Arch. Pharm. Res. 11(3), 230–239(1988)

Monoamine Oxidase-A Inhibitors from Medicinal Plants

Shi Yong Ryu, Yong Nam Han§ and Byung Hoon Han
Natural Products Research Institute, Seoul National University, Seoul 110-460, Republic of Korea
(Received August 28, 1988)

Abstract □ Thirty kinds of medicinal plants were screened to examine inhibitory activities on rat brain monoamine oxidase A, using serotonin as a substrate. As active principles, various kinds of stilbenes were isolated from Veratri Rhizoma, Reynoutriae Radix and Rhei undulati Rhizoma, and several kinds of flavonoids from Sophorae Flos, Chrisanthemi Flos and *Glycine max*. Among the compounds isolated, resveratrol(I) strongly inhibited MAO-A competitively, and its IC_{50} and Ki values were 2 μM and 2.5 μM, respectively. Inhibitory potencies towards MAO-A of some stilbenes and flavonoids were also compared.

Keywords □ Monoamine oxidase-A inhibitor, resveratrol, stilbene, flavonoid, isoflavonoid.

Monoamine oxidase (MAO, EC 1.4.3.4) plays a central role in the metabolism of many amines including the neuro-transmitter monoamines.[1,2] MAO is a flavoprotein found exclusively in the mitochondrial outermembrane, occurring in the MAO-A and MAO-B subtypes.[2-3] MAO-A deaminates serotonin and noradrenaline much better than phenethylamine or benzylamine, and is preferentially inhibited by clorgyline, whereas MAO-B prefers phenethylamine and benzylamine as substrates and is preferentially inhibited by deprenyl. MAO inhibitors were among the first drugs used in the treatment of depression[4-5] and Parkinson's disease,[6-8] as well as schizophrenia,[9] and it is known to be the inhibition of MAO-A which is important for the antidepressant effect of MAO inhibitors.[10]

For the purpose of isolating MAO-A inhibitors from natural resources, thirty kinds of medicinal plants were screened by tracing the inhibitory activity against rat brain mitochondrial MAO-A, utilizing serotonin as a substrate. Among them, Sophorae Flos, Perillae Herba, Chrisanthemi Flos, Veratri Rhizoma, Reynoutriae Radix and Rhei undulati Radix showed the potent inhibitory activities against MAO-A. In this paper, we describe the isolation of some stilbenes and flavonoids having the MAO-A inhibitory effects from the crude drugs and also report the MAO-A inhibitory activities of some stilbene derivatives obtained by chemical modification. In the previous paper,[11] we already reported that some medicinal plants inhibited MAO-B and several kinds of flavonoids were isolated as the MAO-B inhibitors from Chrysanthemi Flos.

§To wham correspondence should be addressed.

EXPERIMENTAL METHODS

Instrumentals and reagents

Centrifugations were performed with a Sovall RT 6000 refrigerated centrifuge and a Sovall OTD 65B ultracentrifuge. The mps were taken on Mitamura-Riken apparatus and were uncorrected. A recording spectrophotometer, Gilford Type 2600 was used for the measurement of UV-visible absorption spectra. The IR spectra were determined in KBr tablets on a Perkin Elmer Model 281B IR spectrophotometer. NMR spectra (80 MHz) were determined in $CDCl_3$, CD_3OD 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). Mass spectra were obtained on a Hewlett Packard GC/MS spectrometer Type 5985B equipped with a direct inlet system and operating at 70 eV.

Serotonin creatinine sulfate, iproniazid phosphate and Amerlite CG50 were purchased from Sigma Co., USA., benzylamine HCl, trans-stillbene, diethylstilbestrol and 1,2-dibromo-diphenylethane from Tokyo Kasei Co., Japan, and *d,l*-tranylcypromine HCl from SK & F, USA. Pd/C (10%), Kiesel-gel 60 for column chromatography and precoated Kiesel gel plate (Type 60 F254) for TLC were purchased from E. Merck Co. Medicinal

plants were obtained from a market in Chongno-5Ka, Seoul, Korea.

Preparation of test samples for MAO-A inhibition

Each ten g of crude drug was refluxed with 70% methanol (100 ml) for 5hr in a boiling water bath. After cooling, the methanolic solution was extracted with 100 ml of hexane, and then concentrated *in vacuo*. The residues were suspended in 100 ml of water, and then extracted with ether (3 × 100 ml). The ethereal solutions were combined and concentrated to give ether fr. The aqueous solution was extracted with 100 ml of n-butanol. The butanol solution was concentrated *in vacuo* to give BuOH fr. Each fraction was dissolved in 2 ml of dimethylsulfoxide and then suspended in water to make 100 ml volume. The suspended solution was used for screening the inhibitory activity against MAO-A.

Assay of MAO-A activity

Rat brain mitochondrial MAO was prepared by Zeller's method.[12] Activity of MAO-A was measured according to Ichiyama *et al.*[13], using serotonin as a substrate. The enzyme (0.5 ml) suspended in 10 mM phosphate buffered saline was mixed with one ml of test solution. The mixture was preincubated at 37 °C for 15 min, and 0.5 ml of 1.0 mM serotonin creatinine sulfate in the buffer was added to it. This mixture was further incubated at 37 °C for 90 min with shaking. The reaction stopped by heating for 3 min in a boiling water bath. After centrifugation, 1.6 ml of supernatant was applied to a Amberlite CG 50 colum (0.6 i.d. × 4 cm). The column was washed with over 40 ml of water, and three ml of 4N acetic acid was added to it. The absorbance of serotonin which was remained after reacting with MAO-A was measured at 277 nm.
Activity was calculated as follows:

Inhibitory ratio (%) = (A-B)/A × 100

(A = MAO-A activity in the absence of inhibitor,

B = MAO-A activity in the presence of inhibitor)

Isolated samples were dissolved in DMSO, which was found to have no effect of MAO-A activity at below 5.0% concentration. The final concentration of DMSO in incubation mixture were below one %. Kinetic data were calculated from MAO-A activity in the absence and the presence (1.25, 2.5 and 5.0 μM) of resveratrol, and at three concentrations (0.05, 0.1 and 0.2 mM) of serotonin.

Isolation of compound I from veratri rhizoma

Veratri Rhizoma(600g) was extracted with hot methanol (5 L × 3 times). The methanol extract (37g) was partitioned with ether and water, and ten g of ether extract was obtained, which was divided into three fractions by the usual method of extraction with ether under alkaline and acidic conditions to give the ether-soluble acidic(Fr.A, 5.61g), basic(Fr.B, 0.15g) and neutral(Fr.N, 3.13g). Fr.A which showed the most potent inhibitory activity towards MAO-A was subjected to silica gel column chromatography using $CHCl_3$/MeOH (20:1→5:1 →3:1→2:1→1:1→0:1) as eluting solvent system. Fr.A2 (1.2g) eluted by the solvent mixture of $CHCl_3$ and MeOH (5:1) was further chromatographed over silica gel using n-hexane/$CHCl_3$/MeOH/HA_c (5:5:1:0.2) to yield compound **I** (RF = 0.3).

Compound I (Resveratrol)

Colorless needles from MeOH, mp 255-260 °C. UV(MeOH) λ_{max}: 300, 310. MS m/z(%): 228(M^+, 100), 227(25), 211(16), 181(22), 115(11). ^{1}H-NMR (CD_3OD): 7.35(2H, d, J = 8.6Hz, $C_{2'}$- and $C_{6'}$-H), 6.79(2H, d, J = 8.6Hz, $C_{3'}$- and $C_{5'}$-H), 6.98, 6.74 (each d, J = 16Hz, each olefinic H), 6.46(2H, d, J = 2.2Hz, C_2- and C_6-H), 6.17(1H, m, C_4-H).

Acetylation of **I** with Ac_2O/pyridine afforded a triacetate (**Ia**). Colorless needles from hexane/$CHCl_3$. mp 112-115 °C. UV(MeOH) λ_{max}:300, 310. MS m/z(%): 354(M^+, 35), 312(28), 270(31), 228 (100). ^{1}H-NMR($CDCl_3$): 7.48 (2H, d, J = 8.6Hz, $C_{2'}$ and $C_{6'}$-H), 7.07(2H, d, J = 8.6Hz, $C_{3'}$ and $C_{5'}$-H), 7.10-7.00(4H, two olefinic-H, C_2- and C_6-H), 6.82(1H, m, C_4-H), 2.30(9H, s, 3 × CH_3COO).

Methylation of **I** with ethereal diazomethane yielded 3,4′, 5-trimethylresveratrol(**Ib**), Colorless needles from methanol. mp 55-56 °C. MS m/z (%): 270(M^+, 100), 269(16), 224(20), 152(29), 115(20) ^{1}H-NMR($CDCl_3$): 7.41(2H, d, J=8.8Hz, $C_{2'}$-and $C_{6'}$-H), 7.08, 6.84(each 1H, d, J = 16Hz, two olefinic H), 6.88(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.65(2H, d, J = 2.2Hz, C_2- and C_6-H), 6.37(1H, m, C_4-H), 3.82(9H, s, 3 × OCH_3)

Isolation of compounds I and II from Reynoutriae Radix

Reynoutriae Radix(1.8Kg) was extracted with hot methanol(5L × 3 times). The methanol extract (0.5Kg) was suspended in water and partitioned with hexane, ether and then butanol to yield the hexane(3.0g), ether(60g) and BuOH(350g) extracts. Compound **I**(8g) was isolated from the ether extract by the same procedure as that of Veratri Rhizoma. An aliquot(30g) of the BuOH extract was gradiently eluted over silica gel using $CHCl_3$/MeOH to isolate compound **II**(Rf = 0.2 in $CHCl_3$/MeOH = 4:1) (5g).

Compound II(piceid)

Colorless needles from 80% MeOH. mp 225-228 °C. UV(MeOH) λ_{max}: 300, 310. MS m/z (%): 390(M^+, 2), 228(100), 211(11), 181(20). ^{1}H-NMR (DMSO-d_6): 7.40(2H,d,J = 8.5Hz, $C_{2'}$- and $C_{6'}$-H), 7.07, 6.82(each 1H, J = 16Hz, two olefinic H), 6.75 (2H, d, J = 8.5Hz, $C_{3'}$- and $C_{5'}$-H), 6.70(1H, d, J = 2.0Hz, C_6-H), 6.57(H, d, J = 2.0Hz, C_2-H), 6.34(1H, m, C_4-H), 4.80(1H, d, J = 7.5Hz, anomeric H of glucose).

Acetylation of **II** gave a peracetate (**IIa**). Colorless powder. MS m/z(%): 642(M^+, 4.5), 331(12), 228(4.5), 169(100). ^{1}H-NMR($CDCl_3$): 7.49(2H, d, J = 8.6Hz, $C_{2'}$- and $C_{6'}$-H), 7.09(2H, d, J = 8.6Hz, $C_{3'}$- and $C_{5'}$-H), 6.97(2H, d, J = 2.0 Hz, C_2- and C_6-H), 7.08, 6.87(each 1H, d, J = 16Hz, two olefinic H), 6.66(1H, m, C_4-H), 2.30(6H, s, 2 × CH_3COO), 2.07(3H, s, CH_3COO), 2.04(9H, s, 3 × CH_3COO).

Isolation of compounds III, IV and V

Rhei undulati Rhizoma (1.2 Kg) was extracted with hot methanol (5 L × 4 times). The methanol extract (600g) was suspended into water(4L), and then extracted with EtOAc (4L × 3). The EtOAc solutions were combined and concentrated (EtOAc extract, 180g). The aquous layer was filtered to obtain precipitates(PPT, 30g), and then extracted with BuOH (4L × 3). The BuOH solution were combined and then concentrated *in vacuo* to yield BuOH extract(225g).

An aliquot(40g) of EtOAc extract was chromatographed over silica gel using $CHCl_3$/MeOH(10:1) as eluting solvent to obtain compound **III**(1.2g) (Rf = 0.4). PPT was suspended in the mixture of MeOH(300 m*l*) and 20% H_2SO_4(300 m*l*) and was refluxed for 30 min at 95 °C. After removing MeOH, the reaction mixture was diluted with water to make 1L volume, and then extracted with EtOAc (1L × 3). The EtOAc solutions were combined and concentrated in vacuo. Chromatography of the residue over silica gel using $CHCl_3$/MeOH(10:1) as an eluting solvent gave compound **V** (yield, 1.1g; Rf = 0.5). An aliquot (50g) of the BuOH extract was chromatographed over silica gel using $CHCl_3$/MeOH(4:1) as a solvent to yield compound **IV** (yield, 4g; Rf = 0.2).

Compound III (rhapontigenin)

Colorless plates from methanol. mp 196-198 °C. UV(MeOH) λ_{max}: 302, 325. MS m/z (%): 258(M^+, 100), 225(17), 197(64), 129(14), 115(25). ^{1}H-NMR (DMSO-d_6): 9.16(2H, br.s, D_2O exchangeable), 8.91(1H, br.s, D_2O exchangeable), 7.00(1H, d, J = 1.6Hz, $C_{2'}$-H), 6.96(1H, dd, J = 1.6 & 8.0Hz, $C_{6'}$-H), 6.92(1H, d, J = 8.0Hz, $C_{5'}$-H), 6.91, 6.62(each 1H, d, J = 16Hz, two olefinic H), 6.38(2H, d, J = 2.1Hz, C_2- and C_6-H), 6.12(1H, m, C_4-H), 3.78(3H, s, -OCH_3).

Acetylation of **III** yielded a triacetate (**IIIa**). Colorless needles from hexane/EtOAc. UV(MeOH) λ_{max} = 302, 320. MS m/z(%): 384(M^+, 4.8), 300 (2.8), 258(30). ^{1}H-NMR($CDCl_3$): 7.33(1H,d, J = 1.5Hz, $C_{2'}$-H), 7.28(1H, dd, J = 1.5 & 8.0Hz), 7.26 (1H, d, J = 8.0Hz, $C_{5'}$-H), 7.18, 6.97(each 1H, d, J = 16Hz, two olefinic H), 6.92(2H, d, J = 2.1Hz, C_2- and C_6-H), 6.32(1H, m, C_4-H), 3.84(3H, s, -OCH_3), 2.33(3H, s, CH_3COO), 2.29(6H, s, 2 × CH_3COO).

Compound IV (rhaponticin)

Palely yellowish needles from methanol. mp 246-249 °C. UV(MeOH) λ_{max}: 302, 325. MS m/z(%): 420(M^+, 1), 258(35), 197(26), 181(4), 129(11), 115(16). ^{1}H-NMR(DMSO-d_6): 9.39(1H, br.s, D_2O exchangeable), 8.92(1H, br.s, D_2O exchangeable), 7.02(1H, d, J = 1.2Hz, $C_{2'}$-H), 6.97 (1H, dd, J = 1.2 & 8.0Hz, C_6-H), 6.72(1H, d, J = 8.0Hz, $C_{5'}$-H), 7.04, 6.84(each 1H, d, J = 16Hz, two olefinic H), 6.72, 6.57(each 1H, br.s-like, C_2-and C_6-H), 6.34(1H, m, C_4-H), 4.80(1H, d, J = 6.8 Hz, anomeric H), 3.78(3H, s, -OCH_3).

Acetylation of **IV** gave a pentaacetate(**IVa**). Colorless fine needles from MeOH. UV(MeOH) λ_{max}: 302, 325. MS m/z(%): 672(M^+, 7.6), 258(4.2), 169(100). ^{1}H-NMR($CDCl_3$): 7.33(1H, d, J = 1.2Hz, $C_{2'}$-H), 7.15-7.25(2H, m, $C_{5'}$- and $C_{6'}$-H), 6.65(1H, m, C_4-H), 3.85(3H, s, OCH_3), 2.33(3H, s, CH_3COO), 2.30(3H, s, CH_3COO), 2.05(12H, s, 4 × CH_3COO). 6.65(1H, m, C_4-H), 5.17(1H, d, J = 8.0 Hz, anomeric H), 3.85(3H, s, OCH_3), 2.33(3H, s, CH_3COO), 2.05(12H, s, 4 × CH_3COO).

Compound V (3,5-dihydroxy-4′-methoxystilbene)

Colorless needles from 85% methanol. mp 175-178 °C. UV(MeOH) λ_{max}: 307, 320. MS m/z(%): 242(M^+, 100), 241(15), 115(14). ^{1}H-NMR(DMSO-d_6): 7.51(2H, d, J = 8.8Hz, $C_{2'}$- and $C_{6'}$-H), 6.93 (2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 7.02, 6.82(each 1H, J = 16Hz, two olefinic H), 6.40(2H, d, J = 2.0 Hz, C_2- and C_6-H), 6.13(1H, m, C_4-H), 3.77(3H, s, OCH_3).

Acetylation of **V** gave a diacetate (**Va**). Colorless needles from hexane/EtOAc. UV(MeOH) λ_{max}: 307, 320. MS m/z(%): 326(M^+, 2.8), 284(5.6), 242 (45). ^{1}H-NMR($CDCl_3$): 7.42(2H, d, J = 8.8Hz, $C_{2'}$- and $C_{6'}$-H), 7.08, 6.87(each 1H, d, J = 17Hz, two olefinic H), 7.03(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.93(2H, d, J = 2.0Hz, C_2- and C_6-H), 6.83 (1H, m, C_4-H), 3.82(3H, s, OCH_3), 2.29(6H, s, 2 ×

CH_3COO).

Isolation of compounds VI and VII

Compounds VI and VII were isolated from Mori ramulus and Polygoni multiflori Radix by the methods described by Deshpande *et al.*[13] and Hata *et al.*[14], respectively.

Compound VI (oxyresveratrol)

Colorless needles from methanol. UV(MeOH) λ_{max}: 300. MS m/z(%): 244(M^+, 100), 226(30), 198 (21), 115(24). ^{1}H-NMR(DMSO-d_6): 9.50, 9.32(each 1H, br.s, D_2O exchangeable), 9.08(2H, br.s, D_2O exchangeable), 7.32(1H, d, J = 8.4Hz, $C_{6'}$-H), 7.15, 6.73(each 1H, d, J = 16Hz, two olefinic H), 6.32(2H, d, J = 1.6Hz, C_2- and C_6-H), 6.30(1H, dd, J = 1.6 & 8.4 Hz, $C_{5'}$-H), 6.19(1H, m, C_4-H), 6.06 (1H, m, $C_{3'}$-H).

Its acetate(**VIa**), colorless needles from methanol. UV(MeOH) λ_{max}: 300. MS m/z(%): 412 (M^+, 6), 370(7), 328(5), 286(5), 244(12). ^{1}H-NMR ($CDCl_3$): 7.60(1H, d, J = 8.2Hz, $C_{6'}$-H), 7.17, 6.87 (each 1H, d, J = 16Hz, two olefinic H), 7.07(2H, d, J = 2.0Hz, C_2- and C_6-OH), 7.00(1H, d, J = 8.6Hz, $C_{5'}$-H), 6.95(1H, m, C_4-H), 6.84(1H, m, $C_{3'}$-H), 2.35(3H, s, CH_3COO), 2.30(6H, s, 2 × CH_3COO), 2.28(3H, s, CH_3COO).

Compound VII(2,3,4',5-tetrahydroxystilbene-2-O-β-glucoside)

Colorless needles from methanol. mp 182-185 °C. UV(MeOH) λ_{max}: 311, 322. MS m/z(%): 406 (M^+, 2), 244(30), 181(4). ^{1}H-NMR(DMSO-d_6: 9.46, 9.09, 8.76(each 1H, br.s, D_2O exchangeable), 7.69, 6.87(each 1H, d, J = 16Hz, two olefinic H), 7.43(2H, d, J = 8.6Hz, $C_{2'}$- and $C_{6'}$-H), 6.73(2H, d, J = 8.4Hz, $C_{3'}$- and $C_{5'}$-H), 6.55(1H, d, J = 2.4 Hz, C_6-H), 6.18(1H, d, J = 2.4Hz, C_4-H), 4.40(1H, d, J = 6.1Hz, anomeric H).

Its acetate(**VIIa**). Colorless needles from methanol. mp 165-168 °C. UV(MeOH) λ_{max}: 230, 303, 319 (sh). MS m/z(%): 700(M^+, 1), 412(1), 169(100). ^{1}H-NMR(DMSO-d_6): 7.64(2H, d, J = 8.6Hz, $C_{2'}$-and $C_{6'}$-H), 7.48(1H, d, J = 2.6Hz, C_6-H), 7.42, 7.22(each 1H, d, J = 16Hz, two olefinic H), 7.16 (2H, d, J = 8.5Hz, $C_{3'}$- and $C_{5'}$-H), 7.01(1H, d, J = 2.6Hz, C_4-H), 5.13(1H, d, J = 6.8Hz, anomeric H), 2.30(3H,s, CH_3COO), 2.28(6H, s, 2×CH_3COO), 2.02(3H, s, CH_3COO), 1.95(6H, s, 2×CH_3 COO), 1.88(3H, s, CH_3COO).

Preparation of 2,3,4',5-tetraacetoxystilbene(VIIIa)

Compound **VII** (400 mg) was dissolved in the mixture of methanol (10 ml) and 20% H_2SO_4(10 ml) and refluxed for 1 hr in a boiling water bath. After cooling, water(100 ml) was added to it. A precipitate formed was extracted with EtOAc (100 ml × 3), and the EtOAc extracts were concentrated *in vacuo*. Acetylation of the residues by Ac_2O/pyridine yielded **VIIIa**(50 mg, colorless needles from hexane/EtOAc). UV(MeOH) λ_{max}: 230, 302, 319(sh). MS m/z(%): 412(M^+, 3.5), 370(4.5), 328(1.2), 286 (8.5), 244(37), 115(3.2). ^{1}H-NMR(DMSO-d_6): 7.67 (2H, d, J = 8.6Hz, $C_{2'}$- and $C_{6'}$-H), 7.57(1H, d, J = 2.8Hz, C_6-H), 7.38, 7.18(each 1H, d, J = 16Hz, two olefinic H), 7.13 (2H, d, J = 8.4Hz, $C_{3'}$- and $C_{5'}$-H), 7.17(1H, d, J = 2.6Hz, C_4-H), 2.40(3H, s, CH_3COO), 2.28(9H, s, 3 × CH_3COO).

Preparation of 3,4'-dimethoxy-5-hydroxystilbene (IX)

Compound **II**(100 mg) was dissolved in methanol(10 ml) and treated with ethereal diazomethane. After drying up under N_2 stream, a residue was hydrolyzed with 10% H_2SO_4 in 50% MeOH for 30 min at 95 °C. After cooling, water(50 ml) was added to it. A precipitate formed was extracted with EtOAc (50 ml × 2), and the EtOAc extracts were concentrated *in vacuo*. The residue was chromatographed over silica gel using $CHCl_3$/MeOH(50:1) as eluting solvent, to isolate compound **IX**[16] (yield 10 mg). Colorless needles from 90% MeOH. UV (MeOH) λ_{max}: 307, 319. m/z(%): 256(M^+, 100), 225(14), 152(24), 115(26), 128(26). ^{1}H-NMR ($CDCl_3$): 7.43(2H, d, J = 8.7Hz, $C_{2'}$- and $C_{6'}$-H), 7.05, 6.80(each 1H, d, J = 17Hz, two olefinic H), 6.89(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.58(2H, d, J = 2.1Hz, C_2- and C_6-H), 6.31(1H, m, C_4-H), 3.82(6H, s, 2 × OCH_3).

Synthesis of 3,3',4',5-tetraacetoxystilbene(Xa)

Compound **III**(1g) was treated with pyridine·HCl salt[17,18] (5g) for 3hr in a oil bath(180 °C). After cooling, the reaction mixture was diluted with 0.1N HCl (100 ml), and then extracted with EtOAc(100 ml × 2). The EtOAc extract concentrated was acetylated with Ac_2O/pyridine, and then purified over silica gel using hexane/EtOAc(2:1). Compound **Xa** was recrystallized from 90% MeOH (yield 100 mg, colorless needles). mp 124-125 °C. UV(MeOH) λ_{max}: 298, 310. MS m/z(%): 412(M^+, 2.5), 370(3), 328(4), 286(5), 244(18), 197(5), 115(2). ^{1}H-NMR ($CDCl_3$): 7.40(1H, d, J = 1.6Hz, $C_{2'}$-H), 7.17, 6.98 (each 1H, d, J = 16Hz, two olefinic H), 6.98(2H, d, J = 1.6Hz, C_2- and C_6-H), 7.25(2H, m, $C_{5'}$- and $C_{6'}$-H), 6.83(1H, m, C_4-H), 2.29(12H, s, 4 × CH_3 COO).

Synthesis of 3,4',5-trihydroxybibenzyl(XI)

Compound **Ia**(200 mg) dissolved in HAc(10 ml)

was treated with 10% Pd/C (50 mg) under H_2 stream for 20 min at room temp. with stirring. After filtration, the filtrate freed from solvent under N_2 stream. The residue was crystallized from MeOH to yield colorless needles (XIa) (yield 150 mg). UV (MeOH) λ_{max}: 279. MS m/z(%): 356(M^+, 1), 314 (8), 272(16), 230(31), 123(9.5), 107(100). ^{1}H-NMR ($CDCl_3$): 7.16(2H, d, J = 8.8Hz, $C_{2'}$- and $C_{6'}$-H), 6.97(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.79(3H, s, C_2-, C_4- and C_6-H), 2.90(4H, s, 2 × CH_2), 2.26(9H, s, 3 × CH_3COO). Deacetylation of **XIa** with 0.1 M K_2CO_3 in 90% methanol (10 m*l*) afforded compound **XI**, which was crystallized from MeOH (yield 20 mg, colorless needles). mp 155-160°C. UV (MeOH) λ_{max}: 279. MS m/z(%): 230(M^+, 11), 123(6.5), 107(100). ^{1}H-NMR(DMSO-d_6): 9.06(1H, br.s, D_2O exchangeable), 8.97(2H, br.s, D_2O exchangeable), 6.98(2H, d, J = 8.4Hz, $C_{2'}$- and $C_{6'}$-H), 6.63(2H, d, J = 8.4Hz, $C_{3'}$- and $C_{5'}$-H), 6.04(3H, s, C_2-, C_4- and C_6-H), 2.64(4H, s, 2×CH_2)

Synthesis of α,β-dibromo-α-(3,5-diacetoxy)-β-(4'-acetoxy)diphenylethane (XIIa)

Br_2(180 mg) was added to **Ia**(350 mg) in ether (60 m*l*) with stirring. After further stirring for 20 min, the reaction mixture stood overnight to obtain colorless plates(**XIIa**)(yield 250 mg). MS m/z(%): 514 (M^+, 1), 435(M^+-Br, 3.3), 433(M^+-Br, 3.2), 393(4), 270(12), 228(19). ^{1}H-NMR($CDCl_3$): 7.46(2H,d, J = 8.7Hz, $C_{2'}$- and $C_{6'}$-H), 7.03(2H, d, J = 8.7Hz, $C_{3'}$- and $C_{5'}$-H), 7.14(2H, d, J = 2.0Hz, C_2- and C_6-H), 5.33(2H, s, 2 × CHBr), 2.30(9H, s, 3 × CH_3COO).

Synthesis of α,β-dihydroxy-α-(3,5-diacetoxy)-β-(4'-acetoxy)diphenylethane(XIIIa) and α,β-diacetoxy-α-(3,5-diacetoxy)-β-(4'-acetoxy)diphenylethane (XIVa)

The mixture of **Ia**(350 mg) and OsO_4(250 mg) in absolute benzene (50 m*l*) and pyridine (1 m*l*) was left standing in the dark for 2 days at room temperature. The reaction mixture was treated with H_2S gas to give precipitates, which was filtered and then washed with EtOAc. The filtrate and the washing solvent were combined and then evaporated in vacuo to yield dark brown residue. The residue was chromatographed over silica gel using hexane/EtOAc(2:1) as an eluting solvent. A fraction having Rf = 0.2 on TLC was freed from solvents to yield colorless oils (compound **XIIIa**)(yield 200 mg). UV(MeOH) λ_{max}: 235, 283. MS m/z(%): 388(M^+, 0.3), 266(4.4), 224(24), 182(34), 165(20), 140(47), 139(25), 123(100). ^{1}H-NMR($CDCl_3$): 7.17 (2H, d, J = 8.8Hz, $C_{2'}$- and $C_{6'}$-H), 6.95(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.75(3H, s, C_2-, C_4-and C_6-H), 4.63(2H, s, 2 × (OH)-CH-), 2.24(9H, s, 3 × CH_3COO). Acetylation of **XIIIa** (20 mg) with Ac_2O/pyridine afforded compound **XIVa** (10 mg). UV(MeOH) λ_{max}: 264. MS m/z(%): 472(M^+, 0.1), 223(17), 165(23), 139(9), 123(26). ^{1}H-NMR($CDCl_3$): 7.17(2H, d, J = 8.8Hz, $C_{2'}$- and $C_{6'}$-H), 6.96(2H, d, J = 8.8Hz, $C_{3'}$- and $C_{5'}$-H), 6.79(2H, d, J = 2.0 Hz, C_2- and C_6-H), 6.77(1H, d, J = 2.0Hz, C_4-H), 6.00(2H, s, 2 × (OAc)-CH-), 2.21(9H, s, 3 × CH_3COO), 2.05(6H, s, 2 × CH_3COO).

Isolation of compounds A,B and C from Sophorae Flos

Sophorae Flos(600g) was extracted with hot methanol (4L × 3 times). The methanol extract(150g) was fractionated with ether and butanol by usual method to obtain ether extract (8.1g) and BuOH extract (28.2g), respectively. Among them, the ether extract showed the strong inhibition on MAO-A, and it was subjected to column chromatography over silica gel using $CHCl_3$/MeOH (10:1) as an eluting solvent to obtain ten subfractions. Rechromatography of fractions 4 and 7 over silica gel using the same solvent afforded compounds A and B, and C (yields 200, 100, 200 mg), respectively.

Compound A (isorhamnetin)

Yellowish needles from methanol. mp > 300°C. UV(MeOH) λ_{max}: 256, 302, 372. MS m/z(%): 316 (M^+, 100), 315(19), 286(10), 153(12). ^{1}H-NMR (DMSO-d_6): 3.84(3H, s, OCH_3), 6.18(1H, d, J = 2.0Hz, C_6-H), 6.46(1H, d, J = 2.0Hz, C_8-H), 6.93 (1H, d, J = 8.1Hz, $C_{5'}$-H), 7.59(1H, d, J = 2.0 & 8.1Hz, $C_{6'}$-H), 7.75(1H, d, J = 2.0Hz, $C_{2'}$-H).

Compound B (kaemperol)

Yellowish fine needles from methanol. mp 275-280°C. UV(MeOH) λ_{max}: 268, 322, 368. MS m/z (%): 286(M^+, 100), 285(20), 153(29), 121(78). ^{1}H-NMR(DMSO-d_6): 6.18(1H, d, J = 1.9Hz, C_6-H), 6.42(1H, d, J = 1.9Hz, C_8-H), 6.92(2H, d, J = 8.7 Hz, $C_{3'}$- and $C_{5'}$-H), 8.04(2H, d, J = 8.7Hz, $C_{2'}$-and $C_{6'}$-H).

Compound C (quercetin)

Yellowish amorphous powders from MeOH. mp > 300°C. UV(MeOH) λ_{max}: 257, 302, 374. MS m/z(%): 302(M^+, 100), 301(24), 153(20). ^{1}H-NMR (DMSO-d_6): 6.18(1H, d, J = 1.9Hz, C_6-H), 6.39 (1H, d, J = 1.9Hz, C_8-H), 6.87(1H, d, J = 8.5Hz, $C_{5'}$-H), 7.54(1H, d, J = 1.8 & 8.5Hz, $C_{6'}$-H), 7.66 (1H, d, J = 1.8Hz, $C_{2'}$-H).

Table 1. MAO-A inhibition by several plants

Plant Name	MAO-A inhibition (%)	
	ether fr.*	BuOH fr.*
1. Lycii Fructus	26(−)**	0(−)**
2. Arisaematis Tuber	42(−)	0(−)
3. Sophorae Flos	98(+++)	20(−)
4. Polygonati Rhizoma	6(−)	27(−)
5. Hoelen	0(−)	0(−)
6. Artemisiae capillaris Herba	81(+++)	62(+)
7. Meliae Radicis Cortex	36(−)	0(−)
8. Alpinae Fructus	61(+)	0(−)
9. Myristicae Semen	39(−)	0(−)
10. Poligoni multiflori Radix	63(+)	10(−)
11. Epimedii Herba	76(+)	18(−)
12. Magnoliae Flos	75(+)	75(+)
13. Perillae Herba	85(++)	81(++)
14. Bupleuri Radix	32(−)	34(−)
15. Polygalae Radix	50(−)	10(−)
16. Chrisanthemi Flos	94(+++)	82(++)
17. Smilacis chinae Rhizoma	22(−)	0(−)
18. Veratri Rhizoma	99(+++)	38(−)
19. Lilii Bulbus	48(−)	31(−)
20. Atractylidis Rhizoma	47(−)	0(−)
21. Reynoutriae Radix	99(+++)	90(+++)
22. Uncariae Ramulus	48(−)	10(−)
23. Nepetae Spica	80(−)	24(−)
24. Rhei undulati Rhizoma	98(+++)	80(++)
25. Picrorrhizae Rhizoma	50(−)	51(+)
26. Tribuli Fructus	28(−)	0(−)
27. Trichosanthis Semen	75(+)	0(−)
28. Cynanchi wilfordi Radix	70(+)	0(−)
29. Dolichoris Semen	0(−)	10(−)
30. Chaenomelis Fructus	39(−)	0(−)

* Each fraction obtained from 10g of medicinal plant was dissolved in 2 ml of DMSO and diluted with water to prepare 100 ml of a test solution. One ml of it was taken and assayed for examining MAO-A inhibitory activity as described in the experimental method.
** +++, inhibition above 90%; ++, 80-89%; +, 50-79%; −, inhibition below 50%

RESULTS AND DISCUSSION

MAO-A inhibition of some medicinal plants

Methanol extracts of 30 kinds of medicinal plants were fractionated by hexane, ether and butanol. The ether and butanol soluble fractions of them were assayed for inhibitory potency towards MAO-A, using serotonin as a substrate. As shown in Table I, the inhibitory activities over 90% were found in the ether soluble fractions of Sophorae Flos, Chrisanthemi Flos, Veratri Rhizoma, Reynoutriae Radix and Rhei undulati Rhizoma, and found in the butanol soluble fraction of Reynoutriae Radix.

Table II. MAO-A inhibitory activities of Veratri Rhizoma

Fractions*	Weight (g)	Total activity (unit)**	Specific activity (unit/g)
A	5.61	66.98	11.96
B	0.15	0.02	0.16
N	3.13	14.97	4.94
BuOH	11.32	20.34	1.80

* The ether-soluble acidic(A), basic(B) and neutral(N) fractions and the BuOH fraction were obtained from the rhizoma(600g).
** Unit is defined as the reciprocal value of sample concentration(g/l) to give 50% inhibition against MAO-A activity.

Table III. MAO-A inhibitory activities of Veratri Rhizoma

Fr.*	Solvent ($CHCl_3$:MeOH)	Weight (g)	Total activity (unit)	Specific activity (unit/g)
A1	20:1	0.6	0.1	0.1
A2	5:1	1.21	60.51	50.01
A3	3:1	1.46	11.49	7.87
A4	2:1	1.2	0.1	0.1
A5	1:1	0.8	0	0.1

* The ether-soluble acid fraction (Fr A in Table II)(5.6g) was subjected to gradient chromatography over silica gel using $CHCl_3$/MeOH as eluting solvent system.

Isolation of stilbenes as MAO-A inhibitors

For elucidating active principle of Veratri Rhizoma, its ether extract was divided into three fractions through solvent fractionation; acidic(A), basic(B) and neutral(N) fractions. Each was assayed for MAO-A inhibitory activity, as shown in Table II. The most potent inhibitory activity was found in the ether-soluble acidic fraction (Fr. A), which was subjected to silica gel column chromatography using chloroform/methanol as eluting solvent system. As shown in Table III, Fr.A_2 was found to exhibit the major inhibitory effect towards MAO-A. Further column chromatography of Fr.A_2 over silica gel using n-hexane/chloroform/methanol/

HAc(5:5:1:0.2) yielded compound **I** as colorless needles, mp 255-260 °C, $C_{14}H_{12}O_3$. Acetylation with Ac_2O/pyridine and methylation with diazomethane afforded a triacetate(**Ia**) and a trimethylether (**Ib**), respectively. The physicochemical properties of **I** indicated the identity of this compound with resveratrol which was previously isolated from *Veratrum album*[18,19] and *Polygonum cuspidatum.*[20] The IC_{50} value of resveratrol(**I**) towards MAO-A was obtained from the inhibition curve as shown in Fig. 1. The inhibitory potency($IC_{50} = 2\ \mu M$) was similar to that of harman ($IC_{50} = 1.6\ \mu M$), but was more stronger than that of iproniazid ($IC_{50} = 26 \mu M$) when serotonin was used as a substrate of rat brain MAO-A(Fig. 1).

The similar methods to those for isolating the active principle from Veratri Rhizoma were applied to Reynoutriae Radix and Rhei undulati Rhizoma. Resveratrol(**I**) and its β-glucoside, piceid(**II**) were isolated from Reynoutriae Radix, and rhapontigenin(**III**), rhaponticin(**IV**) and 3,5-dihydroxy-4′-methoxystilbene(**V**) from Rhei undulati Rhizoma, all which are the known stilbene compounds. Their IC_{50} values were measured as shown in Table IV. The inhibitory potencies of **II** ($IC_{50} = 30\ \mu M$), **III** ($IC_{50} = 24\ \mu M$) and **V**($IC_{50} = 20\ \mu M$) were weaker than that of **I** ($IC_{50} = 2\ \mu M$), and **IV** had no inhibitory activity (IC_{50} 1000μM).

Another two stilbene compounds, oxyresveratrol (**VI**) and 2,3,4′,5-tetrahydroxystilbene-2-o-β-glucoside(**VII**) were isolated from Mori ramulus and Polygoni multiflori Radix, respectively, which did not show any inhibitory effects on MAO-A (Table IV). Through the chemical modification of the isolated stilbenes, several stilbene derivatives were prepared as follows:

i) acid hydrolysis of **VII** and a dimethylether of **II** yielded 2,3,4′,5-tetrahydroxystilbene(**VIII**) and

Table IV. Inhibition of MAO-A by stilbene derivatives

Structure	Compound	R	$IC_{50}(\mu M)$ Stilbenes(Acetate)
RO, HO, OH	I	H	2(2)*
	II	Glu**	30(60)
	Ib***	—	1000
HO, RO, OCH_3	V	H	20(20)
	IX	CH_3	120
HO, RO, OH, OCH_3	III	H	24(30)
	IV	Glu	>1000(>1000)
HO, HO, OH, OH	X		15(15)
HO, OR, HO, OH	VIII	H	100(100)
	VII	Glu	>1000(>1000)
HO, HO, HO, OH	VI		900(900)
	stilbene		>1000

*In parentheses were IC_{50} values of the acetates of various kinds of stilbenes.
**β-Glucopyranoside
*** Trimethyl ether of resveratrol(**I**).

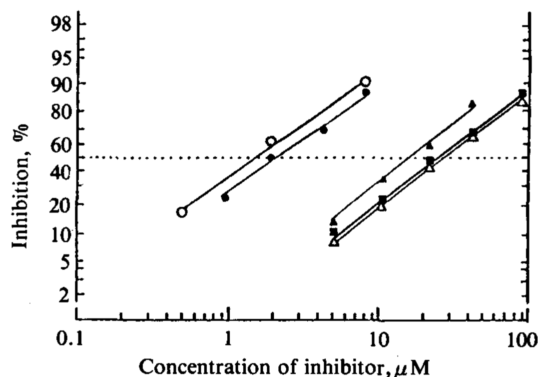


Fig. 1. Inhibition of MAO-A by some stilbenes, harman and iproniazid.
IC_{50} values of resveratrol(I)(-●-), piceatanol(X) (-▲-), rhapontigenin(III)(-■-), harman(-○-) and iproniazid(-△-) were measured as 2.0, 15, 24, 1.6 and 26μM, respectively.

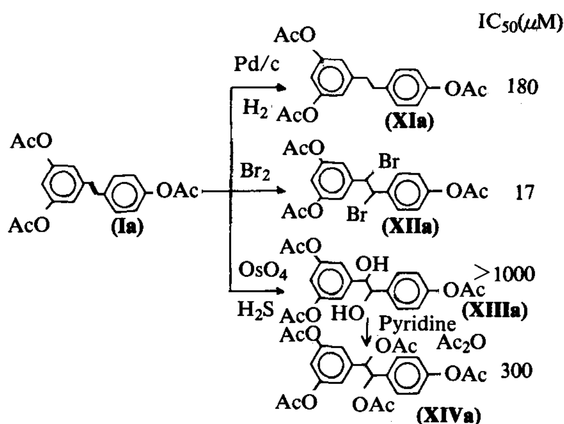


Fig. 2. Synthesis of bibenzyl derivatives from resveratrol triacetate(Ia) and their inhibitory activities on MAO-A.

3,4′-dimethoxy-5-hydroxystilbene(**IX**), respectively;

ii) demethylation of **III** gave 3,3′,4′,5-tetrahydroxystilbene(**X**, astrigenin or piceatanol);

iii) hydrogenation, bromination and OsO_4 oxidation on the olefinic bond of resveratrol triacetate (**Ia**) afforded 3,4′,5-triacetoxybibenzyl(**XIa**), 7,8-dibromo-3,4′,5-triacetoxybibenzyl(**XIIa**) and 7,8-dihydroxy-3,4′,5-triacetoxybibenzyl(**XIIIa**), respectively (Fig. 2);

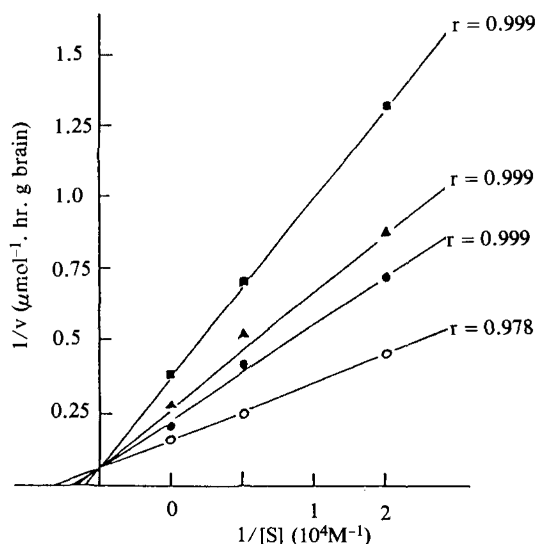


Fig. 3. Inhibition of MAO-A by resveratrol(I), using serotonin as a substrate.

The MAO-A activities were measured in the absence and the presence(1.25 μM, -●-; 2.5 μM, -▲-; 5.0 μM, -■-) of resveratrol(I) and at three concentrations (0.05, 0.1 0.2 mM) of serotonin.

Table V. Inhibition of MAO-B by resveratrol(I) and tranylcypromine

Compound	Concentration (M)	Inhibition* (%)
Resveratrol(**I**)	5.0×10^{-5}	5
	1.0×10^{-4}	8
	2.0×10^{-4}	10
Tranylcypromine	1.6×10^{-7}	25
	4.0×10^{-7}	50
	8.0×10^{-7}	70
	4.0×10^{-6}	98

* Inhibition of MAO-B was assessed with rat liver mitochondrial fraction as the enzyme source, using benzylamine as a substrate.[11] Absorbance of benzaldehyde produced was measured at 242 nm.

iv) acetylation of **XIIIa** gave 3,4′,5,7,8-pentaacetoxybibenzyl(**XIVa**) (Fig. 2).

All the stilbenes and bibenzyl derivatives were assessed in the aspects of their inhibitory activities against MAO-A as shown in Table IV and Fig. 2, respectively.

And some structure-activity relations were found as follows: The best inhibitor was resveratrol (**I**) ($IC_{50} = 2\,\mu M$), which possesses two phenolic hydroxy groups at *meta*-positions on A ring and one group at *para*-position on B ring in stilbene moiety. When an additional phenolic group presents at the *ortho* position on A or B ring of resveratrol(**I**), there is a great diminution in the inhibitory activity (IC_{50}: **VIII**, 100; VI, 900 μM). The stilbene glucosides such as **II**, **IV** and **VII** were less active than their aglycones (IC_{50}: **II** = 30, **I** = 2; **IV** 1000, **III** = 24;

Table VI. MAO-A inhibition by some flavonoids

	R_1	R_2	R_3	$IC_{50}(\mu M)$
Apigenin[a,b]	-H	-OH	-H	10
Luteolin[b]	-H	-OH	-OH	100
Acacetin[b]	-H	$-OCH_3$	-H	>1000
Diosmetin[b]	-H	$-OCH_3$	-OH	>1000
Kaemperol[a]	-OH	-OH	-H	10
Quercetin[a]	-OH	-OH	-OH	100
Isorhamnetin[a]	-OH	-OH	$-OCH_3$	100
Rutin[a]	-O-sugar	-OH	-OH	>1000
Eriodictyo[b]	-H	-OH	-OH	>1000

[a]Isolated from Sophorae Flos.
[b]Isolated from Chrisanthemi Flos.[11]

Table VII. MAO-A inhibition by some isoflavonoids isolated from *Glycine max*

	R_1	R_2	$IC_{50}(\mu M)$
Deidzein	-H	-H	800
Deidzin	-H	-O-Glu	1000
Genistein	-OH	-H	40
Genistin	-OH	-O-Glu	150

VII > 1000, **VIIIa** = 100 μM). Acetylation of the phenolic hydroxyl groups of stilbenes exhibited no changes in their inhibitory activities (**Ia, IIIa, Va, VIa, IXa, Xa**), whereas methylation of them diminished in the activities (**I** = 2, **V** = 20, **IX** = 120, **Ib** = 1000 μM). The acetyl radicals turned out to be removed from the phenolic hydroxyl groups of stilbenes by rat brain mitochondrial fraction, but the methyl ethers did not(data not shown). The chemical modification of the olefinic bond of stilbenes severely affected the activities(**XIa** = 180, **XIIa** = 17, **XIIIa** > 1000 μM) (Fig. 2).

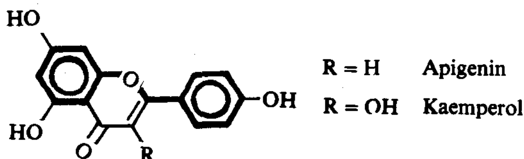
Resveratrol(**I**) was found to inhibit MAO-A competitively (Ki = 2.5 μM), using serotonin as a substrate(Fig. 3), whereas it sparingly inhibited MAO-B above 200 μM concentration when IC_{50} of tranylcypromine, a known MAO-B inhibitor was measured as 0.4 μM, using benzylamine as a substrate (Table V).

Isolation of flavonoids as MAO-A inhibitors

Screening of Sophorae Flos and Chrisanthemi Flos for isolating their active principles afforded several kinds of flavonoids as shown in Table VI. Among the flavonoids, apigenin and kaemperol showed the strong inhibitory effects towards MAO-A, although their activities(both IC_{50} = 10 μM) were five-fold weaker than that of resveratrol(**I**), but both compounds did not inhibit MAO-B.[11]

Some isoflavonoids found in *Glycine max*[21] were also examined in the aspects of their inhibitory effects on MAO-A. As shown in Table VII, genistein had the IC_{50} value of 40 μM.

The flavonoids and isoflavonoids isolated were less active than the stilbenes, but the structure-activity relationship of flavonoids and isoflavonoids was found to resemble that of stilbenes. Indeed, apigenin, kaemperol and genistein involve the structure of resveratrol(**I**).



Rescently, Yamazaki *et al.*[22] isolated norsolorinic acid from a fungus, *Emericella navahoensis,* as MAO inhibitor. They demonstrated that the compound inhibited MAO in mouse liver non-competitively when kynuramine was used as a substrate, and its IC_{50} was 0.3 μM, and that the inhibition constants(Ki) for MAO-A and -B in mouse brain were 2.9 and 0.32 μM, respectively. Our results showed that resveratrol competitively inhibited MAO-A in rat brain when serotonin was used as a substrate, but it did not inhibit MAO-B in rat liver when benzylamine was used as a substrate, and that the IC_{50} value of resveratrol was 2 μM and its Ki value was 2.5 μM. Thus, the inhibitory potencies of resveratrol and norsolorinic acid could not be assessed without direct comparison under same experimental condition. However, it is noteworthy to mention that norsolorinic acid, although it is an anthraquinone derivative, possesses resveratrol moity in its structure. Our results on MAO-A inhibitory activities of some anthraquinones can be seen in other article.[23]

ACKNOWLEDGEMENT

This study was supported by a Basic Research Grant from the Korean Science and Engineering Foundation(KOSEF).

LITERATURE CITED

1. Neff, N.H. and Yang, H.-Y.: Another look at the monoamine oxidases and the monoamine oxidase inhibitor drugs. *Life Sci.* **14**, 2061 (1974).
2. Fowler, C.J., Callingham, B.A., Mantle, T.J. and Tipton, K.F.: Monoamine oxidase A and B: a useful concept. *Biochem. Pharmac.* **27**, 97 (1978).
3. Cawthon, R.M., Pintar, J.E., Haseltine, F.P. and Breakefield, X.O.: Differences in structure of A and B forms of human monoamine oxidase. *J. Neurochem.* **37**, 363 (1981).
4. Ban, T.A.: *Psychopharmacology,* Williams & Wilkins, Baltimore (1969).
5. Quitin, F., Rifkin, A. and Klein, D.F.: Monoamine oxidase inhibitors: a review of antidepressant effectiveness. *Archs Gen. Psychiat.* **36**, 749 (1979).
6. Riederer, P., Reynolds, G.P., Jellinger, K., Seemann, D. and Danielczyk, W.: Tranylcypromine isomers in Parkinson's disease. Effect of low doses on monoamine oxidase inhibition and blood pressure response. *Modern Problems of Pharmacopsychiatry.* Vol. **19** *Monoamine oxidase and its selective inhibitors.* S. Karger, p. 154 (1983).
7. Birkmayer, W., Knoll, J., Riederer, P. and Youdim, M.B.H.: (-)-Deprenyl leads to prolongation of L-dopa efficacy in Parkinson's disease. *ibid* p. 170 (1983).
8. Stern, G.M., Lees, A.J., Hardie, R. and Sandler, M.: Clinical and pharmacological aspects of (-)-deprenyl treatment in Parkinson's disea-

ses. *ibid* p. 231 (1983).
9. Rigal, F. and Zarifian, E.: MAO inhibitors in psychiatric therapy: effects and side effects. *ibid* p. 162 (1983).
10. Lipper, S., Murphy, D.L., Slater, S. and Buchsbaum, M.S.: Comparative behavioral effects of clorgyline and pargyline in man: a preliminary evaluation. *Psychopharmacology.* **62,** 123 (1979).
11. Han, Y.N., Noh, D.B. and Han, D.S.: Studies on the Monoamine oxidase inhibitors of medicinal plants I. Isolation of MAO-B inhibitors from *Chrysanthemum indicum. Arch. Pharm. Res.* **10,** 132 (1987).
12. Zeller, E.A.: Oxidation of amines, in Sumner, J.B., Myrbäck(eds.), *The Enzymes* 1st ed. Vol II. Academic Press. New York, p 536 (1951).
13. Ichiyama, A., Nakamura, S., Nishizuka, Y. and Hayaishi, O.: Enzymatic studies on the biosynthesis of serotonin in mammalian brain. *J. Biol. Chem.* **254,** 1699 (1970).
14. Desphande, V.H., Srinivasan, R. and Rao, A.V.R.: *Indian J. Chem.* **13,** 453 (1975).
15. Hata, K., Kozawa, M. and Baba, K.: A new stilbene glucoside from Chinese crude drug "Heshouwu", the roots of *Polygonum multiflorum. Yakugaku Zassi* **95,** 211 (1975).
16. Nonomura, S., Kanagawa, H. and Makimoto, A.: Chemical constituents of Polygonaceous plants I. *Yakugaku Zassi* **83,** 988 (1963).
17. Bachelor, F.W., Loman, A.A. and Snowdon, L.R.: Synthesis of pinosylvin and related heartwood stilbenes. *Canadian J. Chem.* **48,** 554 (1970).
18. Drewes, S.E. and Fletcher, I.P.: Polyhydroxystilbenes from the heartwood of *Schotia brachypetala. J. Chem. Soc.* Perkin 1. 961 (1974).
19. Takaoka, M.: *J. Fac. Sci. Hokkaido Univ.* **3,** 1 (1940).
20. Kubo, M., Kimura, Y., Shin, H., Haneda, T., Tani, T. and Namba, K.: Studies on the antifungal substance of crude drug(II), on the root of *Polygonum cuspidatum* (Polygonaceae). *Shoyakugaku Zasshi.* **35,** 58 (1981).
21. Encyclopaedia Chimica **3,** 391A, Japan (1980).
22. Yamazaki, M., Satoh, Y., Maebayashi, Y. and Horie, Y.: Monoamine oxidase inhibitors from a fungus, *Emericella navahoensis. Chem. Pharm. Bull.* **36,** 670 (1988).
23. Han, Y.N., Ryu, S.Y., Chung, M.S. and Han, B.H.: Aromatic L-amino acid decarboxylase inhibitors from medicinal plants. *Arch. Pharm. Res.* **11,** in press (1988).