# 5-Aminocoumarans: Dual Inhibitors of Lipid Peroxidation and Dopamine Release with Protective Effects against Central Nervous System Trauma and Ischemia

Shigenori Ohkawa,* Kohji Fukatsu, Shokyo Miki, Tadatoshi Hashimoto, Junko Sakamoto, Takayuki Doi, Yasuo Nagai, and Tetsuya Aono†

*Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., 17-85 Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan*

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A series of 2,3-dihydro-5-benzofuranamines (5-aminocoumarans) were developed for the treatment of traumatic and ischemic central nervous system (CNS) injury. Compounds within this class were extremely effective inhibitors of lipid peroxidation *in vitro* and antagonized excitatory behavior coupled with peroxidative injury induced by spinal intrathecal injection of $FeCl_2$ (mouse-$FeCl_2$-it assay) *in vivo.* Selected compounds were tested for antagonistic activity on methamphetamine (MAP)-induced hypermotility resulting from dopamine release in the mouse brain. Among the compounds synthesized, compound **26n** (2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine) exhibited potent effects in these assays (inhibition of lipid peroxidation, $IC_{50} = 0.07$ $\mu$M; mouse-$FeCl_2$-it assay, $ID_{50} = 10.4$ mg/kg, po; MAP-induced hypermotility, 98% inhibition, 10 mg/kg, ip). The *S*-(+)-form of compound **26n** dihydrochloride (TAK-218), which has 30 times more potent antagonistic activity on MAP-induced hypermotility than the *R*-(−)-form, improved more significantly the survival rate in the cerebral ischemia model (rat, 1−3 mg/kg, ip) during the period of 1−14 days after ischemia and decreased functional disorders in the traumatic brain injury model (rat, 0.1−1 mg/kg, ip) 3−14 days after injury. These results imply a role for dopamine in deterioration of CNS function after ischemic and traumatic injury. TAK-218 is a promising compound for the treatment of stroke and CNS trauma and is now under clinical investigation.

Delayed biochemical changes play an important role in tissue damage resulting from central nervous system (CNS) trauma and ischemia.[1] Many possible secondary factors have been proposed to contribute to this damage including excitatory amino acids,[2] monoamines,[3] ions such as calcium[4] and sodium,[5] arachidonate metabolites,[6] and oxygen radicals.[7] Among these, the generation of oxygen radicals and subsequent lipid peroxidation have become the focus of attention for investigators in the field of CNS trauma and ischemia. Reactive oxygen radicals are commonly formed in normal cell metabolism. However, under normal conditions their production is localized and the body's natural defenses including antioxidative vitamins (A, C, and E), glutathione, superoxide dismutase (SOD), and catalase protect against the damage caused by oxygen radicals.[8] Under pathological conditions, these systems can be overwhelmed and the formation of oxygen radicals is enhanced.[9] Lipid peroxidation initiated by oxygen radicals results in membrane degradation and cell death. Pharmacological strategies have therefore aimed at inhibiting this degradative process. Several antioxidative compounds[10] including Tirilazad (**1**) are currently in clinical trials for CNS trauma and ischemia.

In addition to oxygen radicals, dopamine is released significantly after brain injury and ischemia. There are a number of possible mechanisms through which dopamine release could exacerbate the cell damage produced by cerebral ischemia and trauma.[3] The oxidation of dopamine by molecular oxygen results in the formation of superoxide anions.[11] The reaction between dopamine and hydroxy radical generates the neurotoxin 6-hydroxydopamine.[12] Experimental evidence suggests that decreases in brain dopamine levels protect brain tissues from ischemic damage.[13]

These factors, oxygen radicals and dopamine, are components of an interactive cascade leading to membrane damage and cell death. Consequently, compounds capable of regulating these factors would potentially be able to limit posttraumatic tissue damage and enhance neurological recovery.

Here, we report the synthesis and biological evaluation of 5-aminocoumarans. Compounds within this class have shown excellent antioxidative activities and antagonistic activity on methamphetamine (MAP)-induced hypermotility resulting from dopamine release in the CNS.

## Drug Design

Tocopherols (e.g., α-tocopherol, **2**) are known to be efficient inhibitors of lipid peroxidation *in vivo.* Compound **3** which has a coumaran (2,3-dihydrobenzofuran) structure was reported to be a more efficient antioxidant than compounds that have the chroman (tocopherol type) structure.[14] Since the oxygen lone pair in position 1 of the coumaran structure is perpendicular to the aromatic plane, the coumaranoxyl radical is more stabilized by conjugate delocalization.[15] On this basis, a number of coumaran type compounds were reported as antioxidants for clinical purposes.[16] However, generally these types of compounds are metabolically un-

* Corresponding author. Phone: 0-0118163006078. Fax: 0-011816-30-06306.
† Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd.
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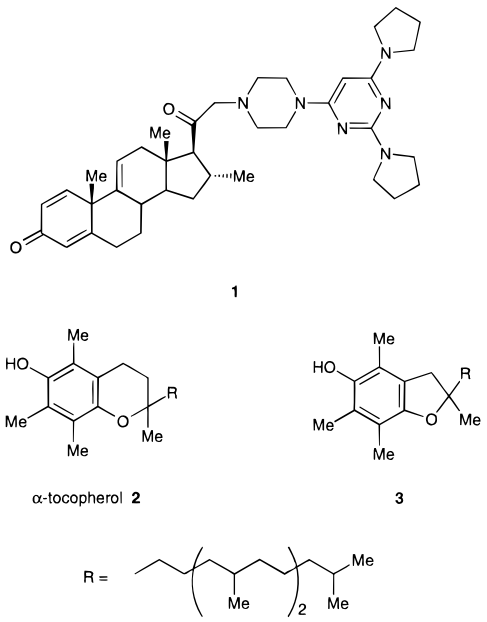
**Chart 1**




stable *in vivo* because of the ease of formation of *O*-glucuronide and *O*-sulfate on the phenolic hydroxy group.[17] To overcome this metabolic instability, we introduced an amino group instead of the hydroxy group in position 5 of coumaran. The amino group can donate an electron to a reactive radical similarly to the hydroxy group[18] but has the advantages of hydrophilicity and metabolical stability. Moreover, various substituents including a cyclic amino moiety were introduced into position 2 of 5-aminocoumaran to improve inhibition of dopamine release.

## Chemistry

The general synthetic pathways for preparation of 5-aminocoumarans listed in Table 1 are shown in Schemes 1−9. The parent compound, 2,3-dihydro-2,2,4,6,7-pentamethyl-5-benzofuranamine hydrochloride (**8a**), was synthesized as follows. The starting phenol **4a**[19] was methallylated using methallyl chloride and potassium carbonate as a base to give an ether (**5a**) (Scheme 1). Claisen rearrangement of **5a** provided *C*-methallylated compound **6a** in good yield. Cyclization of **6a** under acidic conditions gave coumaran **8a** with deprotection of the formamide group in quantitative yield. The demethyl derivatives of **8a** (**8b**−**e**) were synthesized from phenols **4b**−**e**[20] in a similar manner as for the synthesis of **8a**.

Compounds with an additional amino group in position 4 were synthesized as shown in Scheme 2. The coumaran **7d** was nitrated to give **9**. Hydrolysis of the acetamide group of **9** gave the 5-amino-4-nitro compound **10**, which was converted to diamine **11** by catalytic hydrogenation. The nitro group of **9** was reduced to afford an amino group by catalytic hydrogenation followed by methylation to give *N*,*N*-dimethylamino compound **13**. The hydrolysis of the acetamide group of **13** was accomplished by refluxing with hydrochloric acid and methanol.

Compounds with an aminomethyl group in position 7 were synthesized as shown in Scheme 3. Methallylphenol **16**, prepared from 3,5-dimethylphenol via **15**, was converted to (aminomethyl)phenols **17a,b** using the Mannich reaction. Acid-catalyzed cyclization followed by basic hydrolysis of acetamide groups provided 7-(aminomethyl)coumarans **19a,b**.

As shown in Scheme 4, compounds with a hydrophobic group on the benzene ring were synthesized from 2,2-dimethallylphenol **21**, which was obtained by *O*-methallylation of 2-methallylphenol **6b** followed by Claisen rearrangement of **20**. Cyclization of **21** under acidic conditions gave coumaran **22** with deprotection of the formamide group and double-bond isomerization. Compound **22** was converted to **23** by catalytic hydrogenation.

Compounds with a substituted methyl group in position 2 were synthesized using 2-methallylphenol **6a** as a starting material (Scheme 5). Cyclization of **6a** using bromine afforded 2-(bromomethyl)coumaran **24**. The arylthio or alkylthio group-substituted derivatives were obtained by condensation of **24** with various thiols in DMF at 100 °C, using NaH as a base. Subsequent acidic hydrolysis of the formamide group of **25a**−**j** gave 5-aminocoumarans **26a**−**j**. Since a series of 2-alkoxymethyl or aminomethyl derivatives was obtained in very low yields under the same conditions, condensation was carried out by heating in sealed tubes at 180 °C, with an excess of alcohols using NaH as a base, or an excess of amines in the absence of NaH. When the excess of nucleophilic reagents was used, the formamide group was deprotected concurrently to give 5-aminocoumarans **26k**−**w**. In the case of phenylpiperidine, the free base of the 5-amino compound **27**, prepared from **24** by acidic hydrolysis, was used to avoid the formation of *N*-formylated piperidine.

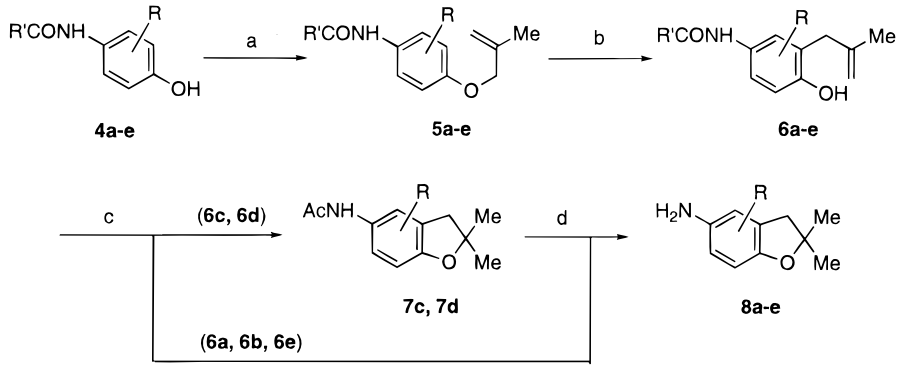
Oxidation of phenyl sulfide **25a** to sulfoxide or sulfone was carried out using sodium periodate in MeOH−water (scheme not shown). Sulfoxide **28** was prepared from **25a** at room temperature, and sulfone **29** was obtained under refluxing conditions. The acidic hydrolysis of formamide groups of both oxidized compounds (**28**, **29**) gave 5-aminocoumarans **30** and **31**. Sulfoxide **30** was obtained as a mixture of diastereoisomers.

As shown in Scheme 6, oxidation of 2-methallylphenol **6a** using *m*-chloroperbenzoic acid in the presence of aqueous $NaHCO_3$ afforded alcohol **32** via epoxide. Swern oxidation of **32** followed by Horner−Emmons olefination provided acrylate **34**, which was subsequently deprotected of the formamide group in MeOH to give the methyl ester **35**. Treatment of aldehyde **33** with benzylide gave *Z* olefin **36**. Subsequent catalytic hydrogenation of **36** gave phenethylcoumaran **37**, and this intermediate was then deprotected by acid hydrolysis.

2-(2-Aminoethyl)coumarans **46a,b** were synthesized as shown in Scheme 7. Bromide **40**, prepared from 2,3,5-trimethylphenol by a sequence of reactions similar to the synthesis of **24**, was converted to carboxylic acid **42** by cyanation followed by basic hydrolysis. Compound **42** was coupled with amines by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride to provide amides **43a,b**, which were subsequently reduced with $LiAlH_4$ to give amines **44a,b**. Nitration in position 5 of **44a,b** followed by catalytic hydrogenation of the introduced nitro group gave **46a,b**.

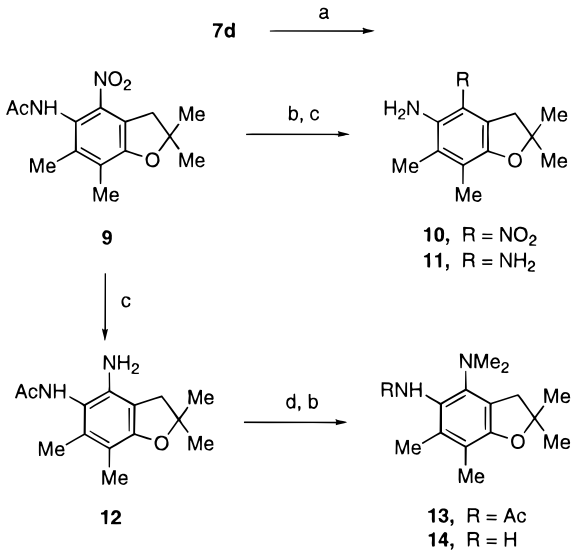
Synthesis of compounds with an aryl or alkyl group in position 3 was carried out as shown in Scheme 8. Lithiation of bromoanisole (**47**)[21] followed by addition

**Scheme 1**[a]



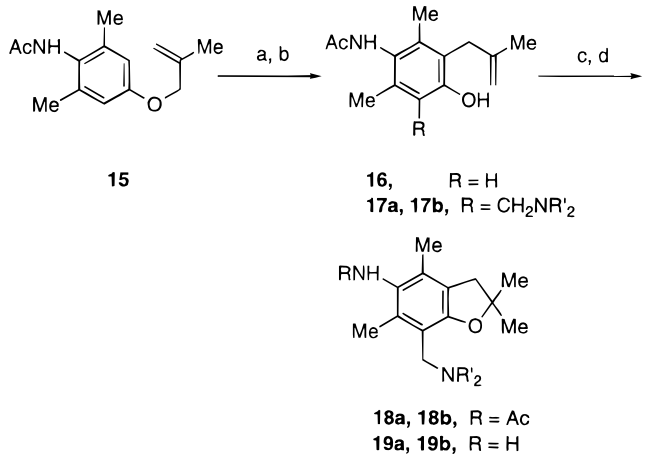

[a] (a) Methallyl chloride, $K_2CO_3$/DMF; (b) *N*,*N*-diethylaniline, 200 °C; (c) 35% aq HCl−MeOH (3:10, v/v); (d) 35% aq HCl−MeOH (1:1, v/v).

**Scheme 2**[a]




[a] (a) $HNO_3$, $Ac_2O$; (b) 35% aq HCl−MeOH (3:10, v/v); (c) $H_2$, Pd/C; (d) MeI, $K_2CO_3$.

**Scheme 3**[a]




[a] (a) *N*,*N*-Diethylaniline, 200 °C; (b) $(HCHO)_n$, $R_2NH$; (c) 35% aq HCl−MeOH (3:10, v/v); (d) NaOH/$H_2O$.

to isopropyl ketones afforded tertiary alcohols **48a**−**h** in good yields, except for addition to diisopropyl ketone (**48h**, 12%). Compounds **48a**−**h** were converted to coumarans **49a**−**h** by treatment with boiling hydrobromic acid via dehydration of the tertiary alcohol group, hydrolysis of the methyl ether group, and cyclization reaction. Nitration of **49a**−**h** with acetyl nitrate followed by catalytic hydrogenation gave 5-amino compounds **51a**−**h**.

5-(Alkylamino)coumarans were synthesized as follows (scheme not shown). The parent compound **8a** was acylated to give amides **52a**−**d**, and $LiAlH_4$ reduction of **52a**−**d** afforded *N*-alkylated compounds **53a**−**c**. Sulfamides **54a,b** were obtained by sulfonylation of **8a** using aryl- or alkylsulfonyl chlorides.

As shown in Scheme 9, 5-(arylamino)coumarans were synthesized utilizing Weingarten's method.[22] Quinone **55**[23] and aromatic amines were condensed using $TiCl_4$ as a dehydrating agent. The reaction proceeded perfectly regiospecifically in position 4. The quinonimines **56a**−**c** thus obtained were reduced using sodium hydrosulfite, and subsequent acid-catalyzed cyclization of aminophenols **57a**−**c** gave *N*-arylated aminocoumarans **58a**−**c**. When aminocoumaran **8e** was used as an aromatic amine, the compound isolated was aminophenol **57d** which was produced by reduction of quinonimine **56d**. In this event, aminocoumaran **8e** was supposed to work as a reducing agent. Compound **57d** was cyclized to give bis-coumaran **58d**. However, when we used aminocoumaran **8a** instead of aminocoumaran **8e**, quinone **55** was recovered as its hydroquinone form because of the high reducing activity of aminocoumaran **8a**.[24]

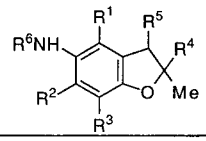
Optical resolution of **26n** with (*S*)-(+)- and (*R*)-(−)-mandelic acid afforded the two diastereomeric salts in high optical purities. The (+)-isomer of **26n** was shown to have the *S*-configuration by X-ray crystallographic analysis of (*S*)-(+)-mandelate.

## Pharmacological Results and Discussion

The compounds listed in Table 1 were initially tested for their antioxidant activities *in vitro* and *in vivo*, and selected compounds were evaluated for dopamine release inhibitory activity.

**Lipid Peroxidation Inhibition.** Inhibitory activities against lipid peroxidation were evaluated with homogenized rat liver microsomes. Lipid peroxidation was assessed by the formation of 2-thiobarbituric acid reactive products.[25] The compouds were tested at doses up to 1 $\mu$M, and $IC_{50}$ values are listed in Table 2. The important factors related to *in vitro* lipid peroxidation inhibitory activity were (1) lipophilicity of the compound, (2) electron density of the benzene ring of the coumaran structure, and (3) substitution manner of the amino group in position 5.

**Table 1.** Physical Properties of 5-Aminocoumarans



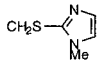
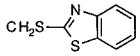
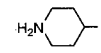
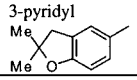
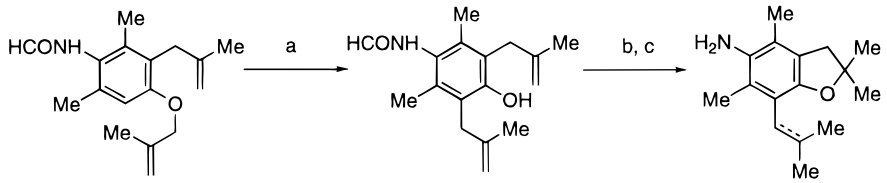

| no. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | % yield[a] | mp, °C | recrystn solvent | formula | analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **8a** | Me | Me | Me | Me | H | H | 99 | 248-250 | MeOH | $C_{13}H_{19}NO\cdot HCl$ | C, H, N |
| **8b** | Me | Me | H | Me | H | H | 43 | 215-217 | IPA[b] | $C_{12}H_{17}NO\cdot HCl$ | C, H, N |
| **8c** | Me | H | Me | Me | H | H | 95 | 216-218 | EtOH-$Et_2O$ | $C_{12}H_{17}NO\cdot HCl$ | C, H, N |
| **8d** | H | Me | Me | Me | H | H | 95 | 235-238 | EtOH | $C_{12}H_{17}NO\cdot HCl$ | C, H, N |
| **8e** | H | H | H | Me | H | H | 48 | 265-270 | EtOH-IPE[c] | $C_{10}H_{13}NO\cdot HCl$ | C, H, N |
| **10** | $NO_2$ | Me | Me | Me | H | H | 80 | 119-121 | EtOH-$Et_2O$ | $C_{12}H_{16}N_2O_3\cdot HCl$ | C, H, N |
| **11** | $NH_2$ | Me | Me | Me | H | H | 97 | 248-251 | EtOH | $C_{12}H_{18}N_2O\cdot HCl$ | C, H, N |
| **14** | $NMe_2$ | Me | Me | Me | H | H | 65 | 240-244 | EtOH | $C_{14}H_{22}N_2O\cdot 2HCl$ | C, H, N |
| **19a** | Me | Me | $CH_2NMe_2$ | Me | H | H | 42 | 178-180 | EtOH | $C_{15}H_{24}N_2O\cdot C_2H_2O_4$ | C, H, N |
| **19b** | Me | Me |  | Me | H | H | 56 | 110-112 | EtOH | $C_{18}H_{28}N_2O\cdot C_2H_2O_4$ | C, H, N |
| **22** | Me | Me | $CH{=}CMe_2$ | Me | H | H | 80 | 207-208 | EtOH | $C_{16}H_{23}NO\cdot HCl$ | C, H, N |
| **23** | Me | Me | $CH_2CHMe_2$ | Me | H | H | 96 | 223-225 | EtOH | $C_{16}H_{25}NO\cdot HCl$ | C, H, N |
| **26a** | Me | Me | Me | $CH_2SC_6H_5$ | H | H | 95 | 190-194 | EtOH-IPE | $C_{19}H_{23}NOS\cdot HCl$ | C, H, N |
| **26b** | Me | Me | Me | $CH_2S$-4-F-$C_6H_4$ | H | H | 81 | 205-210 | EtOH-IPE | $C_{19}H_{22}FNOS\cdot HCl$ | C, H, N |
| **26c** | Me | Me | Me | $CH_2S$-4-OH-$C_6H_4$ | H | H | 96 | 230-236 | EtOH-IPE | $C_{19}H_{23}NO_2S\cdot HCl$ | C, H, N |
| **26d** | Me | Me | Me | $CH_2S$-4-pyridyl | H | H | 80 | 96-97 | EtOAc-IPE | $C_{18}H_{22}N_2OS$ | C, H, N |
| **26e** | Me | Me | Me |  | H | H | 65 | 204-208 | EtOH-IPE | $C_{17}H_{23}N_3OS\cdot 2HCl$ | C, H, N[d] |
| **26f** | Me | Me | Me |  | H | H | 89 | 220-225 | EtOH-IPE | $C_{20}H_{22}N_2OS_2\cdot HCl$ | C, H, N |
| **26g** | Me | Me | Me | $CH_2SCH_2C_6H_5$ | H | H | 74 | 170-172 | EtOH-IPE | $C_{20}H_{25}NOS\cdot HCl$ | C, H, N |
| **26h** | Me | Me | Me | $CH_2SPr$ | H | H | 75 | 186-188 | EtOH-IPE | $C_{16}H_{25}NOS\cdot HCl$ | C, H, N |
| **26i** | Me | Me | Me | $CH_2S(CH_2)_2OH$ | H | H | 32 | 108-109 | EtOAc-IPE | $C_{15}H_{23}NO_2S$ | C, H, N |
| **26j** | Me | Me | Me | $CH_2S(CH_2)_2COOH$ | H | H | 79 | 139-140 | EtOAc-IPE | $C_{16}H_{23}NO_3S$ | C, H, N |
| **26k** | Me | Me | Me | $CH_2OCH_2C_6H_5$ | H | H | 37 | 195-200 | EtOH-IPE | $C_{20}H_{25}NO_2\cdot HCl$ | C, H, N[e] |
| **26l** | Me | Me | Me | $CH_2OMe$ | H | H | 50 | 180-182 | EtOH-IPE | $C_{13}H_{19}NO_2\cdot HCl$ | C, H, N[f] |
| **26m** | Me | Me | Me |  | H | H | 82 | 60-61 | IPE | $C_{18}H_{28}N_2O$ | C, H, N |
| **26n** | Me | Me | Me |  | H | H | 82 | 142-144 | $CHCl_3$-IPE | $C_{24}H_{32}N_2O$ | C, H, N |
| (*S*)-(+)-**26n**[g] | | | | | | | 36 | 206 | MeOH-EtOAc | $C_{24}H_{32}N_2O\cdot 2HCl$ | C, H, N |
| (*R*)-(−)-**26n**[g] | | | | | | | 37 | 206 | MeOH-EtOAc | $C_{24}H_{32}N_2O\cdot 2HCl$ | C, H, N |
| **26o** | Me | Me | Me |  | H | H | 81 | 114-115 | IPE | $C_{17}H_{26}N_2O_2$ | C, H, N |
| **26p** | Me | Me | Me |  | H | H | 76 | 76-77 | IPE | $C_{18}H_{29}N_3O$ | C, H, N |
| **26q** | Me | Me | Me |  | H | H | 75 | 94-95 | IPE | $C_{23}H_{31}N_3O$ | C, H, N |
| **26r** | Me | Me | Me |  | H | H | 34 | 193-196 | EtOH-$Et_2O$ | $C_{30}H_{37}N_3O\cdot 3HCl$ | C, H, N[h] |
| **26s** | Me | Me | Me | $CH_2NHC_6H_5$ | H | H | 36 | 162-168 | EtOH-$Et_2O$ | $C_{19}H_{24}N_2O\cdot 2HCl$ | C, H, N |
| **26t** | Me | Me | Me | $CH_2NHCH_2C_6H_5$ | H | H | 65 | 228-232 | EtOH-$Et_2O$ | $C_{20}H_{26}N_2O\cdot 2HCl$ | C, H, N |
| **26u** | Me | Me | Me | $CH_2NH(CH_2)_2C_6H_5$ | H | H | 63 | 178-181 | EtOH | $C_{21}H_{28}N_2O\cdot 2HCl$ | C, H, N[i] |
| **26v** | Me | Me | Me | $CH_2NH(CH_2)_4C_6H_5$ | H | H | 73 | 201-202 | EtOH-$Et_2O$ | $C_{23}H_{32}N_2O\cdot 2HCl$ | C, H, N |
| **26w** | Me | Me | Me | $CH_2$-1-imidazolyl | H | H | 33 | 278-283 | EtOH-IPE | $C_{16}H_{21}N_3O\cdot 2HCl$ | C, H, N[j] |
| **27** | Me | Me | Me | $CH_2Br$ | H | H | 90 | 235-245 | EtOH-IPE | $C_{13}H_{18}BrNO\cdot HCl$ | C, H, N |
| **31** | Me | Me | Me | $CH_2SO_2C_6H_5$ | H | H | 92 | 150-151 | EtOAc-IPE | $C_{19}H_{23}NO_3S$ | C, H, N |
| **35** | Me | Me | Me | CH=CHCOOMe (*E*) | H | H | 75 | 225-234 | EtOH-IPE | $C_{16}H_{21}NO_3\cdot HCl$ | C, H, N |
| **38** | Me | Me | Me | $(CH_2)_2C_6H_4$-4-F | H | H | 85 | 62-63 | EtOAc-IPE | $C_{20}H_{24}FNO$ | C, H, N |
| **46a** | Me | Me | Me | $(CH_2)_2NMe_2$ | H | H | 59 | 200-203 | EtOH-IPE | $C_{16}H_{26}N_2O\cdot 2HCl$ | C, H, N[k] |

**Table 1** (Continued)

| no. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | % yield[a] | mp, °C | recrystn solvent | formula | analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **46b** | Me | Me | Me | $(CH_2)_2N$  | H | H | 48 | 260-270 | EtOH-IPE | $C_{19}H_{30}N_2O\cdot 2HCl$ | C, H, N |
| **51a** | Me | Me | Me | Me | $C_6H_5$ | H | 74 | 131-132 | hexane | $C_{19}H_{23}NO$ | C, H, N |
| **51b** | Me | Me | Me | Me | $C_6H_4$-4-Me | H | 54 | 119-120 | hexane | $C_{20}H_{25}NO$ | C, H, N |
| **51c** | Me | Me | Me | Me | $C_6H_4$-4-Pr | H | 66 | 68-69 | MeOH | $C_{22}H_{29}NO$ | C, H, N |
| **51d** | Me | Me | Me | Me | $C_6H_4$-4-pentyl | H | 56 | 67-68 | MeOH | $C_{24}H_{33}NO$ | C, H, N |
| **51e** | Me | Me | Me | Me | $C_6H_4$-4-$^i$Pr | H | 85 | 134-135 | hexane | $C_{22}H_{29}NO$ | C, H, N |
| **51f** | Me | Me | Me | Me | $C_6H_4$-4-F | H | 70 | 126-127 | hexane | $C_{19}H_{22}FNO$ | C, H, N |
| **51g** | Me | Me | Me | Me | 3-pyridyl | H | 54 | 130-131 | IPE | $C_{18}H_{22}N_2O$ | C, H, N |
| **51h** | Me | Me | Me | Me | $^i$Pr | H | 77 | 225-230 | EtOH | $C_{16}H_{26}NO\cdot HCl$ | C, H, N |
| **52a** | Me | Me | Me | Me | H | HCO | 93 | 177-179 | $CH_2Cl_2$-IPE | $C_{14}H_{19}NO_2$ | C, H, N |
| **52b** | Me | Me | Me | Me | H | Ac | 76 | 190-191 | $CH_2Cl_2$-IPE | $C_{15}H_{21}NO_2$ | C, H, N |
| **52c** | Me | Me | Me | Me | H | EtCO | 99 | 146-147 | $CH_2Cl_2$-IPE | $C_{16}H_{23}NO_2$ | C, H, N |
| **52d** | Me | Me | Me | Me | H | EtOCO | 75 | 102-104 | IPE-PE | $C_{16}H_{23}NO_3$ | C, H, N |
| **53a** | Me | Me | Me | Me | H | Me | 41 | 205-206 | EtOH | $C_{14}H_{21}NO\cdot HCl$ | C, H, N |
| **53b** | Me | Me | Me | Me | H | Et | 72 | 205-209 | EtOH-IPE | $C_{15}H_{23}NO\cdot HCl$ | C, H, N |
| **53c** | Me | Me | Me | Me | H | Pr | 43 | 185-187 | EtOH-$Et_2O$ | $C_{16}H_{25}NO\cdot HCl$ | C, H, N |
| **54a** | Me | Me | Me | Me | H | $MeSO_2$ | 66 | 159-160 | $CH_2Cl_2$-IPE | $C_{14}H_{21}NO_3S$ | C, H, N |
| **54b** | Me | Me | Me | Me | H | 4-$MeC_6H_4SO_2$ | 69 | 219-220 | $CH_2Cl_2$-IPE | $C_{20}H_{25}NO_3S$ | C, H, N |
| **58a** | Me | Me | Me | Me | H | $C_6H_5$ | 69 | 148-151 | IPE | $C_{19}H_{23}NO$ | C, H, N |
| **58b** | Me | Me | Me | Me | H | 4-$ClC_6H_4$ | 60 | 106-107 | IPE-pentane | $C_{19}H_{22}ClNO$ | C, H, N |
| **58c** | Me | Me | Me | Me | H | 3-pyridyl | 81 | 187-188 | $CH_2Cl_2$-IPE | $C_{18}H_{22}N_2O$ | C, H, N[l] |
| **58d** | Me | Me | Me | Me | H |  | 61 | 147-148 | pentane | $C_{23}H_{29}NO_2$ | C, H, N |

[a] No attempt was made to optimize yields. Numbers represent the yield for the last step. [b] IPA = 2-propanol. [c] IPE = isopropyl ether. [d] (+0.5$H_2O$) Calcd: C, 51.13; H, 6.56; N, 10.52. Found: C, 51.11; H, 6.49; N, 10.59. [e] (+0.5$H_2O$) Calcd: C, 67.31; H, 7.63; N, 3.93. Found: C, 67.34; H, 7.67; N, 4.19. [f] Calcd: C, 60.58; H, 7.82; N, 5.43. Found: C, 61.83; H, 8.25; N, 5.05. Without further purification. [g] Dihydrochloride. [h] (+0.5$H_2O$) Calcd: C, 62.77; H, 7.20; N, 7.32. Found: C, 62.89; H, 7.59; N, 7.64. [i] (+$H_2O$) Calcd: C, 60.72; H, 7.76; N, 6.74. Found: C, 60.57; H, 7.50; N, 6.79. [j] (+0.5$H_2O$) Calcd: C, 54.40; H, 6.85; N, 11.89. Found: C, 54.61; H, 6.70; N, 11.87. [k] (+$H_2O$) Calcd: C, 54.39; H, 8.56; N, 7.93. Found: C, 54.41; H, 8.53; N, 7.92. [l] Calcd: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.12; H, 7.96; N, 9.74. Without further purification.

**Scheme 4**[a]



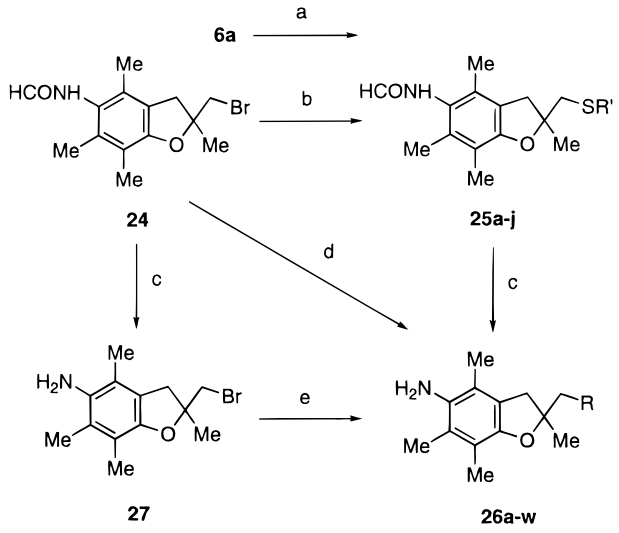

**20** **21** **22**, C≡C = C=C **23**, C≡C = CH−CH

[a] (a) *N*,*N*-Diethylaniline, 200 °C; (b) 35% aq HCl−MeOH (1:1, v/v); (c) $H_2$, Pd/C.

Substitution on the coumaran ring in positions 2, 3, 4, 6, and 7 by lipophilic groups such as methyl (compound **8a**), isobutyl (compound **23**), aryl (compounds **51a**−**f**),[26] and aralkyl (compound **38**) resulted in an increase in the activity. In a series of compounds which has a heteroatom as a linker in position 2, no significant differences were observed with regard to the kind of heteroatom (compare **26g,k,t**). However, it is noteworthy that phenylpiperidinyl (compound **26n**), phenylpiperazinyl (compound **26q**), and (diphenylmethyl)piperazinyl (compound **26r**) groups greatly enhanced the activity. In contrast, introduction of hydrophilic groups such as nitro (compound **10**), (dimethylamino)methyl (compound **19a**), ester (compound **35**), heteroring (compounds **26e,w** and **51g**), alcohol (**26i**), and carboxylic acid (compound **26j**) groups attenuated the activity. Previously, we reported the linear dependence of lipid peroxidation inhibition on the lipophilicity of the molecule for (pyridylmethyl)quinones.[27]

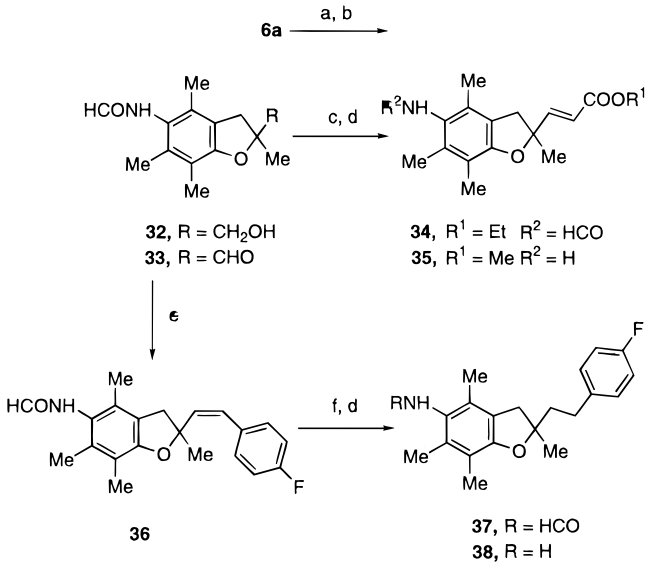
The 5-coumaranoxyl radical formed in the reaction with oxygen radicals has been reported to be stabilized by delocalization of the unpaired electron to the p-type lone pair of oxygen in position 1 and $\pi$-electron of the benzene ring.[15] The same effect is expected in the case of 5-coumaranaminyl radical. Therefore, electron-donating substituents such as amino and methyl groups[28] enhanced the activity due to stabilization of the aminyl radical to exhibit good lipid peroxidation inhibition (compounds **8a** and **11**). To enhance this stabilizing effect, we designed 5-(arylamino)coumarans. With the

**Scheme 5**[a]




[a] (a) $Br_2$, AcONa/AcOH; (b) R′SH, NaH/DMF, 100 °C; (c) 35% aq HCl−MeOH (1:1, v/v); (d) R′OH, NaH, or R′R″NH (10 equiv) in sealed tube, 180 °C; (e) R′R″NH (1.2 equiv), $Et_3N$ in sealed tube, 180 °C.

**Scheme 6**[a]



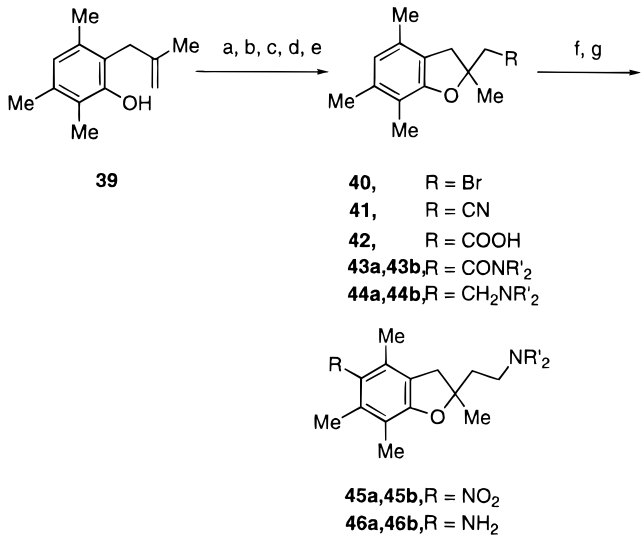

[a] (a) *m*-CPBA, $NaHCO_3/CH_2Cl_2$, $H_2O$; (b) DMSO, $(COCl)_2/CH_2Cl_2$; (c) $(EtO)_2P(O)CH_2COOEt$, NaH/THF; (d) 35% aq HCl−MeOH (1:1, v/v); (e) $Ph_3PCH_2Ar(Br)$, NaH/THF; (f) $H_2$, Pd/C.

exception of **51g** which has a polar pyridyl group, enhancement of the activity was observed with these compounds. As expected, bis-coumaran derivative **58d**, in which two coumaran structures are able to contribute to stabilization of the aminyl radical, was revealed to be the most potent in this series.

Introduction of an alkyl group decreased activity most likely by steric hindrance around the nitrogen atom in position 5. Introduction of an acyl group diminished activity by decreasing electron density on the nitrogen atom in position 5.

**Mouse-$FeCl_2$-it Assay (*in Vivo*).** It is known that the intracortical injection of $FeCl_2$ causes acute focal epileptiform discharges and formation of brain edema along with lipid peroxidation, and these symptoms are reduced by administration of α-tocopherol.[29] Iron added into cerebral cortex causes formation of active oxygen species (e.g., superoxide, hydroxyl radical) via iron-dependent Haber−Weiss reaction. These highly reactive oxidants injure the nerve cell membrane by peroxidation of unsaturated fatty acids, and thus membrane excitation increases as a result of the increase in membrane permeability and brain edema is caused by cell death. Following spinal intrathecal injection of $FeCl_2$, it is assumed from behavioral changes that the increase in membrane permeability caused the excitation of both the sensory and the motor nervous systems in the spinal cord and that excessive degradation of membrane structures caused the necrosis resulting in the paralysis. Since only the compounds which have high antioxidative activity and exhibit good permeability across the blood−brain barrier (BBB) suppress these phenomena, the mouse-$FeCl_2$-it assay is a versatile and sophisticated technique for screening of antioxidative agents for use in the CNS. The compounds tested were orally administered 30 min before $FeCl_2$ injection. $ID_{50}$ values were obtained by the score of behavioral responses evaluated from 15 min to 1 h after $FeCl_2$ injection.

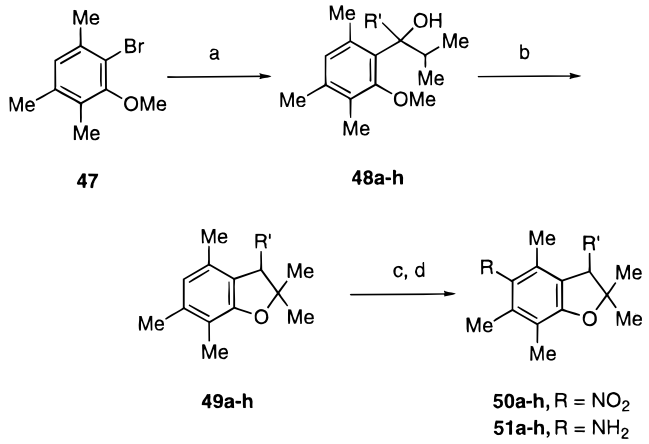
**Scheme 7**[a]




[a] (a) $Br_2$, AcONa/AcOH; (b) NaCN/DMSO; (c) $NaOH/H_2O$; (d) $R'_2NH$, WSC, HOBt/DMF; (e) $LiAlH_4$/THF; (f) $HNO_3$, $Ac_2O$; (g) $H_2$, Pd/C.

The results of the mouse-$FeCl_2$-it assay are also shown in Table 2. In a previous experiment, aminopyrine which has antioxidative activity[30] exhibited inhibitory activity, and its $ID_{50}$ value was determined as 108.0 mg/kg, po (95% confidence limits; 71.1−139.2). α-Tocopherol did not show any significant activity at a dose of 100 mg/kg; however, the 5-hydroxycoumaran type compound showed weak inhibitory activity (23% inhibition at a dose of 100 mg/kg). The parent aminocoumaran **8a** had potent *in vivo* antioxidative activity with an $ID_{50}$ value of 7.8 mg/kg. Inhibitory activity decreased in relation to the decrease in the number of methyl groups. This result is in accordance with *in vitro* assay data. Methyl groups were the best substituents for *in vivo* activity among the substituents introduced in positions 4, 6, and 7 on the benzene ring of the coumaran structure. Introduction of aryl or alkyl substituents in position 3 decreased the activity. Among the compounds that have a heteromethyl group at the 2 position, polar moieties such as hydroxy group and carboxyl group reduced the activity (**26i,j**). Nitrogen

**Scheme 8**[a]




[a] (a) *n*-BuLi/THF, then R′$COMe_2$; (b) HBr/$H_2O$; (c) $HNO_3$, $Ac_2O$; (d) $H_2$, Pd/C.

was the most efficacious linker in position 2. Both optical isomers of **26n** showed almost equivalent inhibitory activity. Bulky substituents reduced *in vivo* activity (**26r** and **58d**). The reason for this might be increased molecular weight because it is known that the BBB permeability is related to lipophilicity of molecules and molecular weight.[31] The alkyl substituents on the amino group in position 5 decreased the *in vitro* activity markedly; however, *in vivo* activity was less attenuated. In contrast, the aryl-substituted compounds **58a,b,d** showed no significant activity in the *in vivo* assay despite their potent activity *in vitro*. Acylation of the amino group diminished both *in vivo* and *in vitro* activity.

**Suppression of MAP-Induced Hypermotility in Mice.**[32] Selected compounds were evaluated for antagonizing hypermotility induced by MAP, a dopamine releaser in mice. Thirty minutes after ip treatment with compounds at a dose of 10 mg/kg, MAP was given ip to male mice at a dose of 1 mg/kg. The results of this assay are shown in Table 3. Basic molecules **8a** and **27** exhibited significant effects against MAP-induced hypermotility. Except in these compounds, a phenyl group adjacent to the methyl group in position 2 at a distance seemed to be indispensable (compare compounds **26m,o,p** with compounds **26n,q,r**). Among these compounds, **26n** which has a phenylpiperidinyl group in position 2 was found to be most effective. To investigate the activities of both optical isomers, **26n** was resolved using (*S*)-(+)-mandelic acid. Both isomers inhibited lipid peroxidation *in vitro* and antagonized excitatory behavior induced by intrathecal injection of $FeCl_2$ to the same extent. However, the *S*-isomer (TAK-218) exhibited a 30-fold more potent antagonistic activity on MAP-induced hypermotility than the *R*-isomer as shown in Table 4. In addition, to clarify whether this effect of TAK-218 was due to inhibition of dopamine release or blockade of dopamine receptors, the effects of TAK-218 on apomorphine (APO)-induced hypermotility were also studied. As shown in Table 4, APO (1 mg/kg, sc)-induced hypermotility was not suppressed by TAK-218 at a dose of 1 mg/kg, ip, suggesting that TAK-218 suppresses aberrant dopamine release. To investigate the role of dopamine in ischemic and traumatic brain injury, we tested both isomers in the transient cerebral ischemia model and penetration-induced head injury model in rats.

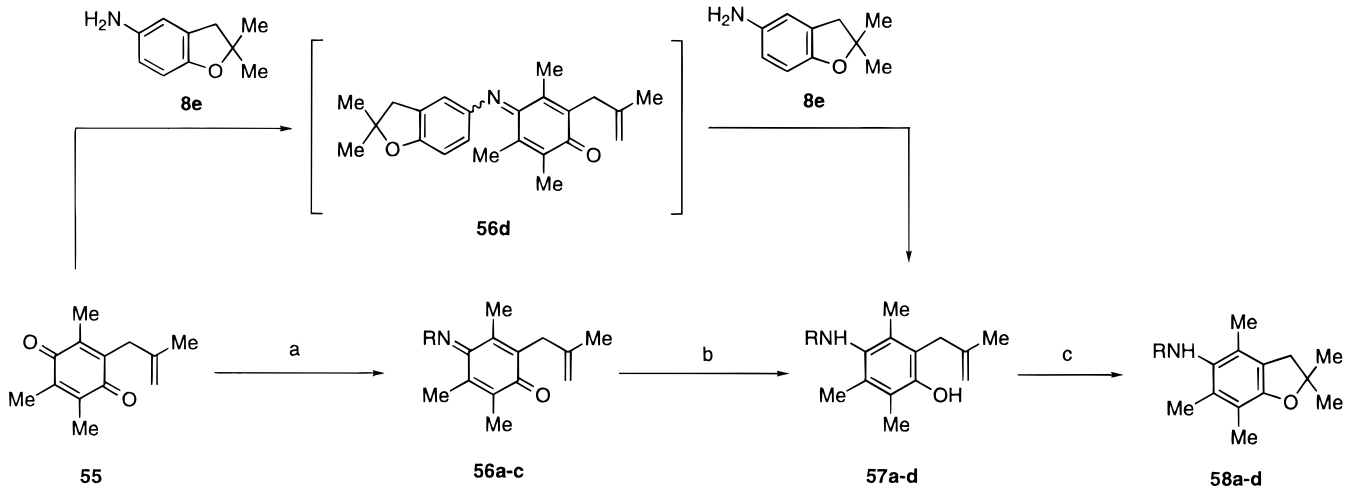
**Effects of TAK-218 and Its Optical Isomer on Mortality after Transient Cerebral Ischemia (Four Vessel Occlusion) Model in Rats.**[33] Transient global ischemia was produced by 45 min occlusion of bilateral common carotid arteries in male rats in which vertebral arteries were cauterized bilaterally on the previous day. TAK-218 and its optical isomer were given ip immediately and then 2 and 24 h after reopening the circulation at doses of 1 and 3 mg/kg. Survival of the animals was monitored for 1, 3, 5, 7, 10, and 14 days after reopening the circulation. As shown in Figure 1, both TAK-218 and its *R*-isomer reduced the mortality; the effect of TAK-218 was more prominent than that of the *R*-isomer from day 1 to day 7 postischemia.

**Effects of TAK-218 and Its Optical Isomer on the Functional Deficit after Penetration-Induced Brain Injury in Rats.** Male Wistar rats were used. Under halothane anesthesia, the striatum was injured by stereotactically inserting a glass rod, 1.5 mm in diameter with a tapered tip, through a burr hole from the cortex to striatum. TAK-218 and its *R*-isomer were given ip immediately and 2 h after injury. Functional changes were evaluated 3, 7, and 14 days after injury utilizing APO-induced circling which has been reported to be specific to animals with damage in the nigrostriatal system. As shown in Figure 2, TAK-218 dose-dependently decreased the functional deficit, and the minimum effective dose was 0.1 mg/kg. Although the *R*-isomer significantly decreased functional deficit at a dose of 1 mg/kg on day 14 postinjury, it did not exhibit any significant effect at doses ranging from 0.03 to 0.3 mg/kg during the observation period.

As described above, TAK-218 decreased the functional deficit in the brain injury model and mortality in the cerebral ischemia model, and the effect of TAK-218 was more potent than that of the *R*-isomer. Since the antioxidant activities of both isomers were equipotent, the inhibitory activity of TAK-218 on aberrant dopamine release appeared to contribute to the protective effects in the cerebral ischemia model and the brain injury model. In other words, dopamine plays an important role in deterioration of CNS function after ischemic and traumatic injury in dopamine-rich regions such as the striatum and nucleus of accubens. In the mouse-$FeCl_2$-it assay, both isomers antagonized excitatory behavior to the same extent because the dopamine content in the spinal cord is very low and only the antioxidative activities of the compounds contribute to the protective effect.

In conclusion, we reported here the discovery of 5-aminocoumarans which have highly potent inhibitory activities on both lipid peroxidation and dopamine release. The selected compound TAK-218 was effective upon systemic administration in *in vivo* models of CNS trauma and ischemia. The *R*-isomer of TAK-218, which has the same level of antioxidative activity and less inhibitory effect on dopamine release, was also effective in *in vivo* models; however, its potency was less than that of TAK-218. This provides evidence for an important role of dopamine as well as lipid peroxidation in traumatic and ischemic brain damage. Pharmacological studies of TAK-218 are currently in progress in our laboratory and will be reported in due course.

**Scheme 9**[a]




[a] (a) $TiCl_4$, $RNH_2$; (b) $Na_2S_2O_4$; (c) 35% aq HCl−MeOH (3:10, v/v).

## Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer, with tetramethylsilane as the internal standard. Optical rotations were determined with a JASCO DIP-370 polarimeter. TLC analyses were carried out on Merck Kieselgel 60 $F_{254}$ plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within ±0.4% of the theoretical values unless otherwise noted. THF and isopropyl ether (IPE) were distilled over calcium hydride prior to use, and other solvents and reagents were used without purification. Solutions in organic solvents were dried over anhydrous magnesium sulfate unless otherwise noted, and concentration of the organic solution was carried out under reduced pressure. Chromatographic purification was carried out on silica gel columns (Kieselgel 60, 0.063−0.200 mm, Merck). Yields were not maximized.

**General Procedure for *O*-Methallylation of Phenols. *N*-[2,3,6-Trimethyl-4-[(2-methyl-2-propenyl)oxy]phenyl]formamide (5a).** To a solution of *N*-(4-hydroxy-2,3,6-trimethylphenyl)formamide[19] (86 g, 0.48 mol) and methallyl chloride (45 g, 0.50 mol) in DMF (300 mL) was added $K_2CO_3$ (74 g, 0.54 mol), and the mixture was stirred under an argon atmosphere at 80 °C for 3 h. The reaction mixture was poured into ice−water, and the resulting solid was washed with water and dried. The crude solid was recrystallized from IPE to yield 80 g (72% yield) of **5a**: mp 144−145 °C; NMR ($CDCl_3$) $\delta$ 1.84 (3H, m), 2.17 (3H, s), 2.19 (1.5H, s), 2.22 (3H, s), 2.26 (1.5H, s), 4.40 (1H, s), 4.42 (1H, s), 4.99 (1H, m), 5.11 (1H, br s), 6.60 (1H, s), 6.75 (1H, m), 7.98 (0.5H, d, $J$ = 12.0 Hz), 8.41 (0.5H, s).

With a similar procedure, **5b**−**e**, **15**, and **20** were prepared.

**General Procedure for Claisen Rearrangement. *N*-[4-Hydroxy-2,3,6-trimethyl-5-(2-methyl-2-propenyl)phenyl]formamide (6a).** A solution of **5a** (80 g, 0.34 mol) in *N*,*N*-diethylaniline (500 mL) was stirred under an argon atmosphere at 200 °C for 3 h. After the reaction mixture had cooled, hexane was added and the resulting solid was collected by filtration, washed with hexane, and dried under reduced pressure. The crude product was recrystallized from EtOAc−IPE to yield 75 g (94% yield) of **6a**: mp 163−164 °C; NMR ($CDCl_3$) $\delta$ 1.80 (3H, s), 2.16 (3H, s), 2.17 (1.5H, s), 2.19 (1.5H, s), 2.20 (1.5H, s), 2.21 (1.5H, s), 3.38 (2H, br s), 4.65 (1H, m), 4.88 (1H, m), 5.16 (0.5H, s), 5.19 (0.5H, s), 6.70 (1H, m), 7.95 (0.5H, d, $J$ = 12.0 Hz), 8.42 (0.5H, d, $J$ = 1.8 Hz).

With a similar procedure, **6b**−**e**, **16**, **21**, and **39** were prepared.

**General Procedure for Acid-Catalyzed Cyclization of 2-Methallylphenols. 2,3-Dihydro-2,2,4,6,7-pentamethyl-5-benzofuranamine Hydrochloride (8a).** To a solution of **6a** (7.3 g, 36 mmol) in MeOH (100 mL) was added 35% aqueous HCl (30 mL) with ice−water bath cooling, and the mixture was refluxed under an argon atmosphere for 2 h. After cooling, the reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated (6.4 g, 99% yield). A portion of the residue was treated with 4 M HCl/EtOH followed by recrystallization of the crude product from MeOH to give **8a**: mp 248−250 °C dec; NMR (DMSO-$d_6$) $\delta$ 1.41 (6H, s), 2.02 (3H, s), 2.20 (6H, s), 3.41 (2H, m), 9.65 (2H, br s).

With a similar procedure, **7c,d**, **8b,e**, **18a,b**, **22**, and **58a**−**d** were prepared.

**General Procedure for Hydrolysis of Acetamide or Formamide Groups under Acidic Conditions. 2,3-Dihydro-2,2,4,7-tetramethyl-5-benzofuranamine Hydrochloride (8c).** To a solution of **7c** (1.0 g, 4.3 mmol) in MeOH (15 mL) was added 35% aqueous HCl (15 mL) with ice−water bath cooling. The mixture was refluxed under an argon atmosphere for 2 h. After cooling, the reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine and dried, and the solvent was removed. The residue was treated with 4 M HCl/EtOH (1.5 mL), and the HCl salt was recrystallized from EtOH−$Et_2O$ to give 0.93 g (yield 95%) of **8c**: mp 216−218 °C; NMR (DMSO-$d_6$) $\delta$ 1.47 (6H, s), 2.13 (3H, s), 2.38 (3H, s), 2.93 (2H, s), 7.18 (1H, s), 10.21 (2H, br s). Anal. C, H, N.

With a similar procedure, **8d**, **10**, **14**, **26a**−**j**, **27**, **30**, **31**, **35**, and **38** were prepared.

**General Procedure for Nitration. *N*-(2,3-Dihydro-2,2,6,7-tetramethyl-4-nitro-5-benzofuranyl)acetamide (9).** To a solution of **7d** (15 g, 64 mmol) in acetic anhydride−acetic acid (150 mL; 1:1) was added dropwise a solution of acetyl nitrate (prepared from 69% nitric acid (7.7 mL) and acetic anhydride (25 mL)) with ice−water bath cooling. The mixture was stirred under the same conditions for 15 min and then poured into ice−water. The aqueous mixture was extracted with EtOAc, and the extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$) followed by recrystallization from $CH_2Cl_2$−IPE to afford 16 g (89% yield) of **9**: mp 203−204 °C; NMR ($CDCl_3$) $\delta$ 1.48 (6H, s), 2.15 (3H, s), 2.18 (3H, s), 2.19 (3H, s), 3.29 (2H, s), 7.79 (1H, br s).

With a similar procedure, **45a,b** and **50a**−**h** were prepared.

**General Procedure for Reduction of the Nitro Group. 2,3-Dihydro-2,2,6,7-tetramethyl-4,5-benzofurandiamine Hydrochloride (11).** A mixture of **10** (4.9 g, 21 mmol) and 10% Pd/C (1.4 g; 50% wet) in EtOH (100 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography ($CHCl_3$) to afford 4.2 g (97% yield) of **11** (free base). A portion of the free base obtained was treated with 4 M HCl/EtOH, and the salt was recrystallized from EtOH to give **11**:

**Table 2.** Effects of 5-Aminocoumarans on Lipid Peroxidation and Mouse-$FeCl_2$-it Assay

| no. | lipid peroxidation[a] $IC_{50}(\mu M)$ | mouse-$FeCl_2$-it assay[b] $ID_{50}$ (mg/kg, po) | 95% confid limits |
|---|---|---|---|
| **8a** | 0.76 | 7.8 | 6.2−10.5 |
| **8b** | (14) | 16.3 | 10.9−23.6 |
| **8c** | (19) | 32.3 | 20.6−42.7 |
| **8d** | (26) | 24.4 | 17.2−33.9 |
| **8e** | (5) | >100 | |
| **10** | (0) | >100 | |
| **11** | 0.30 | >50 | |
| **14** | 0.55 | 22.3 | 18.3−26.6 |
| **19a** | (4) | >50 | |
| **19b** | (3) | >50 | |
| **22** | 0.30 | 21.9 | 16.0−28.0 |
| **23** | 0.14 | 13.3 | 7.5−19.6 |
| **26a** | 0.27 | 24.7 | 20.0−30.3 |
| **26b** | 0.22 | 17.9 | 12.6−22.5 |
| **26c** | 0.22 | >50 | |
| **26d** | 0.63 | 19.9 | 14.1−25.3 |
| **26e** | (11) | 37.1 | 32.0−44.0 |
| **26f** | 0.07 | 33.7 | 30.7−36.7 |
| **26g** | 0.26 | 32.0 | 9.1−49.0 |
| **26h** | 0.28 | 24.6 | 18.7−31.9 |
| **26i** | (11) | >50 | |
| **26j** | (0) | 43.0 | 34.4−70.8 |
| **26k** | 0.28 | 18.6 | 10.4−25.5 |
| **26l** | 0.30 | 20.1 | 5.9−33.2 |
| **26m** | (18) | 11.7 | 9.0−14.8 |
| **26n** | 0.07 | 10.4 | 7.2−13.6 |
| (*S*)-(+)-**26n**[c] | NT[d] | 10.8 | 8.2−13.4 |
| (*R*)-(−)-**26n**[c] | NT | 11.6 | 7.5−16.7 |
| **26o** | 0.41 | 19.2 | 11.8−25.8 |
| **26p** | (10) | 25.3 | 19.9−32.4 |
| **26q** | 0.07 | 13.1 | 9.8−18.1 |
| **26r** | 0.07 | >50 | |
| **26s** | 0.26 | 15.7 | 11.9−19.2 |
| **26t** | 0.29 | 9.1 | 5.4−18.8 |
| **26u** | 0.29 | 14.2 | 8.0−18.8 |
| **26v** | 0.08 | 17.0 | 11.5−21.6 |
| **26w** | (6) | 25.0 | 18.0−34.5 |
| **27** | 0.30 | 16.0 | 12.2−20.6 |
| **30** | 0.66 | 31.3 | 19.1−40.6 |
| **31** | 0.80 | 36.6 | 27.7−48.8 |
| **35** | (38) | >100 | |
| **38** | 0.08 | 11.5 | 8.4−15.1 |
| **46a** | (4) | 19.0 | 16.8−21.8 |
| **46b** | (8) | 18.4 | 14.3−23.4 |
| **51a** | 0.29 | 24.8 | 14.5−41.9 |
| **51b** | 0.30 | >50 | |
| **51c** | 0.29 | >50 | |
| **51d** | 0.05 | 42.2 | 26.3−80.2 |
| **51e** | 0.29 | >50 | |
| **51f** | 0.28 | 26.7 | 20.2−36.6 |
| **51g** | (22) | 32.1 | 24.1−41.6 |
| **51h** | 0.29 | 14.0 | 9.3−19.2 |
| **52a** | (0) | >100 | |
| **52b** | (−2) | >100 | |
| **52c** | (1) | >100 | |
| **52d** | (1) | >100 | |
| **53a** | (18) | 16.6 | 6.6−23.9 |
| **53b** | (16) | 38.9 | 31.3−46.2 |
| **53c** | (24) | 51.1 | 24.2−116.4 |
| **54a** | (−1) | >100 | |
| **54b** | (3) | >100 | |
| **58a** | 0.28 | >50 | |
| **58b** | 0.30 | >50 | |
| **58c** | (4) | >50 | |
| **58d** | 0.03 | >25 | |

[a] The molar concentration of test compound required to reduce by 50% the amount of lipid peroxide formed in rat liver microsomes. $IC_{50}$ values were determined from four concentrations by nonlinear regression analysis. Percent inhibition at the concentration of 1 $\mu$M is shown in parentheses. [b] The dose of test compound required to reduce by 50% the score of excitatory behavior induced by intrathecal injection of $FeCl_2$. $ID_{50}$ values were generated from three or four doses; 10 animals were used per dose. [c] Dihydrochloride was used. [d] Not tested.

**Table 3.** Effects of 5-Aminocoumarans on the Methamphetamine-Induced Increase in Locomotor Activity in Mice[a]

| expt no. | sample | inducer | locomotor activity | % increase |
|---|---|---|---|---|
| 1 | saline | saline | 194 ± 53** | 0 |
| | saline | MAP[b] | 1195 ± 142 | 100 |
| | **8a** | MAP | 509 ± 153** | 31.5 |
| 2 | saline | saline | 747 ± 268** | 0 |
| | saline | MAP | 2168 ± 359 | 100 |
| | **26a** | MAP | 1098 ± 277* | 24.7 |
| | **26b** | MAP | 1625 ± 398 | 61.8 |
| | **26d** | MAP | 892 ± 237* | 10.2 |
| | **26e** | MAP | 2228 ± 403 | 104.2 |
| | **26f** | MAP | 1391 ± 367 | 45.3 |
| | **26k** | MAP | 1657 ± 506 | 64.0 |
| | **51a** | MAP | 1845 ± 190 | 77.3 |
| | **51g** | MAP | 1488 ± 330 | 52.1 |
| 3 | saline | saline | 447 ± 276** | 0 |
| | saline | MAP | 2385 ± 548 | 100 |
| | **26g** | MAP | 1099 ± 288 | 33.6 |
| | **26h** | MAP | 1540 ± 455 | 56.4 |
| | **26l** | MAP | 1934 ± 461 | 76.7 |
| | **26n**[c] | MAP | 482 ± 87** | 1.8 |
| | **26r** | MAP | 1664 ± 440 | 62.8 |
| | **26s** | MAP | 1812 ± 333 | 70.4 |
| | **26t** | MAP | 1340 ± 398 | 46.1 |
| | **27** | MAP | 1115 ± 339 | 34.5 |
| 4 | saline | saline | 495 ± 128** | 0 |
| | saline | MAP | 3127 ± 420 | 100 |
| | **26m** | MAP | 2960 ± 295 | 93.7 |
| | **26o** | MAP | 3209 ± 416 | 103.1 |
| 5 | saline | saline | 336 ± 56** | 0 |
| | saline | MAP | 1892 ± 232 | 100 |
| | **26p** | MAP | 3154 ± 738 | 181.1 |
| | **46a** | MAP | 2129 ± 636 | 115.2 |
| | **46b** | MAP | 3549 ± 552* | 206.5 |
| 6 | saline | saline | 402 ± 118** | 0 |
| | saline | MAP | 2689 ± 591 | 100 |
| | **26q** | MAP | 1484 ± 632 | 47.3 |
| | **26w** | MAP | 3950 ± 452 | 155.1 |
| 7 | saline | saline | 417 ± 38** | 0 |
| | saline | MAP | 1376 ± 348 | 100 |
| | **38** | MAP | 1185 ± 187 | 80.1 |
| | **51f** | MAP | 2156 ± 311 | 181.3 |
| | **53a** | MAP | 1229 ± 115 | 84.7 |

[a] Thirty minutes after ip injection of 5-aminocoumarans at a dose of 10 mg/kg, methamphetamine at a dose of 1 mg/kg was injected ip. The number of mice in each group was 8. Locomotor activity was measured for 1 h after administration of methamphetamine. *$p < 0.05$ and **$p < 0.01$ compared to the respective saline-methamphetamine-treated controls. [b] Methamphetamine. [c] Dihydrochloride was used.

mp 248−251 °C; NMR (DMSO-$d_6$) $\delta$ 1.39 (6H, s), 1.93 (3H, s), 2.09 (3H, s), 2.82 (2H, s), 3.36 (4H, br s).

With a similar procedure, **46a,b** and **51a−h** were prepared. This method was utilized in hydrogenation of the olefin group for the synthesis of **23** and **37**.

***N*-[4-(Dimethylamino)-2,3-dihydro-2,2,6,7-tetramethyl-5-benzofuranyl]acetamide (13).** To a solution of **12** (5.3 g, 21 mmol) in DMF (100 mL) were added $K_2CO_3$ (4.4 g, 32 mmol) and iodomethane (4.0 mL, 21 mmol). The mixture was stirred at room temperature under an argon atmosphere for 3 h. The reaction mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH = 97:3), and the product was recrystallized from $CH_2Cl_2$−IPE to yield 5.5 g (94% yield) of **13**: mp 185−186 °C; NMR ($CDCl_3$) $\delta$ 1.44 (6H, s), 2.09 (6H, s), 2.21 (3H, s), 2.67 (6H, s), 3.09 (2H, s), 7.17 (1H, br s).

**General Procedure for Mannich Reaction of 2-Methallylphenols. *N*-[3-[(Dimethylamino)methyl]-4-hydroxy-2,6-dimethyl-5-(2-methyl-2-propenyl)phenyl]acetamide (17a).** To a suspension of paraformaldehyde (1.6 g, 43 mmol) in EtOH (10 mL) was added 50% aqueous dimethylamine (6.5 mL, 64 mmol), and the mixture was stirred at room temper-

**Table 4.** Effects of (*S*)-(+)- and (*R*)-(−)-**26n** Dihydrochloride on the Methamphetamine- and Apomorphine-Induced Increase in Locomotor Activity in Mice[a]

| sample | dose (mg/kg) | inducer | $n$[b] | locomotor activity | % increase |
|---|---|---|---|---|---|
| saline | | saline | 10 | 175 ± 46** | 0 |
| saline | | MAP[c] | 9 | 1878 ± 431 | 100 |
| (*S*)-(+)-**26n**[d] | 0.1 | MAP | 10 | 2103 ± 451 | 113.2 |
| | 0.3 | MAP | 9 | 1102 ± 317 | 54.4 |
| | 1 | MAP | 9 | 773 ± 173* | 35.1 |
| saline | | saline | 16 | 245 ± 74** | 0 |
| saline | | MAP | 14 | 1196 ± 314 | 100 |
| (*R*)-(−)-**26n**[d] | 1 | MAP | 15 | 1472 ± 257 | 129.0 |
| | 3 | MAP | 13 | 1852 ± 493 | 169.0 |
| | 10 | MAP | 16 | 889 ± 159 | 67.7 |
| saline | | saline | 13 | 145 ± 46** | 0 |
| saline | | APO[e] | 11 | 619 ± 160 | 100 |
| (*S*)-(+)-**26n**[d] | 1 | APO | 11 | 841 ± 251 | 124.5 |

[a] Thirty minutes after ip injection of (*S*)-(+)- and (*R*)-(−)-**26n** dihydrochloride, methamphetamine at a dose of 1 mg/kg, ip, or apomorphine at a dose of 1 mg/kg, sc, was injected. Locomotor activity was measured for 1 h after administration of methamphetamine. *$p$ < 0.05 and **$p$ < 0.01 when compared to the respective saline-methamphetamine-treated control group (two-tailed Student's $t$-test). [b] Number of mice. [c] Methamphetamine. [d] Dihydrochloride was used. [e] Apomorphine.

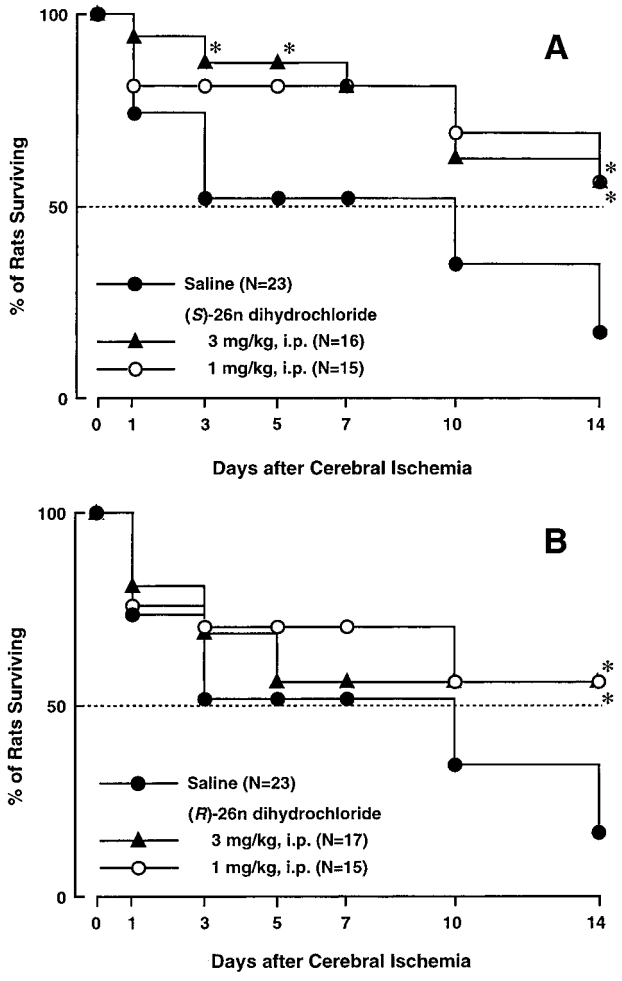



**Figure 1.** Effects of (A) (*S*)-**26n** dihydrochloride (TAK-218) and (B) (*R*)-**26n** dihydrochloride on the survival rates following 45-min transient cerebral ischemia in rats; *$p$ < 0.05 when compared to the saline-treated control group (two-tailed Fisher's exact probability test).

ature for 30 min. Then the resulting solution was added to a solution of **16** (5.0 g, 21 mmol) in EtOH (30 mL). The mixture was refluxed under an argon atmosphere for 3.5 h and then cooled and concentrated. The residue was used for the next reaction without further purification.

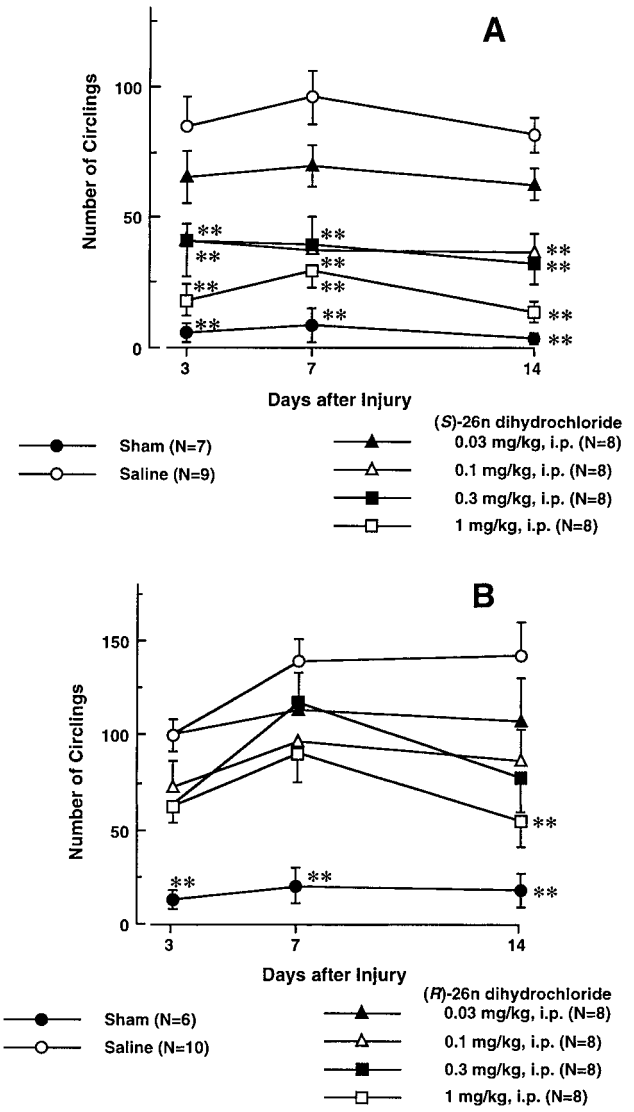



**Figure 2.** Effects of (A) (*S*)-**26n** dihydrochloride (TAK-218) and (B) (*R*)-**26n** dihydrochloride on the functional changes after penetration-induced brain injury in rats; **$p$ < 0.01 when compared to the saline-treated control group (two-tailed Dunnett's multiple range test following 2-way ANOVA).

With a similar procedure, **17b** was prepared.

**General Procedure for Hydrolysis of the Acetamide Group under Basic Conditions. 5-Amino-2,3-dihydro-*N*,*N*,2,2,4,6-hexamethyl-7-benzofuranmethanamine Ethanedioate (1:1) (19a).** A mixture of **18a** (4.8 g, 17 mmol), MeOH (3 mL), and 5 M aqueous NaOH (25 mL) was stirred under an argon atmosphere in a sealed tube at 200 °C for 13 h. After cooling, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH = 88:12) to yield the free base of **19a** (1.7 g, 42% yield). A portion of the product was treated with oxalic acid, and the salt obtained was recrystallized from EtOH to give **19a**: mp 178−180 °C; NMR (DMSO-$d_6$) $\delta$ 1.39 (6H, s), 2.02 (3H, s), 2.07 (3H, s), 2.74 (6H, s), 2.93 (2H, s), 4.13 (2H, s).

With a similar procedure, **19b** was prepared.

**General Procedure for Bromination of 2-Methallylphenols. *N*-[2-(Bromomethyl)-2,3-dihydro-2,4,6,7-tetramethyl-5-benzofuranyl]formamide (24).** To a suspension of **6a** (30 g, 0.13 mol) and sodium acetate (21 g, 0.26 mol) in acetic acid (500 mL) was added bromine (7.9 mL, 0.15 mol). After stirring for 10 min at room temperature, the reaction mixture was concentrated and water was added to the residue. Precipitates formed were collected by filtration, washed with water and IPE, and dried. The crude product was recrystallized from

EtOAc−IPE to yield 33 g (81% yield) of **24**: mp 157−158 °C; NMR ($CDCl_3$) $\delta$ 1.61 (1.5H, s), 1.63 (1.5H, s), 2.09 (3H, s), 2.11 (3H, s), 2.13 (1.5H, s), 2.16 (1.5H, s), 2.93 (1H, d, $J$ = 15.8 Hz), 3.28 (0.5H, d, $J$ = 15.8 Hz), 3.29 (0.5H, d, $J$ = 15.8 Hz), 3.51 (1H, s), 3.53 (1H, s), 6.77 (0.5H, br s), 6.85 (0.5H, d, $J$ = 12.0 Hz), 7.96 (0.5H, d, $J$ = 12.0 Hz), 8.40 (0.5H, d, $J$ = 1.4 Hz).

With a similar procedure, **40** was prepared.

**General Procedure for Condensation of Thiols and 24. *N*-[2,3-Dihydro-2,4,6,7-tetramethyl-2-[(phenylthio)methyl]-5-benzofuranyl]formamide (25a).** To a solution of **24** (6.0 g, 19 mmol) and thiophenol (2.3 g, 21 mmol) in DMF (50 mL) was added NaH (1.0 g, 21 mmol; 60% in oil), and the mixture was stirred under an argon atmosphere at 80 °C for 1 h. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (IPE:EtOAc = 1:1) followed by recrystallization from IPE−hexane to afford 5.5 g (83% yield) of **25a**: mp 130−131 °C; NMR ($CDCl_3$) $\delta$ 1.55 (1.5H, s), 1.56 (1.5H, s), 2.00 (3H, s), 2.06 (1.5H, s), 2.09 (1.5H, s), 2.11 (1.5H, s), 2.14 (1.5H, s), 2.91 (1H, d, $J$ = 15.8 Hz), 3.23 (0.5H, d, $J$ = 15.8 Hz), 3.43 (0.5H, d, $J$ = 15.8 Hz), 3.27 (2H, s), 6.74 (0.5H, br s), 6.84 (0.5H, d, $J$ = 12.0 Hz), 7.15−7.40 (5H, m), 7.97 (0.5H, d, $J$ = 12.0 Hz), 8.40 (0.5H, d, $J$ = 1.4 Hz).

With a similar procedure, **25b−j** were prepared.

**General Procedure for Condensation of Alcohols and 24. 2,3-Dihydro-2,4,6,7-tetramethyl-2-[(phenylmethoxy)-methyl]-5-benzofuranamine Hydrochloride (26k).** To a mixture of NaH (1.0 g, 25 mmol; 60% in oil) and benzyl alcohol (20 mL) was added **24** (2.0 g, 6.4 mmol) with cooling. The mixture was stirred under an argon atmosphere at 180 °C for 18 h in a sealed tube. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (IPE), and the product was treated with 4 M HCl/EtOH (8.0 mL). The crude salt was recrystallized from EtOH−IPE to afford 0.68 g (31% yield) of **26k**: mp 195−200 °C; NMR (DMSO-$d_6$) $\delta$ 1.40 (3H, s), 2.05 (3H, s), 2.22 (6H, s), 2.88 (1H, d, $J$ = 15.8 Hz), 3.17 (1H, d, $J$ = 15.8 Hz), 3.51 (2H, s), 4.56 (2H, s), 7.31 (5H, m), 9.71 (2H, br s).

With a similar procedure, **26l** was prepared.

**General Procedure for Condensation of Amines and 24 (In the Absence of Triethylamine). 2,3-Dihydro-2,4,6,7-tetramethyl-2-(1-piperidinylmethyl)-5-benzofuranamine (26m).** A mixture of **24** (2.0 g, 6.4 mmol) and piperidine (6.3 mL, 64 mmol) was stirred under argon atmosphere at 180 °C for 18 h in a sealed tube. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was recrystallized from IPE to afford 1.5 g (82% yield) of **26m**: mp 60−61 °C; NMR ($CDCl_3$) $\delta$ 1.30−1.60 (6H, m), 1.42 (3H, s), 2.07 (6H, s), 2.10 (3H, s), 2.35−2.65 (6H, m), 2.80 (1H, d, $J$ = 15.9 Hz), 3.10 (2H, br s), 3.11 (1H, d, $J$ = 15.9 Hz).

With a similar procedure, **26o−w** were prepared.

**2,3-Dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine (26n).** A mixture of **27** (36 g, 0.13 mol; free base), 4-phenylpiperidine (41 g, 0.25 mol), and triethylamine (53 mL, 0.38 mol) was stirred under an argon atmosphere at 180 °C for 15 h in a sealed tube. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH = 97:3) followed by recrystallization from $CHCl_3$−IPE to yield 38 g (82% yield) of **26n**: mp 142−144 °C; NMR ($CDCl_3$) $\delta$ 1.46 (3H, s), 1.70−1.82 (4H, m), 2.08 (6H, s), 2.11 (3H, s), 2.18−2.34 (2H, m), 2.37−2.49 (1H, m), 2.52 (1H, d, $J$ = 13.4 Hz), 2.61 (1H, d, $J$ = 13.4 Hz), 2.83 (1H, d, $J$ = 15.4 Hz), 2.94−3.06 (1H, m), 3.14 (1H, d, $J$ = 15.4 Hz), 3.16 (2H, br s), 3.18−3.28 (1H, m), 7.15−7.35 (5H, m).

***N*-[2,3-Dihydro-2,4,6,7-tetramethyl-2-[(phenylsulfinyl)-methyl]-5-benzofuranyl]formamide (28).** To a solution of **26a** (2.3 g, 6.7 mmol) in MeOH (20 mL) was added 1 M aqueous $NaIO_4$ (20 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was recrystallized from EtOAc−IPE to afford 1.5 g (64% yield) of **28**: mp 112−115 °C; NMR ($CDCl_3$) $\delta$ 1.62 (3H, s), 2.08 (3H, s), 2.12 (1.5H, s), 2.14 (1.5H, s), 2.16 (1.5H, s), 2.18 (1.5H, s), 3.00−3.40 (4H, m), 6.78 (1H, m), 7.45−7.70 (5H, m), 7.96 (0.25H, d, $J$ = 12.0 Hz), 7.99 (0.25H, d, $J$ = 12.0 Hz), 8.40 (0.25H, d, $J$ = 1.4 Hz), 8.42 (0.25H, d, $J$ = 1.4 Hz).

***N*-[2,3-Dihydro-2,4,6,7-tetramethyl-2-[(phenylsulfonyl)methyl]-5-benzofuranyl]formamide (29).** To a solution of **26a** (2.1 g, 6.2 mmol) in MeOH (20 mL) was added 2 M aqueous $NaIO_4$ (20 mL), and the mixture was refluxed for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was recrystallized from EtOAc−IPE to afford 1.4 g (66% yield) of **29**: mp 154−155 °C; NMR ($CDCl_3$) $\delta$ 1.70 (1.5H, s), 1.71 (1.5H, s), 1.81 (1.5H, s), 1.84 (1.5H, s), 2.05 (1.5H, s), 2.07 (1.5H, s), 2.12 (1.5H, s), 2.14 (1.5H, s), 3.01 (1H, d, $J$ = 15.6 Hz), 3.56 (1H, s), 3.58 (1H, s), 3.62 (0.5H, d, $J$ = 15.6 Hz), 3.67 (0.5H, d, $J$ = 15.6 Hz), 6.71 (0.5H, br s), 6.74 (0.5H, d, $J$ = 12.0 Hz), 7.15−7.70 (3H, m), 7.89 (2H, m), 7.96 (0.5H, d, $J$ = 12.0 Hz), 8.40 (0.5H, d, $J$ = 1.6 Hz).

***N*-[2,3-Dihydro-2-(hydroxymethyl)-2,4,6,7-tetramethyl-5-benzofuranyl]formamide (32).** To a solution of **6a** (2.0 g, 7.7 mmol) in $CH_2Cl_2$ (20 mL) were added saturated aqueous $NaHCO_3$ (10 mL) and *m*-chloroperbenzoic acid (3.2 g, 19 mmol) with ice−water bath cooling. After the reaction mixture was stirred at room temperature for 1 h, the solvent was removed. The residue was dissolved in a mixture of EtOAc and THF (3:1). The resulting solution was washed with water, 10% aqueous sodium hydrosulfite, aqueous $NaHCO_3$, and brine, dried, and concentrated. The residue was recrystallized from EtOAc−IPE to afford 1.4 g (64% yield) of **32**: mp 149−150 °C; NMR (DMSO-$d_6$) $\delta$ 1.33 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 2.00 (3H, s), 2.73 (1H, d, $J$ = 15.4 Hz), 3.13 (1H, d, $J$ = 15.4 Hz), 3.42 (2H, d, $J$ = 5.8 Hz), 5.01 (1H, t, $J$ = 5.8 Hz), 7.83 (0.2H, d, $J$ = 11.6 Hz), 8.21 (0.8H, d, $J$ = 1.2 Hz), 9.05 (0.2H, d, $J$ = 11.6 Hz), 9.20 (0.8H, br s).

***N*-(2-Formyl-2,3-dihydro-2,4,6,7-tetramethyl-5-benzofuranyl)formamide (33).** To a solution of oxalyl chloride (0.40 mL, 4.2 mmol) in $CH_2Cl_2$ (10 mL) was added DMSO (1 mL) at −78 °C. After the mixture was stirred for 10 min, a solution of **32** (1.0 g, 4.0 mmol) in $CH_2Cl_2$ (2 mL) was added and stirring was continued for a further 15 min. To the reaction mixture was added $Et_3N$ (3.5 mL), and the mixture was allowed to warm to room temperature, washed with 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was recrystallized from EtOAc−IPE to afford 0.68 g (69% yield) of **33**: mp 154−155 °C; NMR ($CDCl_3$) $\delta$ 1.55 (1.5H, s), 1.57 (1.5H, s), 2.08 (3H, s), 2.12 (3H, s), 2.15 (3H, s), 2.94 (1H, d, $J$ = 15.4 Hz), 3.41 (0.5H, d, $J$ = 15.4 Hz), 3.44 (0.5H, d, $J$ = 15.4 Hz), 7.00 (1H, m), 7.95 (0.5H, d, $J$ = 12.0 Hz), 8.34 (0.5H, d, $J$ = 1.8 Hz), 9.73 (0.5H, s), 9.74 (0.5H, s).

**Ethyl (*E*)-3-[5-(Formylamino)-2,3-dihydro-2,4,6,7-tetramethyl-2-benzofuranyl]propenoate (34).** A mixture of **33** (1.0 g, 4.1 mmol), triethyl phosphonoacetate (0.91 g, 4.1 mmol), and NaH (0.16 g, 4.1 mmol; 60% in oil) in DMF (20 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (EtOAc:IPE = 1:1) to afford 0.50 g (39% yield) of **34** as an oil: NMR ($CDCl_3$) $\delta$ 1.29 (3H, t, $J$ = 7.2 Hz), 1.60 (3H, s), 2.06 (1.5H, s), 2.11 (1.5H, s), 2.13 (1.5H, s), 2.15 (1.5H, s), 2.17 (3H, s), 3.05 (1H, d, $J$ = 15.4 Hz), 3.15 (1H, d, $J$ = 15.4 Hz), 4.19 (2H, d, $J$ = 7.2 Hz), 6.02 (1H, d, $J$ = 15.6 Hz), 6.92 (0.5H, br s). 6.95 (0.5H, d, $J$ = 12.0 Hz), 7.02 (1H, d, $J$ = 15.6 Hz), 7.95 (0.5H, d, $J$ = 12.0 Hz), 8.39 (0.5H, d, $J$ = 1.6 Hz).

***N*-[2-[2-(4-Fluorophenyl)ethyl]-2,3-dihydro-2,4,6,7-tetramethyl-5-benzofuranyl]formamide (37).** To a suspension of [(4-fluorophenyl)methyl]triphenylphosphonium bromide

(9.3 g, 23 mmol) in THF (100 mL) was added 1.6 M *n*-BuLi (14 mL, 23 mmol; hexane solution) at −78 °C, and the mixture was stirred for 15 min. To the mixture was added **33** (6.0 g, 23 mmol), and stirring was continued at room temperature for 30 min. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue (**36**, 4.2 g, 59% yield) was diluted with EtOH (50 mL), and 5% Pd/C (0.2 g) was added. The mixture was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was diluted with EtOAc, and insoluble material was removed by filtration. After concentration of the filtrate, the residue was recrystallized from MeOH to yield 3.6 g (86% yield) of **37**: mp 139−140 °C; NMR ($CDCl_3$) $\delta$ 1.48 (1.5H, s), 1.50 (1.5H, s), 2.00 (2H, m), 2.10 (1.5H, s), 2.11 (1.5H, s), 2.12 (4.5H, s), 2.17 (1.5H, s), 2.70 (2H, m), 2.91 (1H, d, $J$ = 15.4 Hz), 3.05 (1H, d, $J$ = 15.4 Hz), 6.66 (0.5H, br s), 6.71 (0.5H, s), 6.95 (2H, t, $J$ = 8.6 Hz), 7.13 (2H, dd, $J$ = 5.6, 8.6 Hz), 7.98 (0.5H, d, $J$ = 12.2 Hz), 8.42 (0.5H, d, $J$ = 1.6 Hz).

**2,3-Dihydro-2,4,6,7-tetramethyl-2-benzofuranacetonitrile (41).** A mixture of **40** (6.5 g, 19 mmol) and sodium cyanide (1.4 g, 19 mmol) in DMSO (30 mL) was stirred at 80 °C for 18 h. The reaction mixture was diluted with water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (hexane:IPE = 2:1) followed by recrystallization from MeOH to afford 4.1 g (80% yield) of **41**: mp 58−59 °C; NMR ($CDCl_3$) $\delta$ 1.66 (3H, s), 2.07 (3H, s), 2.16 (3H, s), 2.20 (3H, s), 2.68 (1H, d, $J$ = 10.8 Hz), 2.75 (1H, d, $J$ = 10.8 Hz), 3.00 (1H, d, $J$ = 15.8 Hz), 3.12 (1H, d, $J$ = 15.8 Hz), 6.54 (1H, s).

**2,3-Dihydro-2,4,6,7-tetramethyl-2-benzofuranacetic Acid (42).** To a solution of **41** (6.9 g, 32 mmol) in MeOH (30 mL) was added 10 M aqueous NaOH (30 mL), and the mixture was refluxed for 18 h. The reaction mixture was made acidic with 6 M aqueous HCl and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. The residue was recrystallized from EtOAc−hexane to afford 6.0 g (80% yield) of **42**: mp 139−140 °C; NMR (DMSO-$d_6$) $\delta$ 1.61 (3H, s), 2.07 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 2.78 (1H, d, $J$ = 10.8 Hz), 2.85 (1H, d, $J$ = 10.8 Hz), 2.97 (1H, d, $J$ = 15.4 Hz), 3.21 (1H, d, $J$ = 15.4 Hz), 6.52 (1H, s), 8.50 (1H, br s).

**General Procedure for Condensation of Amines and 42. 2,3-Dihydro-*N*,*N*,2,4,6,7-hexamethyl-2-benzofuranacetamide (43a).** To a solution of **42** (3.0 g, 13 mmol) in DMF (30 mL) were added 1-hydroxybenzotriazole monohydrate (2.1 g, 14 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.7 g, 19 mmol), and the mixture was stirred at room temperature for 1 h. To the mixture was added 50% aqueous dimethylamine (3 mL), and stirring was continued for a further 30 min. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography (IPE) to yield 3.1 g (93% yield) of **43a** as an oil: NMR ($CDCl_3$) $\delta$ 1.59 (3H, s), 2.07 (3H, s), 2.14 (3H, s), 2.20 (3H, s), 2.77 (1H, d, $J$ = 15.8 Hz), 2.88 (1H, d, $J$ = 15.8 Hz), 2.94 (3H, s), 3.00 (1H, d, $J$ = 15.8 Hz), 3.03 (3H, s), 3.27 (1H, d, $J$ = 15.8 Hz), 6.50 (1H, s).

With a similar procedure, **43b** was prepared.

**General Procedure for Reduction of Amides. 2,3-Dihydro-*N*,*N*,2,4,6,7-hexamethyl-2-benzofuranethanamine (44a).** To a solution of **43a** (3.1 g, 12 mmol) in THF (50 mL) was gradually added lithium aluminum hydride (0.45 g, 12 mmol) with cooling. After stirring at room temperature for 30 min, the mixture was poured into ice−water. The aqueous mixture was extracted with EtOAc, and the extract was washed with brine and dried. The organic solution was concentrated, and the residue was purified by column chromatography ($CHCl_3$:MeOH = 95:5) to give 2.2 g (82% yield) of **44a** as an oily product: NMR ($CDCl_3$) $\delta$ 1.42 (3H, s), 1.90 (2H, m), 2.06 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.23 (6H, s), 2.40 (2H, m), 2.82 (1H, d, $J$ = 15.4 Hz), 3.00 (1H, d, $J$ = 15.4 Hz), 6.47 (1H, s).

With a similar procedure, **44b** and **53a−c** were prepared.

**General Procedure for Synthesis of 48. 2-Methoxy-3,4,6-trimethyl-α-(1-methylethyl)-α-phenylbenzenemethanol (48a).** To a solution of **47**[15] (3.0 g, 13 mmol) in THF (20 mL) was added 1.6 M *n*-BuLi (8.2 mL, 13 mmol; hexane solution) at −78 °C, and the mixture was stirred for 15 min. To the mixture was added a solution of isobutyrophenone (1.9 g, 13 mmol) in THF (5 mL), and the mixture was stirred at room temperature for an additional 30 min. The reaction mixture was diluted with water and extracted with IPE. The extract was washed with brine, dried, and concentrated. The residue was crystallized from hexane to afford 3.1 g (80% yield) of **48a**. This product was used without further purification: mp 80−81 °C; NMR ($CDCl_3$) $\delta$ 0.88 (3H, d, $J$ = 6.6 Hz), 1.05 (3H, d, $J$ = 6.4 Hz), 2.07 (3H, s), 2.18 (3H, s), 2.58 (3H, s), 2.82 (1H, qq, $J$ = 6.4, 6.6 Hz), 2.90 (3H, s), 6.18 (1H, br s), 6.75 (1H, s), 7.10−7.30 (3H, m), 7.40−7.50 (2H, m).

With a similar procedure, **48b−h** were prepared.

**General Procedure for Preparation of 49 from 48. 2,3-Dihydro-2,2,4,6,7-pentamethyl-3-phenylbenzofuran (49a).** A suspension of **48a** (3.1 g, 10 mmol) in 47% hydrobromic acid (20 mL) was refluxed under an argon atmosphere for 18 h. After cooling, the reaction mixture was extracted with IPE, and the extract was washed with brine, dried, and concentrated. The residue was recrystallized from EtOH to afford 2.4 g (88% yield) of **49a**: mp 86−87 °C; NMR ($CDCl_3$) $\delta$ 1.02 (3H, s), 1.51 (3H, s), 1.84 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 4.13 (1H, s), 6.49 (1H, s), 6.70−7.40 (5H, m).

With a similar procedure, **49b−h** were prepared.

***N*-(2,3-Dihydro-2,2,4,6,7-pentamethyl-5-benzofuranyl)formamide (52a).** A solution of **8a** (1.0 g, 4.9 mmol; free base) in formic acid (20 mL) was refluxed under an argon atmosphere for 48 h. After cooling, the reaction mixture was concentrated, and saturated aqueous $NaHCO_3$ was added to the residue. The aqueous mixture was extracted with $CHCl_3$, and the extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH = 97:3) to afford 1.1 g (93% yield) of **52a**. An analytical sample of **52a** was recrystallized from $CH_2Cl_2$−IPE: mp 177−179 °C; NMR ($CDCl_3$) $\delta$ 1.46 (3H, s), 1.48 (3H, s), 2.09−2.16 (9H, m), 2.94 (2H, s), 6.62−6.80 (1H, m), 7.97 (0.5H, d, $J$ = 12.0 Hz), 8.42 (0.5H, d, $J$ = 1.4 Hz).

**General Procedure for Preparation of *N*-Acylated Compounds Using Acyl Halide. *N*-(2,3-Dihydro-2,2,4,6,7-pentamethyl-5-benzofuranyl)acetamide (52b).** To a solution of **8a** (1.0 g, 4.9 mmol; free base) and $Et_3N$ (0.64 g, 6.3 mmol) in THF (20 mL) was added acetyl chloride (0.46 g, 5.8 mmol) with cooling. The mixture was stirred at room temperature for 4 h and then poured into water. The aqueous mixture was extracted with $CHCl_3$, and the extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by column chromatography ($CHCl_3$:MeOH = 97:3) followed by recrystallization from $CH_2Cl_2$−IPE to give 0.92 g (76% yield) of **52b**: mp 190−191 °C; NMR ($CDCl_3$) $\delta$ 1.46 (3H, s), 1.50 (3H, s), 1.73 (1.5H, s), 2.06 (3H, s), 2.09 (3H, s), 2.14 (3H, s), 2.21 (1.5H, s), 2.93 (2H, s), 6.58 (0.5H, br s), 6.63 (0.5H, br s).

With a similar procedure, **52c,d** were prepared. This method was utilized in sulfonylation of **8a** for the synthesis of **54a**.

***N*-(2,3-Dihydro-2,2,4,6,7-pentamethyl-5-benzofuranyl)-4-methylbenzenesulfonamide (54b).** A solution of **8a** (2.0 g, 9.7 mmol; free base) and *p*-toluenesulfonyl chloride (2.0 g, 11 mmol) in pyridine (30 mL) was stirred at 50 °C for 1 h. The reaction mixture was concentrated, and the residue was diluted with $CHCl_3$. The organic solution was washed with 1 M aqueous HCl and brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 97:3) followed by recrystallization from $CH_2Cl_2$−IPE to afford 2.4 g (69% yield) of **54b**: mp 219−220 °C; NMR ($CDCl_3$) $\delta$ 1.46 (6H, s), 1.80 (3H, s), 1.93 (3H, s), 2.01 (3H, s), 2.43 (3H, s), 2.87 (2H, s), 5.81 (1H, s), 7.24 (2H, d, $J$ = 8.4 Hz), 7.60 (2H, d, $J$ = 8.4 Hz).

**General Procedure for Preparation of Quinonimines 56a−c. 4-[(4-Chlorophenyl)imino]-2,3,5-trimethyl-6-(2-methyl-2-propenyl)-2,5-cyclohexadien-1-one (56c).** To a

solution of pyridine (7.1 mL, 88 mmol) in 1,2-dichloroethane (40 mL) was added $TiCl_4$ (2.4 mL, 22 mmol) with ice−water bath cooling, and the mixture was refluxed under an argon atmosphere for 20 min. After the mixture was cooled in an ice−water bath, a solution of **55**[23] (3.0 g, 15 mmol) and *p*-chloroaniline (5.6 g, 44 mmol) in 1,2-dichloroethane (20 mL) was added and the resulting mixture was stirred at 90 °C for 45 min. The reaction mixture was filtered through Celite, and the filtrate was washed with brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 93:7) to afford 4.3 g (96% yield) of **56c** as an oil: NMR ($CDCl_3$) $\delta$ 1.53−2.20 (12H, m), 3.21 (2H, s), 4.51 (1H, s), 4.74 (1H, s), 6.68 (2H, d, $J$ = 8.8 Hz), 7.30 (2H, d, $J$ = 8.8 Hz).

Compounds **56a,b** were prepared by a similar procedure.

**General Procedure for Reduction of Quinonimines 56a−c. 4-[(4-Chlorophenyl)amino]-2,3,5-trimethyl-6-(2-methyl-2-propenyl)phenol (57c).** To a solution of **56c** (4.4 g, 14 mmol) in THF (20 mL) was added 2.8 M aqueous sodium hydrosulfite (50 mL), and the mixture was stirred at room temperature for 30 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 95:5) to afford 4.3 g (97% yield) of **57c** as an oil: NMR ($CDCl_3$) $\delta$ 1.80 (3H, s), 2.11 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.40 (2H, s), 4.68 (1H, s), 4.87 (1H, s), 5.04 (1H, s), 5.14 (1H, br s), 6.34 (2H, d, $J$ = 8.8 Hz), 7.06 (2H, d, $J$ = 8.8 Hz).

With a similar procedure, **57a,b** were prepared.

**4-[(2,3-Dihydro-2,2-dimethyl-5-benzofuranyl)amino]-2,3,5-trimethyl-6-(2-methyl-2-propenyl)phenol (57d).** To a solution of pyridine (7.1 mL, 88 mmol) in 1,2-dichloroethane (40 mL) was added $TiCl_4$ (2.4 mL, 22 mmol) with ice−water bath cooling, and the mixture was stirred under an argon atmosphere at 90 °C for 30 min. After the reaction mixture was cooled, a solution of **55** (3.0 g, 15 mmol) in 1,2-dichloroethane (5 mL) and a solution of **8e** (12 g, 74 mmol; free base) in 1,2-dichloroethane (20 mL) were added to the reaction mixture. The resulting mixture was stirred under an argon atmosphere at 90 °C for 30 min. The reaction mixture was allowed to cool to room temperature, then Celite and $CHCl_3$ were added, and the resulting mixture was filtered through Celite. The filtrate was washed with brine, dried, and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 9:1) followed by recrystallization from IPE−pentane to give 2.3 g (45% yield) of **57d**: mp 160−162 °C; NMR ($CDCl_3$) $\delta$ 1.44 (6H, s), 1.80 (3H, s), 2.15 (6H, s), 2.19 (3H, s), 2.90 (2H, s), 3.41 (2H, s), 4.65−5.00 (4H, m), 6.18−6.27 (2H, m), 6.53 (1H, d, $J$ = 8.4 Hz).

**Optical Resolution of 26n.** To a solution of **26n** (35 g, 97 mmol) in $CHCl_3$ (500 mL) was added a solution of (*S*)-(+)-mandelic acid (15 g, 97 mmol) in MeOH (300 mL), and the mixture was concentrated. To the residue was added $Et_2O$ (500 mL), and the precipitates formed were collected by filtration, washed with $Et_2O$, and dried to afford 35 g of crude salt. The crude salt was recrystallized as follows: The salt was dissolved in MeOH, the solution was concentrated to a volume of about 100 mL, and crystals formed. To the mixture was added $Et_2O$ (500 mL), and the crystals were collected by filtration, washed with $Et_2O$, and dried (22 g). This solid was recrystallized once again from the same solvent system to afford 20 g (40% yield) of diastereomeric salt: $[\alpha]_D$ +57.1° (*c* 1.23, MeOH); mp 186−190 °C. X-ray crystallographic analysis showed this salt to have the *S*-configuration after recrystallization from 2-propanol. (*S*)-Mandelate of (*S*)-**26n** (20 g, 39 mmol) was dissolved with EtOAc−0.5 M aqueous NaOH. The organic phase was separated, washed with 0.5 M aqueous NaOH, saturated aqueous $NaHCO_3$, and brine, and then dried over anhydrous $Na_2CO_3$ and concentrated. The residue was dissolved in MeOH (140 mL), and 4 M HCl/EtOAc (23 mL) was added to the solution. After the solution was concentrated, the residue was crystallized from EtOAc, and the crude solid was recrystallized from MeOH−EtOAc to afford 14 g (89% yield) of (*S*)-**26n** dihydrochloride: $[\alpha]_D$ +27.8° (*c* 1.05, MeOH); mp 226 °C dec.

The combined filtrate obtained in preparation of (*S*)-**26n** (*S*)-mandelate was concentrated, and the residue (28 g) was dissolved with EtOAc−0.5 M aqueous NaOH. The organic phase was separated, washed with 0.5 M aqueous NaOH, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $Na_2CO_3$, and concentrated. From the residue (20 g) and (*R*)-(−)-mandelic acid (8.4 g), (*R*)-**26n** (*R*)-mandelate (20 g, 40% yield) was obtained in the same manner as for the preparation of (*S*)-**26n** (*S*)-mandelate: $[\alpha]_D$ −57.0° (*c* 1.09, MeOH); mp 186−191 °C. (*R*)-**26n** dihydrochloride was obtained after recrystallization from MeOH−EtOAc of the crude dihydrochloride, which was prepared from (*R*)-**26n** (*R*)-mandelate in the same manner as for the preparation of (*S*)-**26n** dihydrochloride (92% yield): $[\alpha]_D$ −27.9° (*c* 1.28, MeOH); mp 226 °C dec.

**Lipid Peroxidation Inhibition.** To rat liver microsomes (S-9) (0.3 mg of protein/40 mM Tris-malate buffer (pH 7.4), 2.4 mL) (2.4 mL) was added a mixture (1:1; 0.1 mL) of aqueous $FeCl_2$ solution (0.25 mM) and NADPH (3 mM). After incubation of the homogenate for 1 h at 37 °C, peroxide production was determined by the thiobarbituric acid method.[25] Before incubation, test compounds dissolved in DMSO were added to the rat liver microsomes so that their final concentration became $10^{-6}$ M. The inhibitory activities on lipid peroxidation are expressed as $IC_{50}$ values or percent inhibition as compared with the amount of production in the vehicle (DMSO) group.

**Mouse-$FeCl_2$-it Assay.** Male Slc:ICR mice (5 weeks) were used. Each group consisted of 10 mice; 5 $\mu$L of 50 mM $FeCl_2$ in saline was injected into the spinal subarchnoid space between the 1st sacral and the 6th lumbar segments. The behavioral responses were observed from 15 min to 1 h after intrathecal infection of $FeCl_2$ and scored as follows:

| score | behavioral responses |
|---|---|
| 0 | normal (no abnormal behavior) |
| 1 | vigorously biting the lower abdomen or lower extremities |
| 2 | (a) vigorously biting the lower body with rolling, (b) hyperreactivity and aggressive response to external stimuli, (c) tremor, (at least one of the above three behavioral changes were observed) |
| 3 | clonic convulsion |
| 4 | tonic convulsion or paralysis of lower extremities |
| 5 | death |

Water-soluble test compounds were dissolved in distilled water, and water-insoluble ones were suspended in a 0.5% gum arabic solution. Test compounds were orally administered 30 min prior to $FeCl_2$ injection in a volume of 0.2 mL/10 g. The inhibitory activities on mouse-$FeCl_2$-it assay are expressed as $ID_{50}$ values as compared with the score in the vehicle (saline) group.

**Suppression of MAP-Induced Hypermotility in Mice.** Five-week old male ICR mice (25−35 g) were used. Following a 90-min acclimation period, the test compound suspended in 5% gum arabic was injected intraperitoneally in a volume of 20 mL/kg. Thirty minutes after treatment with test compound, methamphetamine dissolved in saline was injected intraperitoneally at a dose of 1 mg/kg in a volume of 20 mL/kg. Immediately after methamphetamine injection, spontaneous motor activity was monitored for 90 min using Animex Auto. In another experiment, subcutaneous apomorphine at a dose of 1 mg/kg was used as an inducer of hypermotility instead of methamphetamine. Two-tailed Student's *t*-test was used for statistical analysis.

**Transient Cerebral Ischemia (Four-Vessel Occlusion) Model in Rats.** The surgical procedure to induce cerebral ischemia in rats was almost identical with that reported by Pulsinelli and Brierly.[34] Eight-week old male Wistar rats in which the vertebral arteries had been cauterized bilaterally with a bipolar electrocoagulator and common carotid arteries had been wrapped with thread bilaterally on the previous day were used. Under light halothane anesthesia, the common carotid arteries were occluded bilaterally with clips for 45 min. Drugs were given intraperitoneally immediately and 2 and 24 h after reopening the circulation. Survival of the animals was monitored for 1, 3, 5, 7, 10, and 14 days after reopening the

circulation. Two-tailed Fisher's exact probability test was used for statistical analysis.

**Penetration-Induced Brain Injury Model in Rats.** Male Wistar rats (10−11 weeks old) were used. Under halothane anesthesia, an animal was mounted on a Kopf stereotactic apparatus, and a glass rod 1.5 mm in diameter with a tapered tip (about 90°) was inserted through a burr hole from cortex to striatum (A/P +2.5, L +2.8, D 6.5; according to the rat brain atlas of Pellegrino and Cushman). The rod was then left in place for 1 min. Following removal of the rod, the incision was sutured. In sham-operated control rats, the brain was not injured. Drugs were given intraperitoneally immediately and 2 h after the removal of the rod. Functional changes were evaluated 3, 7, and 14 days after injury utilizing apomorphine (0.5 mg/kg, sc, starting immediately after injection for 30 min)-induced circling which has been reported to be specific to animals with damage in the nigro-striatal system. Two-tailed Dunnett's multiple range test following 2-way ANOVA was used for statistical analysis.

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**Supporting Information Available:** X-ray crystallographic data of (*S*)-mandelate of (*S*)-**26n** (7 pages). Ordering information is given on any current masthead page.

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