# Potential Neuroleptic Agents, *N*-[(2-Pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide Derivatives

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**A series of 2,3-dihydrobenzofuran-7-carboxamides, presenting a stabilized intramolecular hydrogen bond, was synthesized and evaluated in pharmacological models for antipsychotic activity. Among them, *N*-[(1-butyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide (15) showed an atypical neuroleptic profile similar to that of sulpiride (1) and more lipophilic properties than 1. Compound 15 was 11 times more potent in antagonistic activity on apomorphine-induced hyperactivity in mice ($ED_{50}$ = 30 mg/kg, *p.o.*) and stronger in potentiation of methamphetamine lethality in rats than 1, while it was as weak in inhibitory activity of apomorphine-induced stereotype in rats ($ED_{50}$ > 500 mg/kg, *p.o.*) as 1. On the other hand, *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylthio-2,3-dihydrobenzofuran-7-carboxamide (30) showed a classical neuroleptic profile with a potency comparable to haloperidol in antagonistic activity on apomorphine-induced hyperactivity in mice ($ED_{50}$ = 0.65 mg/kg, *p.o.*). The structure–activity relationships were also discussed.**

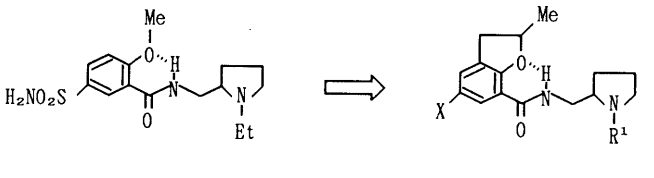
**Keywords** benzamide analogue; neuroleptic agent; 2,3-dihydrobenzofuran-7-carboxamide derivative; structure–activity relationship; lipophilicity; intramolecular hydrogen bond; apomorphine-induced hyperactivity; stereotype; methamphetamine potentiation

Since the antipsychotic properties of chlorpromazine were discovered,[1] many types of neuroleptic drugs, *e.g.*, phenothiazines, thioxantenes, butyrophenones, and benzamides, have been introduced in psychiatry.[2] Among them, sulpiride (**1**), a prototype of the substituted benzamides, has attracted considerable interest due to its unique pharmacological profile.[3] Although sulpiride interferes mainly with dopaminergic transmission in the brain (selective for dopamine $D_2$-receptors),[3c] as do the other neuroleptics, it has neither the antagonistic activity of stereotype nor induction of catalepsy.[3d] It does, however, possess antidepressant and anxiolytic activities[3e] which are not observed in the classical neuroleptics. This atypical pharmacological characteristic is also evident in clinical use of sulpiride. Thus, sulpiride not only reduces the symptoms of schizophrenic disorders with low incidence of extrapyramidal side effects (EPS),[3f] but also activates the neurologically negative symptoms.[3e] Indeed, sulpiride has occupied an important position in psychiatric treatment.[3b]

Sulpiride, however, has low bioavailability as well as low penetration through the blood-brain barrier.[4] The former problem creates the need to use large clinical dosages of the drug, while the latter results in the strong blockade of dopamine receptors in the pituitary inducing excess prolactin secretion as an adverse side effect. The unfavorable pharmacokinetics seem to be attributed to the low lipophilicity of the drug.

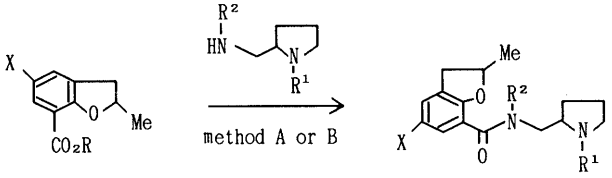
We intended to design more lipophilic and more potent analogues of sulpiride based on the conformation analysis studies of it. A significant structural feature of sulpiride is an intramolecular hydrogen bonding (H-bond) between the amide moiety and the methoxy group (Chart 1).[5] The H-bond has been thought to be responsible for stabilizing the active conformation in which the phenyl ring is positioned coplanar to the carbonyl group orienting in the opposite direction to the methoxy substituent side.[5g] The stabilization of the H-bond may also contribute to the enhancement of the lipophilicity. If so, it is expected that the stronger and/or more stabilized the H-bond, the higher the activity and lipophilicity will be. Evaluating the structure of sulpiride in detail, the H-bond is not strong enough because it is interfered with by the rotation of the C–O bond between the methoxy group and the phenyl ring. When the *O*-alkyl substituent is devised to make an appropriate linkage to the *meta* position of the benzamide so as to prohibit the rotation, the interference will be reduced and the H-bond will be reinforced. This concept led us to synthesize 2,3-dihydrobenzofurancarboxamide derivatives (I, Chart 1). We will herein report the synthesis, physicochemical properties, and structure–activity relationships of the new dihydrobenzofurancarboxamides.

**Chemistry** Dihydrobenzofurancarboxamides **12**—**35** listed in Table I, were prepared by the coupling of 5-substituted 2,3-dihydrobenzofuran-7-carboxylic acids **3**—**10** or methyl ester **11** (listed in Table II) with 1-substituted 2-(aminomethyl)pyrrolidines (Chart 2). The coupling reaction was performed by direct condensation of methyl ester **11** with the amines (method A)[6] or *via* the mixed




sulpiride ( **1** ) I

Chart 1




**3 — 1 1** **1 2 — 3 5**

Chart 2

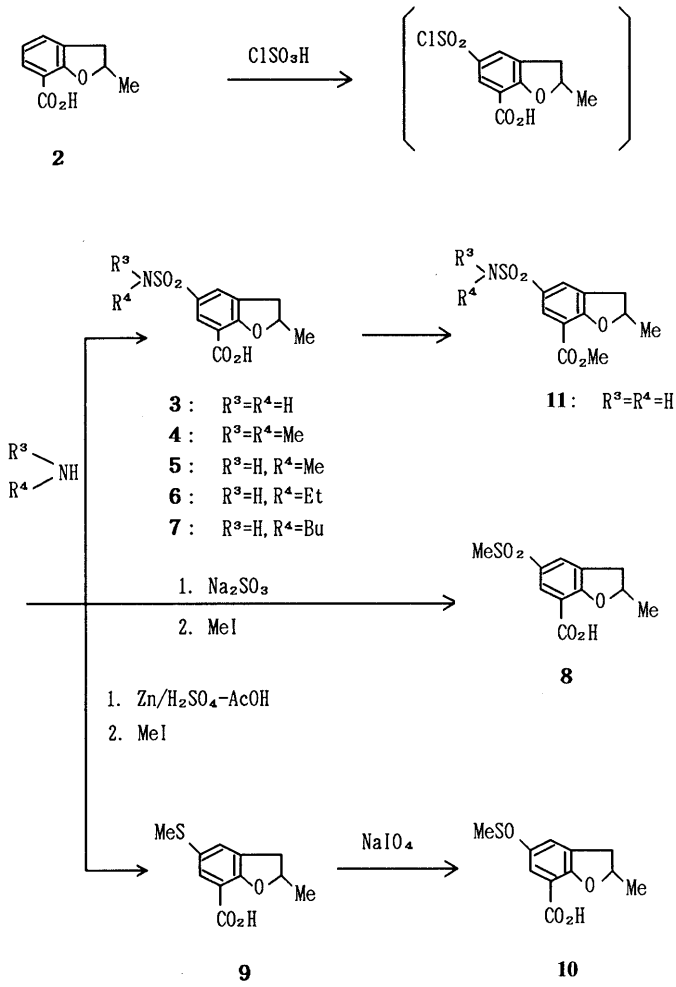



Chart 3

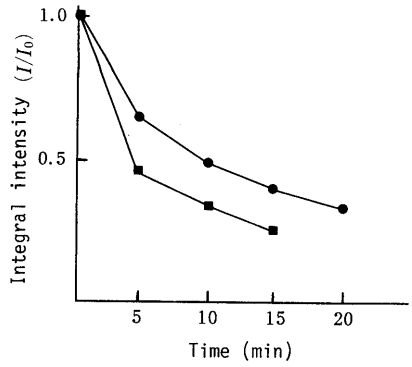



Fig. 1. Time Courses of Hydrogen to Deuterium Exchange

Ratios of the integral intensity of amide proton signal (I) to that of aromatic proton signal as internal standard (Io) are plotted. ■, sulpiride (**1**); ●, compound **12**.

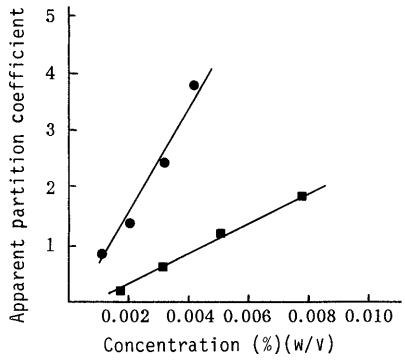



Fig. 2. Relationship between the Apparent Partition Coefficient and the Concentration in Water of Sulpiride (**1**) and Compound **12** after Partition Equilibrium

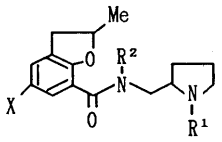
■, sulpiride (**1**); ●, compound **12**.

anhydrides derived from the carboxylic acids (method B).[7] The synthetic pathways for the carboxylic acids **3**—**10** and methyl ester **11** are shown in Chart 3. Treatment of the known 2,3-dihydrobenzofuran-7-carboxylic acid **2**[8] with $ClSO_3H$ provided the 5-chlorosulfonyl intermediate[9] which was converted to the corresponding sulfamoyl compounds **3**—**7** by amidation, to the methylsulfonyl compound **8** by reduction[10] with $Na_2SO_3$ followed by alkylation with MeI–$Na_2CO_3$, and to the thiol derivative **9** by another reduction[11] using Zn dust in $H_2O$–AcOH–$H_2SO_4$ followed by methylation (MeI–NaOH). Chemoselective oxidation[12] of compound **9** with $NaIO_4$ gave compound **10**. Esterification of **3** in MeOH–$H_2SO_4$ gave compound **11**. The 1-substituted 2-(aminomethyl)pyrrolidines excluding 1-isobutyl-2-(aminomethyl)pyrrolidine (**36**) were prepared according to the reported procedure.[13] The new amine **36** was obtained by reduction (Raney Ni/$H_2$ in MeOH) of the corresponding 2-(nitromethylene)pyrrolidine[14] derived in two steps from 2-pyrrolidone. All the synthesized dihydrobenzofurancarboxamides were a diastereomeric mixture since both the starting materials for the coupling reaction were used as racemates. The diastereomeric ratios ($\alpha/\beta$) of some compounds, the diastereomers of which were separable on high performance liquid chromatography (HPLC), were confirmed to be within a range of 0.9 to 1.1 ($\alpha$: shorter $t_R$ under the reversed phase condition, $\beta$: longer $t_R$ under the same condition).

**H-Bond Stability and Lipophilicity** To compare the H-bond stability between sulpiride (**1**) and compound **12**, the latter chosen as the representative of the 2,3-dihydrobenzofuran-7-carboxamides, $CD_3OD$-induced hydrogen to deuterium exchange studies were performed using proton nuclear magnetic resonance ($^1$H-NMR). The relative exchange rates were estimated from the time courses of reduction of the carboxamide proton signal(s) ($\delta = 8.36$ ppm in compound **1** and $\delta = 8.06$ and 8.12 ppm[15] in compound **12**) under the same conditions[16]: Immediately after mixing a solution (45 mM) of compound **1** or **12** in DMSO-$d_6$ (0.6 ml) with 20 $\mu$l of $CD_3OD$, the mixture was placed in the NMR probe and the temperature was maintained at $27 \pm 0.2$ °C. The time courses are depicted in Fig. 1. Also, to compare the lipophilicity between compounds **1** and **12**, the octanol–water partition coefficient of each was measured. The coefficient values of each at several concentrations are plotted in Fig. 2.

**Pharmacology** The biological activities of the synthesized dihydrobenzofurancarboxamides and sulpiride (**1**) were determined by examining inhibitory effects on apomorphine-induced hyperactivity in mice. The results are summarized in Table I ($ED_{50}$ mg/kg, *p.o.*). Some of the above active compounds (**15**—**17**, **22**, and **30**) were also tested for antagonistic activity on apomorphine-induced stereotype (gnawing behavior) in rats ($ED_{50}$ mg/kg, *p.o.*) and for potentiation of methamphetamine lethality in rats (rate of cumulative deaths at dosages of 5—20 mg/kg, i.p.).

TABLE I. Chemical and Pharmacological Data of *N*-[(2-Pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamides (**12**—**35**)



| Compd. No. | Substituent | | | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) | | | Inhibition of hyperactivity |
|---|---|---|---|---|---|---|---|---|---|---|
| | X | $R^1$ | $R^2$ | | | | C | H | N | $ED_{50}$ mg/kg *p.o.*[a] |
| **12** | $SO_2NH_2$ | Et | H | 62[b] | 167—169 (AcOEt) | $C_{17}H_{25}N_3O_4S$ | 55.57 (55.51) | 6.86 (6.74) | 11.44 (11.26) | 80 |
| **13** | $SO_2NH_2$ | Me | H | 32[c] | 187—189 (AcOEt) | $C_{16}H_{23}N_3O_4S$ | 54.37 (54.49) | 6.56 (6.52) | 11.89 (11.69) | 78 |
| **14** | $SO_2NH_2$ | Pr | H | 38[c] | 177—180 (MeOH–iso-PrOH) | $C_{18}H_{27}N_3O_4S$ | 56.67 (56.44) | 7.13 (7.11) | 11.01 (10.85) | 28 |
| **15** | $SO_2NH_2$ | Bu | H | 58[b] | 170—171 (AcOEt) | $C_{19}H_{29}N_3O_4S$ | 57.70 (57.64) | 7.39 (7.53) | 10.62 (10.68) | 30 |
| **16** | $SO_2NH_2$ | iso-Bu | H | 47[b] | 182—184 (MeOH) | $C_{19}H_{29}N_3O_4S$ | 57.70 (57.48) | 7.39 (7.38) | 10.62 (10.42) | 19 |
| **17** | $SO_2NH_2$ | $C_6H_5CH_2$ | H | 59[b] | 161—170 (iso-PrOH) | $C_{22}H_{27}N_3O_4S$ | 61.52 (61.62) | 6.34 (6.35) | 9.78 (9.76) | 6 |
| **18** | $SO_2NH_2$ | 4-$ClC_6H_4CH_2$ | H | 18[c] | 167—169 (MeOH) | $C_{22}H_{26}ClN_3O_4S$ | 56.95 (57.05) | 5.65 (5.68) | 9.06 (9.01) | 17 |
| **19** | $SO_2NH_2$ | 4-$FC_6H_4CH_2$ | H | 4[c] | 133—135 (iso-PrOH) | $C_{22}H_{26}FN_3O_4S$ | 56.05 (58.89) | 5.86 (5.86) | 9.38 (9.28) | 17 |
| **20** | $SO_2NH_2$ | $C_6H_5CH_2CH_2$ | H | 43[b] | 204—209 (MeOH) | $C_{23}H_{29}N_3O_4S$ | 62.28 (62.02) | 6.59 (6.47) | 9.47 (9.43) | >100 |
| **21** | $SO_2NH_2$ | Et | Me | 9[c] | 148—150 (iso-PrOH–AcOEt) | $C_{18}H_{27}N_3O_4S$ | 56.67 (56.71) | 7.13 (7.14) | 11.01 (10.85) | >100 |
| **22** | $SO_2NHMe$ | Et | H | 32[c] | 202—206 (iso-PrOH) | $C_{18}H_{27}N_3O_4S$ ·HCl | 51.73 (51.55) | 6.75 (6.64) | 10.05 (9.93) | 10 |
| **23** | $SO_2NHMe$ | Me | H | 44[c] | 132—135 (AcOEt) | $C_{17}H_{25}N_3O_4S$ | 55.57 (55.60) | 6.86 (7.06) | 11.44 (11.33) | 14 |
| **24** | $SO_2NHMe$ | Pr | H | 64[c] | 141—143 (AcOEt) | $C_{19}H_{29}N_3O_4S$ | 57.70 (57.56) | 7.39 (7.27) | 10.62 (10.49) | 11 |
| **25** | $SO_2NHMe$ | iso-Pr | H | 27[c] | 144—147 (AcOEt–ether) | $C_{19}H_{29}N_3O_4S$ | 57.70 (57.41) | 7.39 (7.34) | 10.62 (10.46) | 25 |
| **26** | $SO_2NHMe$ | iso-Bu | H | 48[c] | 168—172 (AcOEt–EtOH) | $C_{20}H_{31}N_3O_4S$ ·HCl | 53.86 (54.13) | 7.23 (7.47) | 9.42 (9.45) | 45 |
| **27** | $SO_2NMe_2$ | Et | H | 50[c] | 109—111 (AcOEt–iso-PrOH) | $C_{19}H_{29}N_3O_4S$ ·HCl | 52.83 (52.68) | 7.30 (7.25) | 9.73 (9.49) | 22 |
| **28** | $SO_2NHEt$ | Et | H | 49[c] | 102—105 (iso-PrOH–IPE)[d] | $C_{19}H_{29}N_3O_4S$ ·HCl | 52.83 (52.59) | 7.30 (7.14) | 9.73 (9.64) | 48 |
| **29** | $SO_2NHBu$ | Et | H | 81[c] | 150—152 (AcOEt) | $C_{21}H_{33}N_3O_4S$ | 59.55 (59.73) | 7.83 (7.94) | 9.92 (9.95) | 88 |
| **30** | SMe | Et | H | 32[c] | 145—150 (AcOEt–iso-PrOH) | $C_{18}H_{28}N_2O_2S$ ·HCl | 58.28 (58.13) | 7.34 (7.39) | 7.55 (7.48) | 0.65 |
| **31** | SMe | Pr | H | 63[c] | 160—162 (AcOEt–iso-PrOH) | $C_{19}H_{28}N_2O_2S$ ·$C_4H_4O_4$[e] | 59.46 (59.35) | 6.94 (6.97) | 6.03 (5.92) | 2.9 |
| **32** | SOMe | Et | H | 37[c] | 131—134 (AcOEt) | $C_{18}H_{26}N_2O_3S$ | 61.69 (61.42) | 7.48 (7.42) | 7.99 (8.01) | 1.9 |
| **33** | SOMe | Pr | H | 17[c] | 143—145 (AcOEt) | $C_{19}H_{28}N_2O_3S$ | 62.61 (62.66) | 7.74 (7.58) | 7.69 (7.74) | 1.0 |
| **34** | $SO_2Me$ | Et | H | 52[c] | 186—189 (AcOEt–iso-PrOH) | $C_{18}H_{26}N_2O_4S$ ·HCl | 53.66 (53.61) | 6.75 (6.76) | 6.95 (6.83) | 2.9 |
| **35** | $SO_2Me$ | Pr | H | 52[c] | 215—217 (MeOH–iso-PrOH) | $C_{19}H_{28}N_2O_4S$ ·HCl | 54.73 (54.59) | 7.01 (6.97) | 6.72 (6.92) | 1.4 |
| Sulpiride (**1**) | | | | | | | | | | 330 |
| Haloperidol | | | | | | | | | | 0.13 |

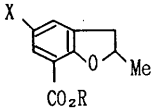
*a*) $ED_{50}$, the dose to reduce the activity counts to 50% of the control, was estimated according to the graphical interpolation. *b*) Method A. *c*) Method B. *d*) Diisopropyl ether. *e*) Fumaric acid.

This data is shown in Table III.

## Discussion

The $^1$H-NMR studies showed that the hydrogen to deuterium exchange rate of compound **12** was about twice as slow as that of sulpiride (**1**) (the half-life periods of **12** and **1** were about 10 and 5 min respectively, Fig. 1). This result indicates that the H-bond of compound **12** is more stabilized than that of compound **1**.[17] The measurements of the partition coefficient also proved that the values of

TABLE II. 2,3-Dihydrobenzofuran-7-carboxylic Acids (**3**—**11**)




| Comp. No. | X | R | Yield[a] (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **3** | $SO_2NH_2$ | H | 68.1 | 245—246 (MeOH) | $C_{10}H_{11}NO_5S$ | 46.69 (46.77 | 4.28 4.23 | 5.44 5.40) |
| **4** | $SO_2NMe_2$ | H | 82.5 | 181—183 ($MeOH-H_2O$) | $C_{12}H_{15}NO_5S$ | 50.52 (50.26 | 5.30 5.25 | 4.91 4.88) |
| **5** | $SO_2NHMe$ | H | 60.3 | 205—207 ($MeOH-H_2O$) | $C_{11}H_{13}NO_5S$ | 48.70 (48.62 | 4.83 4.86 | 5.16 5.08) |
| **6** | $SO_2NHEt$ | H | 71.3 | 194—196 ($MeOH-H_2O$) | $C_{12}H_{15}NO_5S$ | 50.52 (50.73 | 5.30 5.33 | 4.91 4.99) |
| **7** | $SO_2NHBu$ | H | 78.5 | 189—190 ($MeOH-H_2O$) | $C_{14}H_{19}NO_5S$ | 53.66 (53.95 | 6.11 6.12 | 4.47 4.44) |
| **8** | $SO_2Me$ | H | 32.8 | 256—257 ($MeOH-H_2O$) | $C_{11}H_{12}O_5S$ | 51.55 (51.50 | 4.72 4.78) | |
| **9** | SMe | H | 59.6 | 137—138 (iso-PrOH–$H_2O$) | $C_{11}H_{12}O_3S$ | 58.91 (58.83 | 5.39 5.42) | |
| **10** | SOMe | H | 43.5 | 175—177 (iso-PrOH) | $C_{11}H_{12}O_4S$ | 54.99 (54.90 | 5.03 5.13) | |
| **11** | $SO_2NH_2$ | Me | 55.8 | 191—193 (MeOH) | $C_{11}H_{13}NO_5S$ | 48.70 (48.45 | 4.83 4.85 | 5.16 5.18) |

*a*) Total yield from starting material **2**.

TABLE III. Pharmacological Data of 2,3-Dihydrobenzofuran-7-carboxamides (**15**—**17**, **22**, and **30**)

| Compd. No. | Inhibition of stereotype | Potentiation of toxicity[b] | | | | |
|---|---|---|---|---|---|---|
| | $ED_{50}$ mg/kg *p.o.*[a] | Dose (mg/kg, i.p.) | 1st | 2nd | 3rd | 4th |
| **15** | >100 | 5 | 1/8 | 3/8 | 4/8 | 7/8 |
| | | 10 | 1/8 | 1/8 | 3/8 | 6/8 |
| **16** | 60 | 5 | 0/8 | 0/8 | 1/8 | 2/8 |
| | (47—80) | 10 | 1/8 | 1/8 | 1/8 | 3/8 |
| **17** | 21 | 10 | 0/8 | 0/8 | 0/8 | 1/8 |
| | (13—32) | | | | | |
| **22** | >100 | 10 | 2/8 | 2/8 | 4/8 | 5/8 |
| | | 20 | 1/8 | 3/8 | 4/8 | 8/8 |
| **30** | 0.2 | — | — | — | — | — |
| | (0.16—0.26) | | | | | |
| Sulpiride (**1**) | >500 | 80 | 2/8 | 3/8 | 3/8 | 3/8 |

*a*) $ED_{50}$, the dose to inhibit induction of the stereotype in 50% of the rats, was estimated according to either the Probit method or the graphical interpolation; 95% confidence limits are included in parentheses. *b*) The tests were carried out 4 times at 1-week intervals. Each numerator indicates the cumulative number of the dead rats within each test session.

compound **12** were higher than those of compound **1** at any concentration.[18] This suggests that compound **12** is more lipophilic than sulpiride (**1**). As anticipated in the introduction, the replacement of the *o*-methoxybenzamide nucleus with the 2,3-dihydrobenzofuran-7-carboxamide moiety resulted in the stabilization of the H-bond and the enhancement of lipophilicity. Consequently, both ameliorations brought about a great increase in the potency with improvement in the bioavailability. Indeed, compound **12** was about 4 times more potent than sulpiride (**1**) in its inhibition of apomorphine-induced hyperactivity in mice ($ED_{50}$ of **12** = 80 mg/kg, *p.o.*).

The inhibitory potency of compound **12** was further improved by variations of substituents X and $R^1$ (Table I). The structure–activity relationships are as follows. When X is a $SO_2NH_2$ group and $R^2$ is a hydrogen atom (compounds **12**—**20**), replacement of the *N*-substituent ($R^1$) with longer alkyl or aralkyl groups (excluding phenethyl) results in an increase in the potency. For example, butyl, isobutyl, and benzyl substituted compounds **15**, **16**, and **17** were respectively, 2.7, 4, and 13 times more potent than the ethyl compound **12**. However, halogenation at the *para* position of the benzyl substituent, such as compounds **18** and **19**, induced a decrease in the potency. Also, compound **21**, in which the H-bond was not present by methylation of the amide moiety, was inactive. The latter fact substantiates the theory that the H-bond plays an important role in the inhibitory activity. On the other hand, alkylations of the sulfamoyl group (X) increased the potency of the former compounds (**12** *vs.* **22**, **27**, **28**; **13** *vs.* **23**; and **14** *vs.* **24**) although there was less improvement as the alkyl group or the substituent $R^1$ became more bulky. In the cases of compounds **26** and **29**, the potencies were lower than the former compounds **16** and **12**, respectively.

Replacement of the sulfamoyl substituent with a MeS, MeSO, or $MeSO_2$ group at the same position brought a further prominent increase of activity. Compound **30** was about 120 times as potent as compound **12** and the most active in this series ($ED_{50}$ of **30** = 0.65 mg/kg, *p.o.*). This potency was comparable to that of haloperidol ($ED_{50}$ = 0.13 mg/kg, *p.o.*). The potency was not further enhanced by incorporation of one or two oxygen atoms at the MeS substituent nor by change of the ethyl group ($R^1$) for a

propyl. From the above discussion, five compounds, **15**, **16**, **17**, **22**, and **30**, having a different combination of substituents with a high potency in blocking the hyperactivity, were chosen for the following evaluations which characterize the atypical properties of sulpiride.

Among the five compounds chosen, two compounds **15** and **22** lacked potency in inhibition of apomorphine-induced stereotype as did sulpiride (**1**) ($ED_{50}$s of **15** and **22** are $>100$ mg/kg, *p.o.* as shown in Table III). Thus, the inhibitory effect on the stereotype was separated from that on the hyperactivity in the two compounds. As thought in the case of sulpiride,[3f,g] the separation may be due to the specific action of the compounds on the *meso*-limbic dopamine (DA) system rather than the nigro-striatal DA system. The separation indicates that the two compounds are free from the EPS and possess the atypical properties of sulpiride.[19] In addition, the two compounds (**15** and **22**) exhibited a potent activity in potentiation of methamphetamine-induced lethality. The minimum effective dose (MED) of compound **15** was the lower of the two and considerably lower than that of sulpiride (**1**) as seen in Table III (MEDs of **15** and **1** are 5 and 80 mg/kg, i.p., respectively). From this result, it can be also expected that compound **15** produces antidepressant-like effects similar to those of sulpiride. In contrast to the two compounds **15** and **22**, the remaining compounds **16**, **17**, and **30** exhibited an inhibitory effect on the stereotype. In particular, the inhibitory activity of compound **30** was very potent ($ED_{50}=0.2$ mg/kg, *p.o.*). This compound, having potent inhibitory effects both on the stereotype and the hyperactivity, may be better classified as a classical neuroleptic such as haloperidol. In the cases of compounds **16** and **17**, comparison with compounds **15** and **22** allowed us to find an interesting relationship between the antagonistic activity in the stereotype and the methamphetamine potentiation activity. The order of the antagonistic activity was **17**$>$**16**$\gg$**15** and **22**, whereas that of the potentiation activity was **15**$>$**22**$>$**16**$>$**17**. This indicates that the inhibitory effect on the stereotype is inversely related to the potency in the methamphetamine potentiation activity.

In conclusion, compound **15**, which possesses a potent antipsychotic activity accompanied with atypical properties and antidepressant characteristics, was selected as a candidate for clinical trial. In addition, compound **30** was also found to be a classical neuroleptic with a strong potency. Finally, it should be noted that the separation of the four stereoisomers presented by compound **15** and the stereochemistry–activity relationships of them are now under investigation.

## Experimental

Melting points were determined in open capillaries and are uncorrected. $^1$H-NMR spectra were recorded on a JEOL PS-100 spectrometer unless otherwise stated and the chemical shifts are expressed in ppm, with tetramethylsilane as the internal standard. Infrared (IR) spectra were recorded on a JASCO IR-810 instrument. Low-resolution mass spectra (MS) were obtained by a JMS-O1SG spectrometer. HPLC was performed on a Shimadzu LC-6A chromatographic system with a Shimadzu ultraviolet (UV) spectrophotometric detector SPD-6A, using a reversed-phase column, YMC-pack ODS-A (5 $\mu$m, 15 cm $\times$ 6 mm i.d., YMC) unless otherwise indicated. Elemental analyses and measurement of these spectra data were performed by the instrumental analysis-section in the central research laboratory of Yoshitomi Pharmaceutical Industries Ltd., Fukuoka, Japan.

**Materials** Sulpiride (**1**) was synthesized by the method of Justin-Besancon *et al.*[20] 2-Methyl-2,3-dihydrobenzofuran-7-carboxylic acid (**2**) was prepared by the method of Okumura and Inoue.[8]

**Preparation of 2,3-Dihydrobenzofuran-7-carboxylic Acids 3—7. 2-Methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxylic Acid (3) and Its Methyl Ester (11)** 2-Methyl-2,3-dihydrobenzofuran-7-carboxylic acid (**2**, 50.0 g, 0.281 mol) was added by portions to 140 ml of $ClSO_3H$ at 0 °C while being stirred. The mixture was warmed and stirred at room temperature for 8 h, allowed to stand overnight, and then poured by portions into ice-water (1.5 l). The resulting precipitate was collected, washed with cold water, and poured into 200 ml of 28% $NH_4OH$ at 0 °C. After being stirred for 0.5 h at room temperature, the mixture was acidified with conc. HCl at 0 °C. The precipitate was collected, washed with water, and recrystallized from MeOH to give 49.2 g (68.1%) of **3**. IR (KBr): 3260, 1705 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.43 (3H, d, $J=6$ Hz, $CH_3$), 2.85 (1H, dd, $J=7$, 16 Hz), 3.42 (1H, dd, $J=9$, 16 Hz), 5.09 (1H, m), 7.25 (2H, br s, $NH_2$), 7.78 (1H, d, $J=2$ Hz, ArH), 8.07 (1H, d, $J=2$ Hz, ArH). MS *m/z*: 257 ($M^+$).

A mixture of **3** (49.2 g, 0.191 mol), conc. $H_2SO_4$ (4.9 ml), and MeOH (740 ml) was refluxed for 16 h while being stirred. After cooling to 0 °C, the precipitate was collected, washed with cold MeOH, and recrystallized from MeOH to yield 42.5 g (55.8% from **2**) of **11**. IR (KBr): 3300, 3260, 1705 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.43 (3H, d, $J=6$ Hz, $CH_3$), 2.87 (1H, dd, $J=7$, 16 Hz), 3.42 (1H, dd, $J=9$, 16 Hz), 3.83 (3H, s, $OCH_3$), 5.17 (1H, m), 7.28 (2H, br s, $NH_2$), 7.81 (1H, d, $J=2$ Hz, ArH), 8.09 (1H, d, $J=2$ Hz, ArH). MS *m/z*: 271 ($M^+$).

The other 2,3-dihydrobenzo-7-carboxylic acids, **4**—**7**, were prepared by replacement of $NH_4OH$ with the corresponding amine in the same manner as described for **3**.

**2-Methyl-5-methylsulfonyl-2,3-dihydrobenzofuran-7-carboxylic Acid (8)** Chlorosulfonation of **2** (43.0 g, 0.242 mol) with $ClSO_3H$ (120 ml) was carried out in a similar procedure to that described above. After soaking in 1.2 l of ice-water, the precipitate was collected and washed with cold water. The crude product was added by portions to a stirred mixture of $Na_2SO_3$ (53 g, 0.5 mol), $NaHCO_3$ (53 g, 0.63 mol), and $H_2O$ (100 ml) over 0.5 h at 0 °C. The mixture was heated to about 80 °C for 1.5 h. After chilling to 0 °C, the mixture was acidified with conc. HCl. The precipitate was collected and immediately dissolved in 200 ml of $H_2O$. The solution was made basic with $Na_2CO_3$ and followed by addition of EtOH (200 ml) and MeI (30.0 g, 0.211 mol). The mixture was refluxed for 2 h. After removal of EtOH by evaporation under reduced pressure the residue was acidified with conc. HCl at 0 °C. The precipitate was collected, washed with cold water, and recrystallized from 10% aqueous MeOH to afford 20.3 g (32.8%) of **8**. IR (KBr): 1705, 1680 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.44 (3H, d, $J=7$ Hz, $CH_3$), 2.86 (1H, dd, $J=8$, 16 Hz), 3.18 (3H, s, $SO_2CH_3$), 3.44 (1H, dd, $J=8$, 16 Hz), 5.15 (1H, ddd, $J=7$, 8, 8 Hz), 7.89 (1H, d, $J=2$ Hz, ArH), 8.09 (1H, d, $J=2$ Hz, ArH). MS *m/z*: 256 ($M^+$).

**2-Methyl-5-methylthio-2,3-dihydrobenzofuran-7-carboxylic Acid (9)** Treatment of **2** (40.0 g, 0.225 mol) with $ClSO_3H$ (120 ml) by a procedure similar to that described above gave a crude powder which was added to a solution of $H_2O$ (400 ml), AcOH (300 ml), and $H_2SO_4$ (128 ml). After addition of Zn (dust, 120 g) over 15 min at $-10$ °C, the mixture was stirred at room temperature for 1 h, and was then heated to 50 °C until it ceased bubbling. The mixture was refluxed for 3 h while being stirred. After filtration, the solution was extracted three times with AcOEt. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The obtained solid was washed with water, collected, and added to a solution of MeOH (250 ml) and $H_2O$ (200 ml). To the stirred mixture was added dropwise a solution of NaOH (24.5 g, 0.613 mol) in $H_2O$ (70 ml) at 0 °C, and followed by MeI (43.0 g, 0.303 mol). After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo* at 30 °C. The resulting solution was acidified with conc. HCl to give a precipitate which was collected and washed with water. The crude product was recrystallized from 50% aqueous iso-PrOH to afford 30.0 g (59.6%) of **9**. IR (KBr): 1685 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.39 (3H, d, $J=6$ Hz, $CH_3$), 2.43 (3H, s, $SCH_3$), 2.77 (1H, dd, $J=8$, 16 Hz), 3.33 (1H, dd, $J=9$, 16 Hz), 4.99 (1H, m), 7.38 (1H, d, $J=2$ Hz, ArH), 7.46 (1H, d, $J=2$ Hz, ArH). MS *m/z*: 224 ($M^+$).

**2-Methyl-5-methylsulfinyl-2,3-dihydrobenzofuran-7-carboxylic Acid (10)** To a stirred solution of **9** (15.0 g, 0.067 mol) in MeOH (250 ml) was added dropwise a solution of $NaIO_4$ (15.0 g, 0.0701 mol) in $H_2O$ (130 ml) at 0 °C over 0.5 h. The mixture was stirred at room temperature for 2 h. After filtration, MeOH was evaporated *in vacuo*. The resulting solution was saturated with NaCl and extracted three times with $CHCl_3$. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed *in*

*vacuo*. The resulting solid was recrystallized from iso-PrOH to yield 11.8 g (73.3%) of **10**. IR (KBr): 1570 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.44 (3H, d, $J$=6 Hz, $CH_3$), 2.7 (3H, s, $SOCH_3$), 2.86 (1H, dd, $J$=8, 16 Hz), 3.43 (1H, dd, $J$=8, 16 Hz), 5.11 (1H, m), 7.22 (1H, d, $J$=2 Hz, ArH), 7.88 (1H, d, $J$=2 Hz, ArH). MS $m/z$: 240 ($M^+$).

**Method A**[6] ***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide (12)** A mixture of **11** (11.9 g, 43.9 mmol), 2-aminomethyl-1-ethylpyrrolidine (8.40 g, 65.6 mmol), and diethylene glycol (70 ml) was heated to 120 °C while being stirred for 20 h. After cooling to room temperature, the solution was poured into water (500 ml). The resulting precipitate was collected by filtration, washed with water, dried, and then recrystallized from AcOEt to give 10 g (62%) of **12**. The diastereomeric ratio ($\alpha/\beta$) was determined to be 0.9 by HPLC [pH 7.8 buffer (0.05 M $Na_2HPO_4/H_3PO_4$) : MeCN : tetrahydrofuran (THF) = 24 : 3 : 1)]. IR (KBr): 1640 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.12 (3H, t, $J$= 7 Hz, $CH_3$), 1.4—1.9 (4H), 1.55 (3H, d, $J$=6 Hz, $CH_3$), 1.9—3.8 (9H), 5.0—5.5 (3H), 7.83 (1H, d, $J$=2 Hz, ArH), 7.9—8.3 (1H, br, CONH), 8.53 (1H, d, $J$=2 Hz, ArH). MS $m/z$: 367 ($M^+$).

***N*-[(1-Butyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide (15)** This compound was synthesized starting from **11** (4.4 g, 16 mmol) as described for **12**, except for replacement of 2-aminomethyl-1-ethylpyrrolidine with 2-aminomethyl-1-butylpyrrolidine (3.3 g, 21 mmol). Yield, 3.7 g (58%). The $\alpha/\beta$ ratio was determined to be 0.98 by HPLC [pH 7.8 buffer (0.05 M $Na_2HPO_4/H_3PO_4$) : MeCN : THF = 14 : 5 : 1]. IR (KBr): 1640 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.89 (3H, $CH_3$), 1.2—2.4 (10H), 1.55 (3H, d, $J$=6 Hz, $CH_3$), 2.4—3.9 (7H), 5.0—5.6 (3H), 7.83 (1H, d, $J$=2 Hz, ArH), 7.9—8.3 (1H, br, CONH), 8.54 (1H, d, $J$=2 Hz, ArH). MS $m/z$: 396 ($M^+ + 1$).

Compounds **16**, **17**, and **20** were synthesized by a similar procedure to that described above.

**Method B**[7] ***N*-[(1-Propyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide (14)** $ClCO_2Et$ (2.3 g, 21 mmol) was added dropwise to a stirred mixture of **2** (5.00 g, 19.5 mmol), $Et_3N$ (3.3 ml, 24 mmol), acetone (50 ml), and dimethylformamide (DMF) (50 ml) at 10 °C. The mixture was stirred at 10 °C for 0.5 h and then at room temperature for 1 h. To it was added a mixture of 2-aminomethyl-1-propylpyrrolidine (3.60 g, 25.4 mmol) and $Et_3N$ (3.3 ml, 24 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was diluted with water (50 ml) and $Et_3N$ (4 ml) to give a precipitate which was collected and washed with water. The crude product was recrystallized from iso-PrOH–MeOH (1 : 1) to yield 2.8 g (38%) of **14**. IR (KBr): 3350, 3200, 1640 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.92 (3H, t, $J$=7 Hz, $CH_3$), 1.3—2.4 (8H), 1.54 (3H, d, $J$=6 Hz, $CH_3$), 2.4—3.9 (7H), 4.9—5.8 (3H), 7.83 (1H, d, $J$=2 Hz, ArH), 7.9—8.3 (1H, br, CONH), 8.53 (1H, d, $J$=2 Hz, ArH). MS $m/z$: 381 ($M^+$).

Compounds **13**, **18**—**21**, **23**—**25**, and **29** were prepared in a similar manner as described above.

***N*-[(1-Isobutyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylsulfamoyl-2,3-dihydrobenzofuran-7-carboxamide Hydrochloride (26)** A reaction of **5** (5.00 g, 18.5 mmol) with 2-aminomethyl-1-isobutylpyrrolidine (**36**, 3.20 g, 20.5 mmol) was carried out in a similar way to that described for **14** [DMF, 50 ml; acetone, 50 ml; $Et_3N$, 6.2 ml (45 mmol); $ClCO_2Et$, 2.10 g (19.4 mmol)]. After removal of acetone by evaporation, the residual mixture was diluted with 10% $NaHCO_3$ (100 ml) and then extracted three times with $CHCl_3$. The extracts were washed with water and dried over anhydrous $MgSO_4$. Blowing with HCl gas and then evaporation of the solvent gave a crude oil which was crystallized from AcOEt–EtOH (40 ml–10 ml) to afford 3.9 g (48%) of **26**. IR (KBr): 3375, 1655 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.97 (6H, t, $J$=6 Hz, $CH_3$), 1.53 (3H, d, $J$=6 Hz, $CH_3$), 1.7—2.2 (5H), 2.39 (3H, d, $J$=5 Hz, $NHCH_3$), 2.7—4.0 (9H), 5.16 (1H, m), 7.41 (1H, $SO_2NH$), 7.76 (1H, ArH), 8.05 (1H, ArH), 8.54 (1H, CONH), 10.19 (1H, br). MS $m/z$: 410 ($M^+ - HCl$).

Compounds **22**, **27**, and **28** were prepared in a similar way to that described above.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylthio-2,3-dihydrobenzofuran-7-carboxamide Hydrochloride (30)** A reaction of **9** (4.6 g, 21 mmol) with 2-aminomethyl-1-ethylpyrrolidine (3.4 g, 27 mmol) was carried out and treated in a similar manner to that described for **26** [acetone, 50 ml; $Et_3N$, 6.9 ml (50 mmol); $ClCO_2Et$, 2.7 g (25 mmol); recrystallization from AcOEt–iso-PrOH] to give 2.4 g (32%) of **30**. IR (KBr): 1650 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.26 (3H, t, $J$=7 Hz, $CH_3$), 1.48 (3H, d, $J$=6 Hz, $CH_3$), 1.6—2.3 (4H), 2.44 (3H, s, $SCH_3$), 2.6—3.9 (9H), 5.06 (1H, m), 7.38 (1H, ArH), 7.50 (1H, ArH), 8.34 (1H, br, CONH). MS $m/z$: 334 ($M^+ - HCl$).

***N*-[(1-Propyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylthio-2,3-dihydrobenzofuran-7-carboxamide Fumarate (31)** A reaction of **9** (6.00 g, 26.8 mmol) with 2-aminomethyl-1-*n*-propylpyrrolidine (4.20 g, 29.6 mmol) was carried out in a similar manner to that described for **30** [acetone, 100 ml; $Et_3N$, 9.4 ml (67 mmol); $ClCO_2Et$, 3.1 g (29 mmol)]. After evaporation of the solvent *in vacuo*, the residue was diluted with 10% $NaHCO_3$ and extracted three times with AcOEt. The combined extract was washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent by evaporation, the residue was dissolved in a solution of fumaric acid (2.90 g, 25.0 mmol) in iso-PrOH (50 ml). The crystallization by addition of AcOEt (100 ml) gave 7.8 g (63%) of **31**. The $\alpha/\beta$ ratio was determined to be 1.1 by HPLC [pH 7.8 buffer (0.05 M $Na_2HPO_4/H_3PO_4$) : MeCN : THF = 12 : 7 : 1]. IR (KBr): 1650 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.87 (3H, t, $J$=7 Hz, $CH_3$), 1.43 (3H, d, $J$=6 Hz, $CH_3$), 1.4—2.1 (6H), 2.44 (3H, s, $SCH_3$), 2.6—3.1 (4H), 3.1—3.7 (5H), 5.04 (1H, m), 6.58 (2H, s), 7.35 (1H, d, $J$=2 Hz, ArH), 7.54 (1H, d, $J$=2 Hz, ArH), 8.06 (1H, br, CONH). MS $m/z$: 348 ($M^+ - C_4H_4O_4$).

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylsulfinyl-2,3-dihydrobenzofuran-7-carboxamide (32)** This compound was synthesized in a similar manner to that described for **14** starting from **10** (5.0 g, 21 mmol) and 2-aminomethyl-1-ethylpyrrolidine (3.0 g, 23 mmol). Yield, 2.7 g (37%). IR (KBr): 3355, 1645 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.13 (3H, t, $J$=7 Hz, $CH_3$), 1.4—3.9 (13H), 1.57 (3H, d, $J$=6 Hz, $CH_3$), 2.70 (3H, s, $SOCH_3$), 5.19 (1H, m), 7.81 (1H, ArH), 8.0—8.3 (1H, br, CONH), 8.06 (1H, ArH). MS $m/z$: 350 ($M^+$).

Compound **33** was prepared in a similar manner to that described above.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-methylsulfonyl-2,3-dihydrobenzofuran-7-carboxamide Hydrochloride (34)** A reaction of **8** (5.0 g, 19.5 mmol) with 2-aminomethyl-1-ethylpyrrolidine (3.0 g, 23.4 mmol) was carried out and worked up by a similar procedure to that described for **26** [DMF, 40 ml; acetone, 20 ml; $Et_3N$, 6.6 ml (47.3 mmol); $ClCO_2Et$, 2.2 g (20.3 mmol); recrystallization from AcOEt–iso-PrOH] to give 4.1 g (52%) of **34**. IR (KBr): 1655 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.28 (3H, t, $J$=7 Hz, $CH_3$), 1.54 (3H, d, $J$=6 Hz, $CH_3$), 1.6—3.9 (13H), 3.19 (3H, s, $SO_2CH_3$), 5.1—5.4 (1H), 7.91 (1H, d, $J$=2 Hz, ArH), 8.15 (1H, d, $J$=2 Hz, ArH), 8.5—8.7 (1H, br, CONH). MS $m/z$: 366 ($M^+ - HCl$).

Compound **35** was prepared in the same manner as described above.

**2-Aminomethyl-1-isobutylpyrrolidine (36)** To a refluxing suspension of KOH (72 g, 1.3 mol) and $Bu_4N^+Br^-$ (2.0 g, 6.2 mmol) in toluene (500 ml) was added dropwise a solution of 2-pyrrolidone (100 g, 1.18 mol) and isobutylbromide (210 g, 1.53 mol) in toluene (100 ml) over 1 h. The water formed during the reaction was removed by azeotropic distillation for 7 h. After cooling and filtration, the filtrate was washed with a half-saturated NaCl aqueous solution (400 ml). Removal of the solvent *in vacuo* gave a crude oil, 120 g (72%). The crude 1-isobutyl-2-pyrrolidone (120 g, 0.851 mol) was reacted with $Me_2SO_4$ (118 g, 0.937 mol) at 70 °C for 2 h. A 28% NaOMe–MeOH solution (181 g, 0.94 mol of NaOMe) and MeOH (100 ml) was added dropwise to the mixture at 0 °C over a period of 0.5 h. After stirring for 0.5 h at room temperature, $MeNO_2$ (57.1 g, 0.936 mol) was added dropwise at 0 °C. The solution was stirred at room temperature for 5 h and was then poured into stirred ice-water (2 l). The obtained precipitate was collected, washed with water, and dried to yield 84 g (54%) of crude nitromethylene compound. After reduction of this compound (84 g, 0.46 mol) in MeOH (580 ml) with Raney-Ni (NDHT-90, *ca.* 17 g) and $H_2$ (4 equimolar amounts) in an autoclave at 60—70 °C, the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was distilled to give the amine **36** (54.6 g, 76.7%), bp 167—170 °C (760 mmHg). *Anal.* Calcd for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 68.89; H, 12.84; N, 17.85. $^1$H-NMR ($CDCl_3$) $\delta$: 0.84—0.96 (6H, $2CH_3$), 1.24 (2H, s, $NH_2$), 1.50—1.90 (5H), 1.90—2.44 (4H), 2.50—2.84 (2H), 3.1 (1H, m). MS $m/z$: 156 ($M^+$).

**Hydrogen to Deuterium Exchange Studies** $^1$H-NMR spectra were measured on a JEOL GSX-400 spectrometer. Each of sulpiride (**1**) (9.2 mg, 0.027 mmol) and compound **12** (10.0 mg, 0.027 mmol) was dissolved in 0.6 ml of DMSO-$d_6$. To each of the solutions was added 20 $\mu$l (0.56 mmol) of $CD_3OD$. Immediately after being mixed in a NMR tube (10 s), the sample was placed in the probe, the temperature of which was controlled at 27 ± 0.2 °C. Starting at the beginning of mixing, spectra of eight scans each were taken every 5 min over 15—20 min time period. The time courses are plotted in Fig. 1.

**Measurements of the Octanol–Water Partition Coefficients** Aqueous solutions (10 ml) of 0.002 to 0.02% (w/v) sulpiride (**1**) or compound **12** in glass-stoppered tubes were mechanically shaken with an equal volume (10 ml) of *n*-octanol at *ca.* 25 °C for 30 min. After centrifugation, the concentrations of each compound in both phases were determined by HPLC. The HPLC conditions are as follows. Apparatus: A Hewlett

Packard HP-1090 system equipped with a Shimadzu UV spectrophotometric detector SPD-6A monitoring at 254 nm, and Shimadzu chromatopac C-R3A, was used. Mobile phase: 0.1 M ammonium acetate buffer (pH 6)–MeCN (3 : 2). Flow rate: 0.8 ml/min. Stationary phase: Nucleosil $7C_{18}$ (7 $\mu$m, 25 cm × 4.0 mm i.d., Macherey-Nagel). The partition coefficients at several concentrations are plotted in Fig. 2.

**Inhibition of Apomorphine-Induced Hyperactivity in Mice**[19] Motor activity was measured with Animex (FARAD Instruments, Sweden) in groups of 5 male mice. Apomorphine hydrochloride (0.5 mg/kg) was injected subcutaneously 1 h after the oral administration of test compounds. The motor activity was measured for 20 min immediately after the apomorphine injection.

**Inhibition of Apomorphine-Induced Stereotype in Rats**[21] Groups of 7 female rats were observed in individual cages. A dose of 1.25 mg/kg of apomorphine hydrochloride was injected intravenously into each of the rats 1 h after the oral administration of the test compounds. Inhibitory effects of the compounds on stereotype were judged to be positive unless gnawing behavior was observed for 5 min at 5 min and 20 min after the apomorphine injection.

**Potentiation of Methamphetamine Lethality in Rats**[19] Groups of 8 male rats weighing 420—550 g were used. Each rat was individually housed in commercially available cages. Methamphetamine hydrochloride (5 mg/kg) was injected intraperitoneally 15 min after the intraperitoneal injection of each test compound. The number of animals which died within 1 week was recorded. The combination treatment of the test compound with methamphetamine was repeated 4 times at 1-week intervals to the same animals.

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