Synthesis and Pharmacological Evaluation of 1,2,3,4-Tetrahydro-β-carboline Derivatives[1)]

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A series of 1,2,3,4-tetrahydro-β-carbolines has been synthesized and evaluated for cerebral protecting effects against lipid peroxidation and potassium cyanide intoxication in mice. Most of the compounds synthesized had potent effects against lipid peroxidation. Among them, 1-(3,5-dimethoxyphenyl)-2-propyl-1,2,3,4-tetrahydro-β-carboline (22) was found to have a combination of potent effects against both lipid peroxidation and potassium cyanide intoxication. Structure–activity relationships are discussed.

Key words 1,2,3,4-tetrahydro-β-carboline; lipid peroxidation; potassium cyanide intoxication; structure–activity relationship

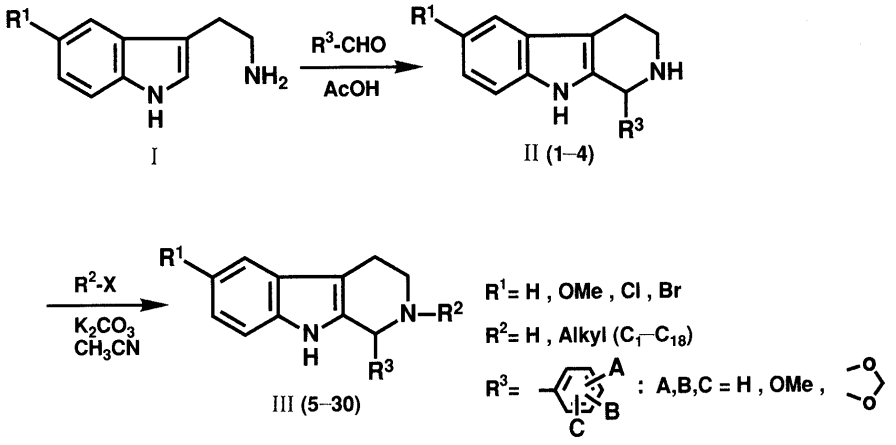
The brain is particularly sensitive to hypoxia because of its high energy demands relative to its scanty stores of energy-rich substances.[2)] When the supply of these substances is interrupted, notably due to a stroke, irreversible anoxic/ischemic brain damage will occur. Amelioration of cerebral ischemic damage by the use of cerebral protective drugs is an important clinical problem that is still far from satisfactorily solved, due to the lack of a specific agent of proven efficacy. The cerebral protecting effects of new drugs have been evaluated in various cerebral ischemic models, for example potassium cyanidelethality, complete ischemia and hypoxia. Furthermore, it was reported that oxidant-mediated lipid peroxidation may be involved in the pathophysiology of post ischemic brain injury.[3)]

In the course of searching for new cerebral protective agents, we have found that 1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline (**5**) had potent cerebral protecting effects against lipid peroxidation and potassium cyanide intoxication in mice. A number of compounds containing the β-carboline structure have been synthesized and evaluated, and have aroused considerable interest in the field of neuropharmacology.[4–6)] However, there has been no report on cerebral protective agents having the 1,2,3,4-tetrahydro-β-carboline skeleton. In the present investigation, new 2-alkyl-1-aryl-6-substituted-1,2,3,4-tetrahydro-β-carbolines (III) were synthesized and evaluated for cerebral protecting effects against lipid peroxidation and potassium cyanide intoxication in mice.

Results and Discussion

The compounds studied here were synthesized starting from tryptamine (I), as summarized in Chart 1. Pictet–Spengler reaction[7)] of I with substituted benzaldehydes gave 1,2,3,4-tetrahydro-β-carbolines (II, **1**—**4**). 2-Alkyl-1-aryl-6-substituted-1,2,3,4-tetrahydro-β-carbolines (III, **5**—**30**) were obtained by *N*-alkylation of II under basic conditions. Physical and analytical data for **5**—**30** are recorded in Tables 1, 2, and 3.

The effect against lipid peroxidation was tested in male Wistar rats by the thiobarbituric acid method according to Ohkawa *et al.*[8)] The effect against cyanide intoxication was tested in male ICR strain mice. Histotoxic anoxia was produced by an intravenous injection of potassium cyanide (5 mg/kg). The time between the potassium cyanide injection and the last gasp (survival time) was determined. Test compounds were administered intraperitoneally 30 min before the injection of potassium cyanide. The activity of **5** against lipid peroxidation was more potent than that of the positive control (vitamin E). Further, **5** significantly prolonged survival time when administered orally at the dose of 100 mg/kg in mice.



I II (**1**–**4**) III (**5**–**30**)

Chart 1

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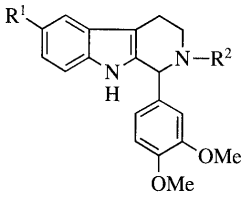
Table 1. Physical and Pharmacological Data for **5**—**16**



Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Inhibition of lipid peroxidation[b]	Cyanide intoxication[c]
5	H	Me	184—186	H–A	$C_{20}H_{22}N_2O_2$	61.07	5.64	7.12	61.09	5.71	7.18	16	133**
6	H	Et	241—242	M–E	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64	6.76	7.51	67.22	6.73	7.23	33	101
7	H	Pr	210—212	M–E	$C_{22}H_{26}N_2O_2 \cdot HCl$	68.29	7.03	7.24	68.50	7.07	7.18	33	181**
8	H	Bu	223—224	M–E	$C_{23}H_{28}N_2O_2 \cdot HCl \cdot 1/2H_2O$	67.70	7.41	6.87	67.76	7.20	6.70	62	160**
9	H	Hexyl	156—158	H–A	$C_{25}H_{32}N_2O_2$	76.49	8.22	7.14	76.29	8.27	7.09	73	105
10	H	Heptyl	146—148	H–A	$C_{26}H_{34}N_2O_2$	76.81	8.43	6.89	76.83	8.49	6.82	78	129**
11	H	Octyl	124—126	H–A	$C_{27}H_{36}N_2O_2$	77.10	8.63	6.66	77.31	8.66	6.61	76	104
12	H	Nonyl	115—118	H–A	$C_{28}H_{38}N_2O_2$	77.38	8.81	6.45	77.08	8.84	6.38	83	114
13	H	Decyl	123—125	H–A	$C_{29}H_{40}N_2O_2$	77.63	8.99	6.25	77.45	9.03	6.10	82	115
14	OMe	Octyl	133—135	H–A	$C_{28}H_{38}N_2O_3$	74.63	8.50	6.22	74.42	8.54	6.07	83	117
15	Br	Octyl	163—166	H–A	$C_{27}H_{35}BrN_2O_2$	64.92	7.06	5.61	64.88	7.08	5.53	70	110
16	Cl	Octyl	162—165	H–A	$C_{27}H_{35}ClN_2O_2$	71.26	7.75	6.16	71.09	7.79	6.04	68	107
Vitamin E												11 (20 μM)	

a) A = AcOEt, E = ether, H = hexane, M = MeOH. *b*) Inhibition % of lipid peroxidation at 10 μM. *c*) Percent of control at 100 mg/kg *p.o.* * $p<0.05$ *vs.* control. ** $p<0.01$ *vs.* control.

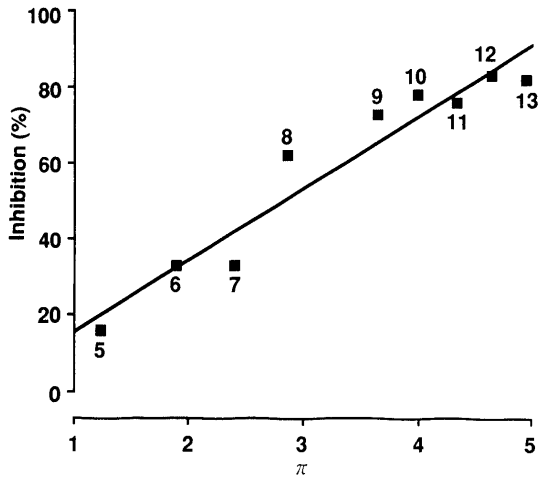


Fig. 1. Relationship between Inhibition of Lipid Peroxidation and the Hydrophobic Parameter π of Substituent R^2 in Compounds **5**—**13**

Inhibition (%) = 18.8π − 3.15, $r = 0.96$.

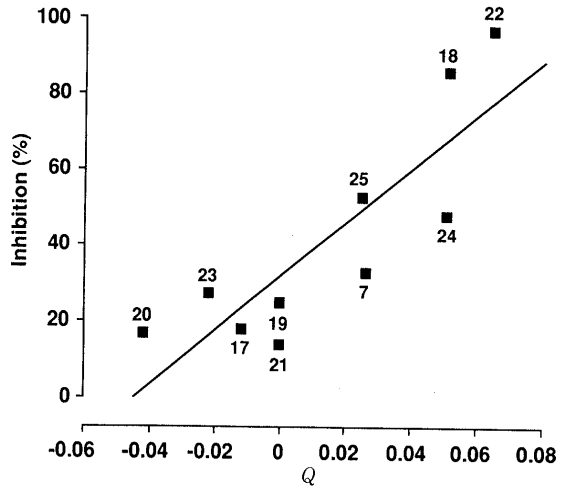


Fig. 2. Relationship between Inhibition of Lipid Peroxidation and Electronic Charge (Q) at the 1 Position of the 1,2,3,4-Tetrahydro-β-carboline Skeleton of Various Compounds to Which the Substituent R^3 is Attached

Inhibition (%) = 709.0Q + 31.9, $r = 0.72$.

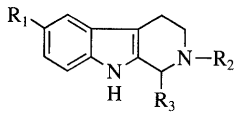
We next investigated the effects of the alkyl substituent (R^2) at the 2 position of **5**. The pharmacological data are shown in Table 1.

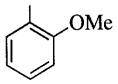
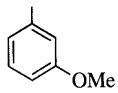
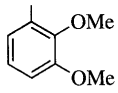
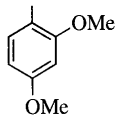
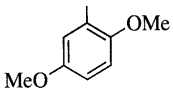
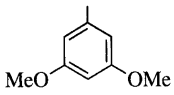
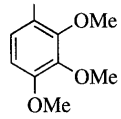
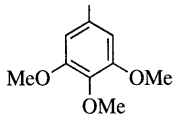
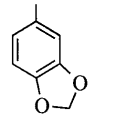
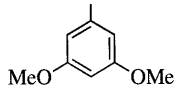
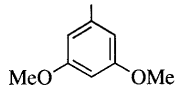
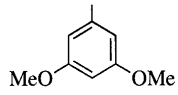
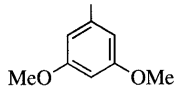
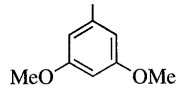
Most of the compounds (**6**—**13**) had strong effects against lipid peroxidation, being more potent than vitamin E. The structure–activity relationships of 2-alkyl-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-β-carbolines suggested that elongation of the R^2 methylene chain resulted in an increase of inhibitory effect against the lipid peroxidation. There seemed to be a relationship between the effect on lipid peroxidation and the hydrophobic parameter π of substituent R^2. The values of π were estimated by using the fragment method reported by Hansch and Leo.[9] The positive coefficient for π may indicate that a hydrophobic substituent R^2 is favorable for the activity. This relationship is shown in Fig. 1. The effect of the substituent R^2 on the activity against potassium cyanide intoxication was rather complicated. Compounds **7**, **8**, and **10** prolonged the survival time in mice. Among these compounds, **7** showed the most potent effect.

The activities against lipid peroxidation and potassium cyanide intoxication of compounds **14**, **15**, and **16** were roughly equivalent to that of **11**. No influence of the substituent R^1, such as H, OMe, Br, and Cl, was observed.

As the next step, the effects of a methoxyphenyl group (R^3) at the 1 position of **5** were examined. The substituent R^2 was fixed as a propyl group, which is the most favorable

Table 2. Physical and Pharmacological Data for **17**—**30**



Compd. No.	R^1	R^2	R^3	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of lipid peroxidation[b]	Cyanide intoxication[c]
17	H	Pr		215—218	M–E	$C_{21}H_{24}N_2O \cdot HCl \cdot 1/4H_2O$	69.79 (69.86	7 7.11 7.02	7.75 7.70)	18	132**
18	H	Pr		195—200	M–E	$C_{21}H_{24}N_2O_2 \cdot HCl$	70.07 (70.50	7.06 7.15	7.85 7.69)	86	100
19	H	Pr		230—232	M–E	$C_{22}H_{26}N_2O_2 \cdot HCl$	68.29 (68.62	6.77 7.16	7.24 7.16)	25	118
20	H	Pr		240 (dec.)	M–E	$C_{22}H_{26}N_2O_2 \cdot HCl$	68.47 (68.66	6.79 7.05	7.26 7.28)	17	173**
21	H	Pr		208—212	M–E	$C_{22}H_{26}N_2O_2 \cdot HCl$	68.29 (67.91	7.03 7.08	7.24 7.35)	14	132
22	H	Pr		153—154	M	$C_{22}H_{26}N_2O_2$	75.39 (75.67	7.48 7.52	8.00 7.92)	97	152**
23	H	Pr		225—227	M–E	$C_{23}H_{28}N_2O_3 \cdot HCl$	66.25 (66.23	7.01 7.00	6.72 6.70)	27	168**
24	H	Pr		226—228	M–E	$C_{23}H_{28}N_2O_3 \cdot HCl$	66.25 (66.31	7.01 7.02	6.72 6.82)	48	143**
25	H	Pr		210—213	M–E	$C_{21}H_{22}N_2O_2 \cdot HCl$	68.01 (67.92	6.25 6.22	7.56 7.39)	53	139**
26	H	Et		149—151	H–A	$C_{21}H_{24}N_2O_2$	74.97 (75.03	7.19 7.25	8.33 8.24)	69	130
27	H	Hexyl		108—110	H–A	$C_{25}H_{32}N_2O_2$	76.49 (76.35	8.22 8.24	7.14 7.09)	98	99
28	H	Octyl		204—206	M–E	$C_{27}H_{36}N_2O_2 \cdot HCl$	70.95 (70.67	8.16 8.16	6.13 6.00)	97	101
29	H	Hexadecyl		88—90	H–A	$C_{35}H_{52}N_2O_2$	78.90 (78.81	9.84 9.92	5.26 5.14)	17	104
30	H	Octadecyl		91—93	H–A	$C_{37}H_{56}N_2O_2$	79.23 (79.02	10.07 10.18	5.00 4.96)	30	101

a—*c*) See Table 1.

Table 3. Physical and Analytical Data for **6**—**30**

Compd. No.	Yield (%)	MS m/z (M^+)	IR ν_{max}^{KBr} cm^{-1}	Solvent[a]	^{1}H-NMR Chemical shifts (ppm)
6	27	336	3353, 1517, 1467, 1297	B	1.33 (3H, t, J=7 Hz), 2.90—3.80 (6H, m), 3.75 (3H, s), 3.81 (3H, s), 5.82 (1H, br s), 6.90—7.40 (6H, m), 7.52 (1H, d, J=6 Hz)
7	36	350	3329,1519, 1468, 1145	B	0.85 (3H, t, J=6 Hz), 1.83 (2H, m), 2.80—3.80 (6H, m), 3.74 (3H, s), 3.79 (3H, s), 5.84 (1H, br s), 6.80—7.40 (6H, m), 7.53 (1H, d, J=6 Hz)
8	25	364	3329, 2386, 1519, 1297	A	0.86 (3H, t, J=7 Hz), 1.25 (2H, sextet, J=7 Hz), 1.80 (2H, m), 2.60—3.60 (6H, m), 3.74 (3H, s), 3.81 (3H, s), 5.82 (1H, br s), 6.80—7.40 (6H, m), 7.53 (1H, d, J=7 Hz)
9	40	392	3368, 2926, 1517, 1265	A	0.85 (3H, t, J=7 Hz), 1.23 (6H, m), 1.55 (2H, m), 2.10—3.12 (5H, m), 3.35 (1H, m), 3.81 (3H, s), 3.90 (3H, s), 4.47 (1H, br s), 6.88 (3H, m), 6.99—7.40 (4H, m), 7.51 (1H, m)
10	72	406	3429, 2925, 1485, 1247	A	0.86 (3H, t, J=7 Hz), 1.15 (2H, m), 1.22 (8H, m), 2.31 (1H, m), 2.47—3.13 (4H, m), 3.36 (1H, m), 3.80 (3H, s), 3.90 (3H, s), 4.46 (1H, br s), 6.88 (3H, m), 7.00—7.38 (4H, m), 7.51 (1H, m)
11	55	420	3367, 2922, 1518, 1265	A	0.87 (3H, t, J=7 Hz), 1.26 (10H, m), 1.52 (2H, quintet, J=7 Hz), 2.28 (1H, m), 2.46—3.14 (4H, m), 3.35 (1H, m), 3.80 (3H, s), 3.88 (3H, s), 4.46 (1H, br s), 6.75—6.98 (3H, m), 6.98—7.33 (4H, m), 7.51 (1H, m)
12	70	434	3368, 2924, 1518, 1265	A	0.87 (3H, t, J=7 Hz), 1.22 (12H, m), 1.53 (2H, m), 2.29 (1H, quintet, J=7 Hz), 2.46—3.10 (5H, m), 3.35 (1H, m), 3.80 (3H, s), 3.90 (3H, s), 4.46 (1H, br s), 6.87 (3H, m), 6.95—7.35 (4H, m), 7.51 (1H, m)
13	72	448	3368, 2923, 1518, 1265	A	0.87 (3H, t, J=7 Hz), 1.53 (2H, m), 2.29 (1H, quintet, J=7 Hz), 2.45—3.13 (4H, m), 3.37 (1H, m), 3.83 (3H, s), 3.88 (3H, s), 4.46 (1H, br s), 6.84 (3H, m), 6.99—7.38 (4H, m), 7.51 (1H, m)
14	94	450	3336, 2926, 1516, 1464	A	0.88 (3H, t, J=7 Hz), 1.22 (10H, m), 1.55 (2H, m), 2.27 (1H, quintet, J=7 Hz), 2.95—3.10 (4H, m), 3.37 (1H, m), 3.80 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 4.46 (1H, br s), 6.65—7.25 (6H, m)
15	70	500	3348, 2925, 1516, 1261	A	0.87 (3H, t, J=7 Hz), 1.22 (10H, m), 1.53 (2H, m), 2.28 (1H, quintet, J=7 Hz), 2.43—3.10 (5H, m), 3.35 (1H, m), 3.79 (3H, s), 3.89 (3H, s), 4.46 (1H, br s), 6.75—6.95 (3H, m), 7.04 (2H, d, J=9 Hz), 7.16 (1H, dd, J=9, 1 Hz), 7.27 (1H, s), 7.63 (1H, d, J=1 Hz)
16	79	455	3350, 2926, 1517, 1301	A	0.87 (3H, t, J=7 Hz), 1.22 (10H, m), 1.49 (2H, m), 2.27 (1H, quintet, J=7 Hz), 2.44—3.07 (4H, m), 3.35 (1H, m), 3.78 (3H, s), 3.89 (3H, s), 4.46 (1H, br s), 6.75—6.95 (3H, m), 6.95—7.17 (2H, m), 7.26 (1H, s), 7.48 (1H, d, J=1 Hz)
17	33	320	3346, 1602, 1492, 1461	B	0.92 (3H, t, J=7 Hz), 1.92 (2H, m), 2.90—3.60 (6H, m), 3.96 (3H, s), 6.12 (1H, s), 6.79 (1H, dd, J=8, 1 Hz), 6.90—7.60 (7H, m)
18	41	320	3130, 1609, 1586, 1456	B	0.84 (3H, m), 1.85 (2H, m), 2.90—3.70 (6H, m), 3.78 (3H, s), 5.90 (1H, s), 6.90—7.50 (7H, m), 7.55 (1H, d, J=8 Hz)
19	15	350	3132, 3095, 1483, 1456	B	0.89 (3H, t, J=7 Hz), 1.89 (2H, sextet, J=7 Hz), 2.90—3.70 (6H, m), 3.92 (3H, s), 3.95 (3H, s), 6.10 (1H, s), 6.62 (1H, d, J=7 Hz), 6.80—7.40 (5H, m), 7.55 (1H, d, J=7 Hz)
20	18	350	3434, 3120, 1617, 1511	B	0.91 (3H, t, J=7 Hz), 1.93 (2H, sextet, J=7 Hz), 2.90—3.70 (6H, m), 3.79 (3H, s), 3.93 (3H, s), 6.02 (1H, s), 6.51 (1H, dd, J=8, 1 Hz), 6.70—6.90 (2H, m), 7.08 (2H, m), 7.20 (1H, d, J=7 Hz), 7.54 (1H, d, J=7 Hz)
21	25	350	3376, 1504, 1460, 1429	B	0.91 (3H, s, J=7 Hz), 1.91 (2H, sextet, J=7 Hz), 2.90—3.70 (6H, m), 3.60 (3H, s), 3.90 (3H, s), 6.10 (1H, s), 7.00—7.20 (4H, m), 7.31 (1H, d, J=8 Hz), 7.57 (1H, d, J=8 Hz)
22	54	350	3397, 3337, 1608, 1595	B	0.81 (3H, t, J=7 Hz), 1.50 (2H, m), 2.20—2.90 (4H, m), 3.10—3.50 (2H, m), 3.70 (6H, s), 4.53 (1H, s), 6.41 (1H, t, J=1 Hz), 6.51 (2H, d, J=1 Hz), 6.94 (2H, m), 7.21 (1H, dd, J=8, 1 Hz), 7.38 (1H, dd, J=8, 1 Hz)
23	59	380	3430, 3057, 2941, 1597	B	0.89 (3H, t, J=8 Hz), 1.89 (2H, sextet, J=8 Hz), 2.90—3.40 (4H, m), 3.40—3.70 (2H, m), 3.83 (3H, s), 3.85 (3H, s), 4.00 (3H, s), 6.00 (1H, br, J=2 Hz), 6.70—6.90 (2H, m), 7.09 (2H, m), 7.30 (1H, d, J=6 Hz), 7.55 (1H, d, J=6 Hz)
24	32	380	3336, 2940, 1599, 1511	B	0.84 (3H, t, J=7 Hz), 1.85 (2H, m), 2.80—3.90 (6H, m), 3.72 (3H, s), 3.77 (6H, s), 5.05 (1H, s), 6.82 (1H, s), 7.03 (2H, s), 7.08 (2H, m), 7.28 (1H, d, J=8 Hz), 7.52 (1H, d, J=8 Hz)
25	49	334	3414, 2536, 1504, 1491	B	0.85 (3H, t, J=7 Hz), 1.83 (2H, m), 2.80—3.90 (6H, m), 5.85 (1H, s), 6.10 (2H, s), 6.90—7.20 (5H, m), 7.28 (1H, d, J=8 Hz), 7.52 (1H, d, J=8 Hz)
26	65	336	3384, 1609, 1596, 1466	A	1.10 (3H, t, J=7 Hz), 2.41 (1H, m), 2.56—3.15 (4H, m), 3.36 (1H, m), 3.76 (3H, s), 3.78 (3H, s), 4.50 (1H, br s), 6.43 (1H, t, J=2 Hz), 6.58 (2H, d, J=2 Hz), 6.96—7.44 (4H, m), 7.51 (1H)
27	57	392	3377, 2942, 1612, 1592	B	0.82 (3H, t, J=7 Hz), 1.20 (6H, s), 1.35 (2H, m), 2.20—2.60 (3H, m), 2.75 (1H, m), 3.20 (2H, m), 3.70 (6H, s), 4.50 (1H, s), 6.42 (1H, t, J=1 Hz), 6.51 (2H, d, J=1 Hz), 6.95 (1H, m), 7.21 (1H, dd, J=8, 1 Hz), 7.38 (1H, dd, J=8, 1 Hz)
28	73	420	2926, 2521, 1599, 1460	B	0.82 (3H, t, J=7 Hz), 1.22 (6H, s), 1.81 (2H, m), 2.80—3.80 (6H, m), 3.76 (6H, s), 5.83 (1H, s), 6.64 (1H, br s), 6.77 (2H, br s), 7.07 (1H, m), 7.38 (1H, d, J=7 Hz), 7.52 (1H, d, J=7 Hz)
29	35	532	3407, 2917, 2850, 1607	A	0.88 (3H, t, J=7 Hz), 1.26 (26H, m), 1.54 (2H, m), 2.33 (1H, m), 2.45—3.07 (4H, m), 3.36 (1H, m), 3.77 (6H, s), 4.46 (1H, br s), 6.41 (1H, m), 6.57 (2H, d, J=1 Hz), 6.97—7.40 (3H, m), 7.50 (1H, m)
30	83	560	3407, 2917, 2850, 1607	A	0.88 (3H, t, J=7 Hz), 1.25 (30H, m), 1.57 (2H, m), 2.15—3.18 (5H, m), 3.37 (1H, m), 3.78 (6H, s), 4.46 (1H, br s), 6.43 (1H, m), 6.58 (2H, m), 6.94—7.43 (4H, m), 7.51 (1H, m)

a) A = $CDCl_3$, B = DMSO-d_6.

for the effect against cyanide intoxication.

The pharmacological data are shown in Table 2. Most of the compounds (**17**—**25**) had potent effects against lipid peroxidation. There seemed to be a relationship between the effect on lipid peroxidation and the value of Q, which is the electronic charge at the 1 position of the 1,2,3,4-tetrahydro-β-carboline skeleton to which the substituent R^3 is attached. The Q values were calculated by using a complete neglect of differential overlap (CNDO) molecular orbital calculation program. A positive coefficient for Q may indicate that electron-withdrawing character, at the 1 position of the 1,2,3,4-tetrahydro-β-carboline skeleton is important. This relationship is shown in Fig. 2.

In the case of potassium cyanide intoxication, **20**, **22**—**25** prolonged the survival time in mice. The 3,5-dimethoxyphenyl group (**22**) appears to increase the activities against both lipid peroxidation and potassium cyanide intoxication.

Finally, the effects of the alkyl subsituent R^2 at the 2 position of 1-(3,5-dimethoxyphenyl)-2-alkyl-1,2,3,4-tetrahydro-β-carbolines were examined. Against lipid peroxidation, the activities of the 2-hexyl and 2-octyl derivatives (**27**, **28**) are more potent than those of the 2-hexadecyl and 2-octadecyl derivatives (**29**, **30**). But, these derivatives did not show any effect against potassium cyanide intoxication.

Among these compounds, 1-(3,5-dimethoxyphenyl)-2-propyl-1,2,3,4-tetrahydro-β-carboline (**22**) was found to have a combination of potent effects against both lipid peroxidation and potassium cyanide intoxication.

Experimental

Melting points were determined on a Yanagimoto Kikai MP-S3 apparatus without correction. Infrared (IR) spectra were taken on a Perkin-Elmer 1760 spectrometer. Mass spectra (MS) were measured on a JEOL JMS-SX 102 or a Shimadzu QP-1000 spectrometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were recorded on a Varian VXL-200 spectrometer. Chemical shifts are given in ppm with tetramethylsilane as an internal standard, and the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), double doublet (dd), triplet (t), quartet (q), and multiplet (m).

1-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydro-β-carboline Hydrochloride (1) A mixture of tryptamine hydrochloride (30.2 g, 154 mmol), 3,4-dimethoxybenzaldehyde (25.6 g, 154 mmol), and AcOH (300 ml) was heated at 100 °C for 12 h under an N_2 atmosphere. The precipitate was collected by filtration, washed with EtOH and then crystallized from MeOH–ether to give **1** as colorless crystals: 42.9 g (81.0%); mp 251—252 °C; MS (EI) m/z 308 (M^+); IR (KBr) 3330, 2780, 1520, 1265; ^{1}H-NMR (DMSO-d_6) δ: 2.73—3.5 (4H, m), 3.78 (3H, s), 3.87 (3H, s), 5.09 (1H, s), 6.8—7.29 (6H, m), 7.53 (1H, m), 7.67 (1H, br s).

Compounds **2**—**4** were synthesized in the same manner.

1-(3,4-Dimethoxyphenyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline Hydrochloride (**2**): Yield 60%; mp 251—252 °C (MeOH); IR (KBr) 3338, 2733, 1521, 1494, 1261 cm^{-1}; MS (EI) m/z 338 (M^+); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.50 (4H, m), 3.75 (3H, s), 3.78 (6H, s), 5.80 (1H, s), 6.75 (1H, dd, J=9, 2 Hz), 6.85 (1H, dd, J=9, 2 Hz), 10.30 (1H, br s), 10.65 (1H, s).

1-(3,4-Dimethoxyphenyl)-6-bromo-1,2,3,4-tetrahydro-β-carboline Hydrochloride (**3**): Yield 74%; mp 278—279 °C (MeOH–ether); IR (KBr) 3331, 2916, 1520, 1260 cm^{-1}; MS (EI) m/z 387 (M^+); ^{1}H-NMR (DMSO-d_6) δ: 2.87—3.55 (4H, m), 3.74 (3H, s), 3.78 (3H, s), 5.85 (1H, s), 6.83 (1H, dd, J=7, 1 Hz), 7.04 (1H, d, J=7 Hz), 7.13 (1H, d, J=1 Hz), 7.25 (2H, m), 11.07 (1H, s).

1-(3,4-Dimethoxyphenyl)-6-chloro-1,2,3,4-tetrahydro-β-carboline (**4**): Yield 76%; mp 266—268 °C (AcOH); IR (KBr) 3225, 2911, 1522, 1267 cm^{-1}; MS (EI) m/z 342 (M^+); ^{1}H-NMR (DMSO-d_6) δ: 2.80—3.60 (4H, m), 3.75 (3H, s), 3.79 (3H, s), 5.85 (1H, s), 6.84 (1H, dd, J=7, 1 Hz), 7.03 (1H, d, J=7 Hz), 7.10 (1H, dd, J=7, 1 Hz), 7.18 (1H, d, J=1 Hz), 7.30 (1H, d, J=7 Hz), 7.60 (1H, d, J=1 Hz), 9.70 (1H, br s), 10.32 (1H, br s), 11.07 (1H, s).

1-(3,4-Dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline (5) A mixture of **1** (3.44 g, 10 mmol), MeI (1.41 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), and MeCN (30 ml) was stirred for 24 h at room temperature under an N_2 atmosphere. The reaction mixture was poured into H_2O, and extracted with AcOEt. The organic layer was washed with H_2O, dried and then concentrated. The residual oil was purified by silica gel column chromatography (Wako-gel C-200, eluent; hexane/AcOEt = 5/1) and recrystallized from hexane–AcOEt to give **5** as colorless crystals: 0.5 g (15%); IR (KBr) 3354, 1516, 1265, 1025 cm^{-1}; MS (EI) m/z 322 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.9—3.8 (4H, m), 3.77 (3H, s), 3.88 (3H, s), 4.46 (1H, br s), 6.8—7.3 (7H, m), 7.51 (1H, m).

Compounds **6**—**30** were synthesized in the same manner. Physical data are listed in Table 3.

Pharmacological Methods **Effect on Lipid Peroxidation** Brain mitochondria from male Wistar rats were incubated with aqueous H_3PO_4 and compounds **5**—**30** in DMSO (10 μM in final concentration) for 30 min at 37 °C. Malonaldehyde formed in the incubation mixture was measured by the thiobarbituric acid method according to Ohkawa *et al.*[8]

Effect on Potassium Cyanide Intoxication The effect on potassium cyanide intoxication was tested in male ICR strain mice. Histotoxic anoxia was produced by an intravenous injection of potassium cyanide (5 mg/kg). The time between the potassium cyanide injection and the last gasp was determined.

References and Notes

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