weight (g)	Rf value benzene : acetone 3 : 1	Inhibition %		
			1/250	1/500	1/1000
Total	1.5	-	77.6	44.9	17.8
S1	0.66	0.9 -0.6	23.5	8.7	-2.9
S2	0.18	0.64–0.36	48.7	32.0	7.2
S3	0.17	0.44–0.16	33.8	32.0	6.3
S4	0.13	0.20–0.04	19.4	15.9	0.8
S5	0.10	0.08–0.00	5.6	3.6	-8.0

Table III. MAO-B inhibition percent of methanol soluble part of the ether extract of Chrysanthemi flos over Sephadex LH-20 column

Fraction No.	Ve/Vo	Weight (g)	Internal absorption	Inhibition (%)
L 1	1.2	1.19	0.54	1.7
L 2	1.5	0.68	1.23	6.5
L 3	1.8	1.83	2.83	18.4
L 4	2.2	1.89	3.67	65.5
L 5	2.5	0.64	0.83	23.4
L 6	3.0	0.36	0.53	16.3
L 7	3.4	0.10	0.14	5.4
L 8	3.7	0.15	0.17	3.6
L 9	4.1	0.11	0.24	76.8
L10	4.5	0.26	0.05	1.6
L11	4.9	0.55	0.09	35.5
L12	5.2	0.69	0.08	31.0
L13	6.4	0.41	0.01	15.6
L14	8.1	0.01	0.04	12.2

fraction. And also compounds I, III to V and VI could be isolated from L11, L12 and L13, respectively.

Determination of chemical structure of the isolated compounds

Compounds I, mp 262-4°, IV, 245-50° and VI, mp 254-6°, were identified as acacetin,[17,24] apigenin[25] and luteolin[17,26] which were already isolated from the plant.

The color reaction and spectral properties indicated that II is a chromone. II, $C_9H_6O_4$ (M^+ 178), showed UV absorption maxima characteristic of a 5-hydroxychromone.[21] Several structural features could be ascertained from its PMR spectrum in DMSO-d_6. It exhibited the two *meta*-coupled protons at C_6 and C_8 at δ 6.18 and 6.33 (J = 2Hz each) and the two *ortho*-coupled protons at C_2 and C_3 appeared at δ 8.14 and 6.24 (each doublet, J = 6Hz each). Acetylation of II gave a diacetate, and methylation of II yielded a dimethyl ester. These data indicated that II was 5,7-dihydroxy chromone. There is no possibility of II to be 5,7-dihydroxy coumarin, because the mass spectrum of II showed the retro-Diels-Alder fragment at *m/z* 152 [(M -CH = CH)$^+$] characteristic of chromone and II gave red-violet color with $FeCl_3$.

Compound III, $C_{16}H_{12}O_6$ (M^+ 300), showed UV absorption maxima characteristic of a 5,7-dihydroxyflavone. The PMR spectrum of II in DMSO-d_6

showed one methoxy siglet at δ 3.86, two *meta*-coupled doublets at δ 6.19 (J = 2Hz, C_6-H) and 6.45 (J = 2Hz, C_8-H), one siglet at 6.72 (C_3-H), one *ortho*-coupled doublet at δ 7.08 (J = 9Hz, $C_{5'}$-H), one *meta*-coupled doublet at δ 7.43 (J = 2Hz, $C_{2'}$-H), and a double-doublet at δ 7.54 (J = 9 and 2Hz, $C_{6'}$-H). These data indicated that II was 5,7,3'-trihydroxy-4'-methoxy flavone or diosmetin.[22]

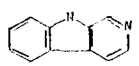
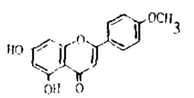
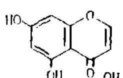
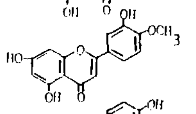
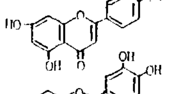
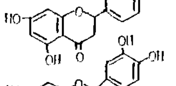
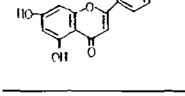
PMR spectrum of compound V, $C_{15}H_{12}O_6$ (M^+ 288), indicated that it is a flavanone, since it exhibited two quartet-quartet protons at δ 2.98 (C_3-H) and one quartet proton at δ 5.35 (J = 12 and 3.5 Hz, C_2-H). And it also showed two singlet protons at δ 5.86 (C_6-H and C_8-H) and three protons at δ 6.74 and 6.87 ($C_{2'}$-H, $C_{5'}$-H and $C_{6'}$-H). Acetylation of V gave a tetraacetate, and methylation of V with diazomethane yielded a tetramethyl ether. These data indicated that V was 5,7,3',4'-tetrahydroxy flavanone or eriodictyol.[23]

Compounds II, III and V were isolated for the first time from this plant.

MAO-B inhibition of Compounds I to VI

Inhibition of the isolated compounds on MAO-B were determined and compared with that of norharmane which is known to be the strong MAO-B inhibitor[27], as shown in Table IV. IC_{50} of I, II, III and norharmane were 2.46, 0.19, 2.11 and 0.01 mM, respectively. Others compounds showed very weak inhibition on the enzyme. Recently, we found that these flavonoids more strongly inhibited MAO-A than MAO-B, when serotonin was used as a substrate.[28]

Table IV. IC_{50} of isolated compounds on MAO-B

Compounds		IC_{50} mg/tube	IC_{50} mM
	Norharmane	—	0.01
	Acacetin (I)	2.1	2.46
	5,7-Dihydroxy chromone (II)	0.1	0.19
	Diosmetin (III)	1.9	2.11
	Apigenin (IV)	> 10	—
	Eriodictyol (V)	> 10	—
	Luteolin (VI)	> 10	—

*Concentration of benzylamine as a substrate was 0.8 mM.

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