Antidopaminergic Effects of the Stereoisomers of *N*-[(1-Alkyl-2-pyrrolidinyl)methyl]-5-sulfamoylbenzamides and -2,3-dihydrobenzofuran-7-carboxamides

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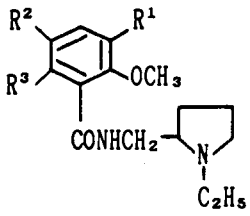
The stereoisomers of some *N*-[(1-alkyl-2-pyrrolidinyl)methyl]-5-sulfamoylbenzamides (**3–8**) and -2,3-dihydrobenzofuran-7-carboxamides (**9–18**) were prepared to compare their dopamine D_2 receptor binding affinities (in vitro) and inhibitory effects on apomorphine-induced hyperactivity (in vivo). In the 1-ethyl substituted compounds of the two series, the stereoisomers with *S* absolute configuration at the 2-position of the pyrrolidine moiety (*S* enantiomer **3** and 2*S* diastereomers **9** and **10**) were more potent in both of the above activities than those with *R* absolute configuration (*R* enantiomer **4** and 2*R* diastereomers **11** and **12**, respectively), whereas the *R* enantiomer (**8**) was more potent than the *S* enantiomer (**7**) in the 1-*n*-hexyl-substituted-benzamides and the 2*R* diastereomers (**15**, **16**, and **18**) were more potent than the 2*S* diastereomers (**13**, **14**, and **17**) in the 1-*n*-butyl- and 1-*n*-hexyl-2,3-dihydrobenzofuran-7-carboxamides. It was found that the stereospecificity of the compound activities altered from the *S* configuration to the *R* configuration as the 1-alkyl side chain became longer in the two series. How these stereoisomers meet the configurational requirements to interact with the dopamine D_2 receptors is also discussed.

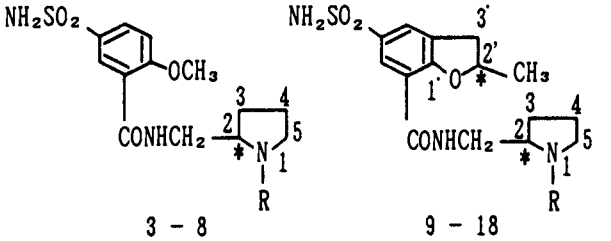
The *N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides, for example, sulpiride (**1**),[1] sultopride,[2] raclopride,[3] and remoxipride (Chart I),[4] have been developed as potential antipsychotics with selectivity for dopamine D_2 receptors. These benzamides have an asymmetric center of the 2-position of the pyrrolidine ring. Recent studies on these benzamides have suggested that they exhibit stereospecificity, with the *S* enantiomer being more potent than the *R* enantiomer in their D_2 receptor binding affinity and in their inhibition of apomorphine-induced hyperactivity and/or stereotypy.[4,5] However, our results on our newly synthesized analogues of sulpiride were inconsistent with this proposal.[6] Thus, we reported in a previous paper[7] that *N*-[(1-butyl-2-pyrrolidinyl)methyl]-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide (**2**) showed an atypical antipsychotic profile similer to that of sulpiride (**1**) and was a more potent neuroleptic than **1**. The four stereoisomers of **2** were recently separated and the diastereomers with *R* absolute configuration at the 2-position of the pyrrolidine ring were more potent than those with *S* configuration in the above antipsychotic screens. This finding

Chart I



sulpiride (1), $R^1 = R^3 = H$; $R^2 = SO_2NH_2$
sultopride, $R^1 = R^3 = H$; $R^2 = SO_2C_2H_5$
raclopride, $R^1 = R^2 = Cl$; $R^3 = OH$
remoxipride (S-enantiomer), $R^1 = H$; $R^2 = Br$; $R^3 = OCH_3$

Chart II



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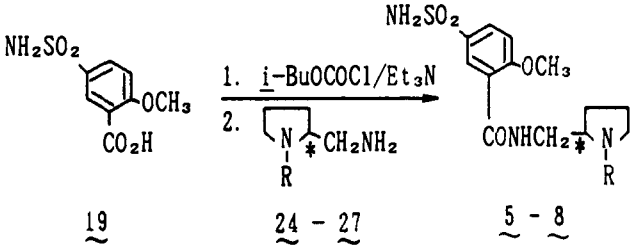
Scheme I



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(6) Data similar to our findings had been reported by the following patents which claimed stereospecificity of the 1-*p*-fluorobenzyl-substituted benzamide in its inhibition of apomorphine-induced stereotypy, but that its stereospecificity was contrary to that of the 1-ethyl-substituted benzamides was not discussed. (a) Kaplan, J. P.; Najer, H.; Obitz, D. C. L. Ger. Offen. 2735036, 1978; *Chem. Abstr.* **1978**, *88*, 152414. (b) Kaplan, J. P.; Raizon, B. M.; Obitz, D. C. L.; Manoury, P. M. J.; Najer, H.; Jalfre, M.; Giudicelli, P. R. L. Fr. Patent 2331345, 1977; *Chem. Abstr.* **1978**, *88*, 89515.
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Table I. Chemical Data of *N*-[(1-Alkyl-2-pyrrolidinyl)methyl]benzamides (5–8)

compd	R	isomer	% yield	mp, °C	recrystn solvent[a]	$[\alpha]^{24}_D$ (c 1.0, DMF), deg	formula	anal.
5	n-C_4H_9	*S*	51	130–132	IPA/IPE	−79.1	$C_{17}H_{27}N_3O_4S$	C, H, N
6	n-C_4H_9	*R*	49	130–132	IPA/IPE	+82.0	$C_{17}H_{27}N_3O_4S$	C, H, N
7	n-C_6H_{13}	*S*	57	139–142	IPA/IPE	−75.0	$C_{19}H_{31}N_3O_4S$	C, H, N
8	n-C_6H_{13}	*R*	60	139–142	IPA/IPE	+74.5	$C_{19}H_{31}N_3O_4S$	C, H, N

[a] IPA = 2-propanol; IPE = Diisopropyl ether.

Table II. 1-Alkyl-2-(aminomethyl)pyrrolidines

compd	R	isomer	$[\alpha]^{24}_D$ (c. 1.0, MeOH), deg
22	C_2H_5	*S*	−105[a]
23	C_2H_5	*R*	+108
24	n-C_4H_9	*S*	−99.2
25	n-C_4H_9	*R*	+103
26	n-C_6H_{13}	*S*	−85.4
27	n-C_6H_{13}	*R*	+86.7

[a] According to ref 5b, $[\alpha]^{20}_D$ = −75.0° (c 2.0, DMF).

led us to synthesize the stereoisomers of some *N*-[(1-alkyl-2-pyrrolidinyl)methyl]-5-sulfamoylbenzamides (**3–8**) and -2,3-dihydrobenzofuran-7-carboxamides (**9–18**) (Chart II) in order to obtain further information.

We will herein report the synthesis and antidopaminergic effects of these stereoisomers.

Chemistry

The enantiomers of the benzamides (**5–8**) presented in Table I were prepared by a coupling reaction of the known 2-methoxy-5-sulfamoylbenzoic acid (**19**) with the enantiomers of the 1-alkyl-2-(aminomethyl)pyrrolidines (**24–27**) listed in Table II. The enantiomers (**3** and **4**) of sulpiride were synthesized in a manner similar to the procedure reported.[5b] The stereoisomers of the 2,3-dihydrobenzofuran-7-carboxamides (**9–18**) in Table III were prepared by coupling the enantiomers of 2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxylic acid[7a] (**20**, *S* enantiomer; **21**, *R* enantiomer) with those of 2-(aminomethyl)-1-ethylpyrrolidine[5b] (**22**, *S* enantiomer; **23**, *R* enantiomer) or the above resolved amines **24–27**. The coupling reaction was performed by a mixed-anhydride method (Scheme I and II). The starting *S* and *R* enantiomers of 2,3-dihydrobenzofuran-7-carboxylic acid (**20** and **21**) were obtained by optical resolution of their salts of cinchonidine and cinchonine, respectively. The absolute configuration of **21** was determined to be *R* on the basis of the X-ray data of its cinchonine salt.[8] This determination also proved

Scheme II

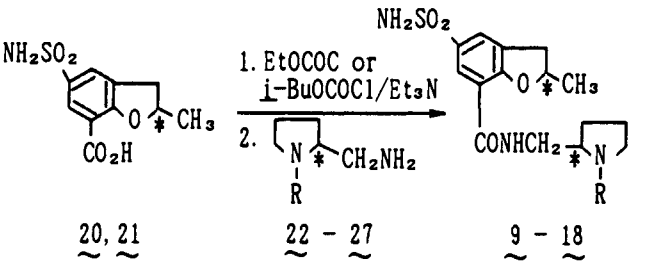

Table III. Chemical Data of *N*-[(1-Alkyl-2-pyrrolidinyl)methyl]dihydrobenzofurancarboxamides (9–18)

compd	R	isomer: amine[a]	isomer: furan[b]	% yield	mp, °C	$[\alpha]^{24}_D$ (c 1.0, DMF), deg	recrystn solvent[c]	formula	anal.
9	C_2H_5	*S*	*S*	49	155–156	−64.7	AcOEt	$C_{17}H_{25}N_3O_4S$	C, H, N
10	C_2H_5	*S*	*R*	54	164–165	−50.8	AcOEt	$C_{17}H_{25}N_3O_4S$	C, H, N
11	C_2H_5	*R*	*S*	46	163–164	+50.8	AcOEt	$C_{17}H_{25}N_3O_4S$	C, H, N
12	C_2H_5	*R*	*R*	35	156–157	+64.6	AcOEt	$C_{17}H_{25}N_3O_4S$	C, H, N
13	n-C_4H_9	*S*	*S*	40	214–216	−2.0	H_2O/acetone	$C_{19}H_{29}N_3O_4S$·HCl	C, H, N
14	n-C_4H_9	*S*	*R*	32	222–225	−5.2	H_2O/acetone	$C_{19}H_{29}N_3O_4S$·HCl	C, H, N
15	n-C_4H_9	*R*	*S*	45	221–223	+5.8	H_2O/acetone	$C_{19}H_{29}N_3O_4S$·HCl	C, H, N
16	n-C_4H_9	*R*	*R*	44	212–215	+2.4	H_2O/acetone	$C_{19}H_{29}N_3O_4S$·HCl	C, H, N
17	n-C_6H_{13}	*S*	*S*	41	117–118	−75.1	IPA/IPE	$C_{21}H_{33}N_3O_4S$	C, H, N
18	n-C_6H_{13}	*R*	*S*	54	131–132	+64.1	IPA/IPE	$C_{21}H_{33}N_3O_4S$	C, H, N

[a] The absolute configuration of the 2-position of the pyrrolidine moiety. [b] The absolute configuration of the 2′-position of the 2,3-dihydrobenzofuran moiety. [c] See Table I, footnote *a*.

Table IV. Structure and Antidopaminergic Effects of the Enantiomers of *N*-[(1-Alkyl-2-pyrrolidinyl)methyl]benzamides (3–8)

compd	R	isomer	[^{3}H]spiperone binding; K_i,[a] nM	inhibn of hyperactivity; ED_{50},[b] mg/kg (95% confidence limits): ip	inhibn of hyperactivity; ED_{50},[b] mg/kg (95% confidence limits): po
3 (−)-sulpiride	C_2H_5	*S*	29	9.3 (6.8–12.8)	299 (212–399)
4 (+)-sulpiride	C_2H_5	*R*	2700	>250	>500
5	n-C_4H_9	*S*	51	49.2 (30.2–81.0)	135 (113–162)
6	n-C_4H_9	*R*	230	92.3 (65.6–130)	184 (145–229)
7	n-C_6H_{13}	*S*	1400	>100	>100
8	n-C_6H_{13}	*R*	59	28.2 (22.6–34.6)	65.0 (51.4–81.3)

[a] Calculated as $K_i = IC_{50}/(1 + [[^3H]spiperone]/K_d)$, where IC_{50} is the concentration causing 50% inhibition of [^{3}H]spiperone binding, K_d is dissociation constant and [[^{3}H]spiperone] is concentration of [^{3}H]spiperone. Each value is the mean from triplicate assays in a single experiment. [b] ED_{50} values and their 95% confidence limits were obtained by parallel line assay as the dose which reduced the counts to 50% of the respective control.

Table V. Structure and Antidopaminergic Effects of the Stereoisomers of N-[(1-Alkyl-2-pyrrolidinyl)methyl]dihydrobenzofurancarboxamides (9–18)

compd	R	isomer		[^{3}H]spiperone binding; K_i,[c] nM	inhibn of hyperactivity; ED_{50},[d] mg/kg (95% confidence limits)	
		amine[a]	furan[b]		ip	po
9	C_2H_5	S	S	9.6	5.7 (3.5–9.8)	60.3 (37.5–101)
10	C_2H_5	S	R	21	11.0 (6.9–16.9)	87.3 (57.9–136)
11	C_2H_5	R	S	400	71.7 (58.2–87.9)	419 (300–628)
12	C_2H_5	R	R	650	145 (102–371)	516 (424–710)
13	n-C_4H_9	S	S	95	38.8 (26.5–54.6)	84.4 (61.3–116)
14	n-C_4H_9	S	R	210	72.1 (52.7–98.7)	163 (125–204)
15	n-C_4H_9	R	S	9.4	3.7 (2.6–5.1)	15.0 (9.2–24.8)
16	n-C_4H_9	R	R	23	11.6 (7.9–16.6)	38.0 (26.3–52.4)
17	n-C_6H_{13}	S	S	630	>100	>100
18	n-C_6H_{13}	R	S	6.7	12.2 (9.7–15.8)	27.4 (24.2–31.2)

[a,b] See Table III, footnotes a and b. [c,d] See Table IV, footnotes a and b.

that the configuration of **20** is S because its optical rotation is opposite to that of **21**. The enantiomers of the 1-alkyl-2-(aminomethyl)pyrrolidines were prepared as follows. The racemic 1-ethyl-2-(aminomethyl)pyrrolidine was purchased from Aldrich Chemical Co., Inc. The racemic 1-*n*-butyl- and 1-*n*-hexyl-2-(aminomethyl)pyrrolidines were prepared according to the procedure reported in the previous paper.[7a] The S and R enantiomers of the racemic amines were resolved by recrystallization of their ditartrate salts of D- and L-tartaric acids, respectively. The absolute configurations of **24** and **25** were determined by X-ray crystallographies of their derivatives **13** and **14**, respectively.[9] The configuration of **26** was confirmed to be S because the *n*-hexyl alkylation of L-prolinamide, followed by reduction with $LiAlH_4$, produced a compound identical with **26** in optical rotation. This determination also proved the configuration of **27** to be R because its optical rotation is opposite to that of **26**.

Results

The stereoisomers of the benzamides (**3–8**) and 2,3-dihydrobenzofuran-7-carboxamides (**9–18**) were evaluated for the antidopaminergic activities in vitro by their ability to displace [^{3}H]spiperone from striatal membranes of the rat brain (D_2 receptor binding assay) and in vivo by their ability to inhibit apomorphine-induced hyperactivity in mice. The results of these derivatives are presented in Tables IV and V, respectively.

Benzamides. It is well-known that the S enantiomer of sulpiride (**1**), the 1-ethyl-substituted benzamide, is pharmacologically active.[5] Also, in our experiments, the S enantiomer (**3**) showed a 90-fold higher affinity to the D_2 receptors and a 27-fold greater inhibitory effect on the hyperactivity (ip) than the R enantiomer (**4**) (Table IV). Replacement of the ethyl substituent with an *n*-butyl group reduced both of the above activities in the S configuration (**5** vs **3**) and increased them in the R configuration (**6** vs **4**), although the S enantiomer (**5**) was slightly more active than the R enantiomer (**6**). When the *n*-butyl substituent was replaced with a longer alkyl group, *n*-hexyl, the above tendency became so prominent that the stereospecificity of the compound activities altered from the S configuration to the R configuration. The R enantiomer (**8**) exhibited a 24-fold higher affinity in the D_2 receptor binding and an inhibitory effect on the hyperactivity (ip) more than three times greater than the S enantiomer (**7**), which almost lost its dopamine antagonistic activities. The IC_{50} of **8** was on the same order of magnitude as that of **3**, and the po inhibitory potency became higher than that of **3** (ED_{50}s of **8** and **3** were 65 and 299 mg/kg, respectively).

Dihydrobenzofuran-7-carboxamides. Among the four stereoisomers of the 1-ethyl-substituted dihydrobenzofurancarboxamide, compounds **9** and **10** with the S configuration at the pyrrolidine moiety (2S diastereomers) showed a much higher affinity to the D_2 receptors and more potent inhibitory effects on the hyperactivity than compounds **11** and **12** with the R configuration (2R diastereomers), respectively (Table V). For example, **9** was 42 times higher in its binding affinity and 12 times more potent in its inhibitory effect on the hyperactivity (ip) than **11**, respectively. However, replacement of the ethyl substituent with *n*-butyl and *n*-hexyl groups reversed the stereospecificity in the above activities. The 2R diastereomers **15**, **16**, and **18** were more potent in both of the in vitro and in vivo activities than the corresponding 2S diastereomers **13**, **14**, and **17**, respectively. A high stereospecificity was observed with 1-*n*-hexyl substitution. Compound **18** showed a 94-fold higher affinity to the D_2 receptors than compound **17** (IC_{50} of **18** = 6.7 nM). The latter compound (**17**) lost its inhibitory effect on the hyperactivity. It should be noted here that the stereospecificity of the 2′-position of the dihydrobenzofuran part (2′S vs 2′R diastereomers) was lower than that of the amine part (2S vs 2R diastereomers) and the difference in potency between the 2′S and 2′R diastereomers was less than three times as great in any 1-alkyl-substituted series and any

(8) Crystal data: $C_{29}H_{33}N_3O_6S$, M_r = 551.66, monoclinic, $P2_1$, a = 10.854 (1) Å, b = 13.552 (1) Å, c = 9.668 (2) Å, β = 101.84 (1)°, V = 1391.8 (3) Å^3, Z = 2, D_{calcd} = 1.316 g cm^{-3}. Intensities were collected on the Enraf-Nonius CAD4F-11 diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). 2143 unique reflections with $I \geq 2.3\sigma(I)$ were used for the refinement. The structure was solved by the direct method. Atomic parameter were refined by a block-diagonal least-squares method and the final R value was 0.035.

(9) Ueda, I.; Marubayashi, N.; Hayano, K.; Murakami, S.; Tahara, T., submitted for publication in *Acta Crystallogr., Sect. C.*

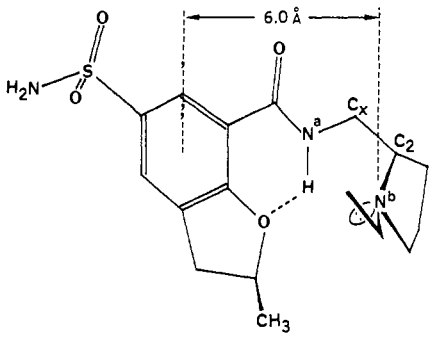

Figure 1. A solid-state conformation obtained from X-ray analysis of the 2*S* diastereomer (**9**), which is similar to the de Paulis model.

test, with the 2′*S* diastereomers being more active (i.e., **9** and **15** vs **10** and **16**, respectively).

Discussion

From the above results, it was revealed that the stereospecificity of the amine moiety altered from the *S* configuration to the *R* configuration as the 1-alkyl substituent became longer. In this case, it seems that the inversion of the stereospecificity is not owed to the difference in pharmacokinetics, such as absorption and metabolism, because their in vitro activities are well-correlated with their in vivo inhibitory effects. The inversion can be discussed in terms of their direct interaction with the D_2 receptors. There have been many reports concerning the active conformation of the benzamides interacting with the D_2 receptors.[10-12] In common recognition of the active conformation, the phenyl ring is maintained coplanar to the carbonyl by an intramolecular hydrogen bond between the carboxamide group and the methoxy oxygen atom on the phenyl, and the basic nitrogen, which plays a crucial role in the receptor binding, locates at a distance of ca. 6.0 Å from the center of the phenyl ring.[10,11] The basic nitrogen lone pair also orients in an antiparallel position with the carbonyl group.[12] A similar solid-state conformation to the de Paulis' model[11] was observed in the result of X-ray crystallography[13] of **9** (2*S* diastereomer), which is depicted in Figure 1. However, any topographical model so far studied has been constructed on the basis of the premise that the configuration of the pyrrolidine moiety is *S*. How can the active isomers with the opposite *R* configuration on the amine moiety interact with the D_2 receptors? One clue may also be obtained from the result of X-ray crystallography of **16** (2*R* diastereomer).[9] Among

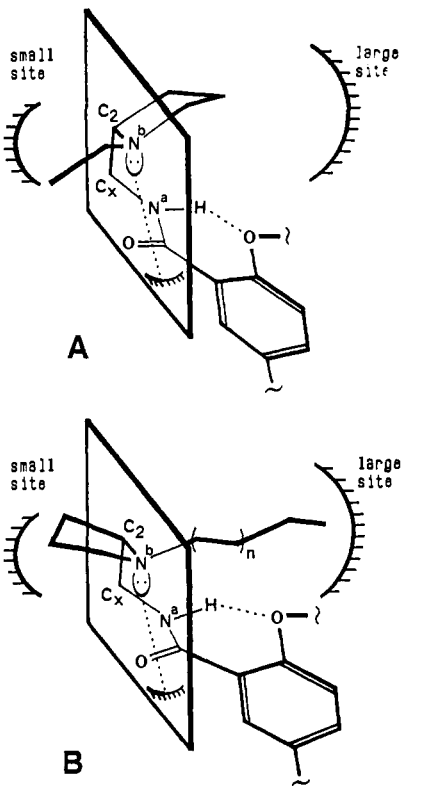

Figure 2. (A) The interaction of the 2*S* diastereomer with the D_2 receptor near the N-binding site proposed from the result of X-ray analysis of **9**; (B) that of the 2*R* diastereomer proposed as a result of X-ray analysis of **16**: $n = 1$, **16**; $n = 2$, **18**.

the four conformers observed in the X-ray analysis, one is useful because the solid-state conformation of the main chain C(=O)-N^a-C_x-C_2-N^b was analogous to the above model of **9**. The only conformational difference was the position of the pyrrolidine ring which sat on the opposite side to that of the 2*S* diastereomer **9** through the C_x-C_2-N^b plane (Figure 2, part A vs B), on which the nitrogen lone pair also almost rode with the same orientation. This indicates that the 2-enantiomeric difference of the amine moiety can be interpreted to be the positional difference of the pyrrolidine ring. Thus, the ring of the stereoisomers having the *S* configuration is on the right side of the plane (Figure 2A), and that of the isomers having the *R* configuration is on the left side (Figure 2B). On the basis of this interpretation, the alteration of the stereospecificity by the longer alkyl substitutions might be explained by the following suppositions concerning the D_2 receptor: (1) there are stereospecifically two (small and large) spatial and/or lipophilic sites near the N^b-atom binding site of the receptor; (2) the small site is acceptable for the ethyl and *n*-butyl groups and the ring alkyl chain, but not for the *n*-hexyl because of its length; (3) the relatively long and/or lipophilic alkyl groups on the N^b-atom prefer to interact with the large site (right) or to avoid the small site (left) before the N^b-atom binds to the receptor; (4) the order of length and/or lipophilicity is ethyl < ring alkyl chain (C_5-C_4-C_3-) = *n*-butyl < *n*-hexyl.

In the 1-ethyl compounds, the conformation of the isomers with the *S* configuration at the amine moiety meets the above requirements to fit the receptors since the ring alkyl chain is more likely to interact with the large spatial site rather than the ethyl group (Figure 2A). On the other hand, in the 1-*n*-hexyl compounds, the *n*-hexyl group prefers to sit in the large spatial site rather than the ring alkyl chain, so that the conformation of the isomers with the *R* configuration fits the receptors (Figure 2B). In the

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(13) Crystal data: $C_{17}H_{25}N_3O_4S$, $M_r = 367.46$, monoclinic $P2_1$, $a = 34.13$ (4) Å, $b = 13.025$ (6) Å, $c = 8.608$ (3) Å, $\beta = 90.24$ (6)°, $V = 3826$ (5) Å^3, $Z = 8$, $D_{calcd} = 1.28$ g cm^{-3}. Data collection and structure analysis were performed in the same manner as described in ref 8. The final *R* value was 0.093 for 3826 unique reflections.

case of the 1-*n*-butyl substitutent, the situation is complicated because the stereospecificity is reverse between the benzamides and 2,3-dihydrobenzofurancarboxamides. This reversal might be due to the other structural difference between the two types: i.e., the gap between them in the relative position of the N^b-atom to the phenyl ring might overcome the subtle difference of size between the *n*-butyl group and the ring alkyl chain.

At present, there are limitations on fully solving this configurational problem. Further studies, including detailed conformational analyses and the synthesis of further derivatives, are needed.

In conclusion, it was found that the stereospecificity of the amine moiety (2-position) in the two series altered from the *S* configuration to the *R* configuration as the 1-alkyl substituent became longer. It was also found that the alteration occurred at the stage of direct interaction with the D_2 receptors. These findings will provide further insight for elucidating structural features of the D_2 receptors.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected. NMR spectra were recorded on a JEOL PS-100 or JEOL GSX-400 spectrometer, and shifts are reported in parts per million from internal tetramethylsilane. Mass spectra were obtained on a JMS-01SG instrument. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. The elemental analyses were performed by the Instrumental Analysis Section in the Central Research Laboratory of Yoshitomi Pharmaceutical Industries Ltd., Fukuoka, Japan, and were within ±0.3% of the theoretical values. The enantiomeric purities of benzamides **3–8** and carboxamides **9–18** were confirmed to be >99% ee by chiral HPLC [apparatus, Waters ALC/GPC 209 type; detection, UV at 254 nm; column, CHIRALPAK AD (DAICEL Chemical Industries, Ltd.) 250 × 4.6 (i.d.) mm; mobile phase, *n*-hexane–ethyl alcohol–diethylamine (70:30:0.07)].

Optical Resolution of 2-Methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxylic Acid. Preparations of 20 and 21. Racemic 2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxylic acid was prepared by chlorosulfonation of 2-methyl-2,3-dihydrobenzofuran-7-carboxylic acid with $ClSO_3H$ and the subsequent amidation with 28% aqueous NH_3 according to the previous paper.[7a] A mixture of cinchonidine (206 g, 0.70 mol) and MeOH (1 L) was added to a mixture of the racemic benzofurancarboxylic acid (180 g, 0.70 mol) and MeOH (1 L). Having been dissolved by warming, the mixture was allowed to stand overnight at room temperature. The precipitates were collected by filtration, recrystallized from MeOH (ca. 6 L), and then recrystallized twice from water–MeOH (0.4 L–2.5 L) to give 67 g of the cinchonidine salt of **20**: $[\alpha]^{24}_D = -34.9°$ (*c* 1.0, DMF); mp 238–239 °C dec. The salt (67 g) was suspended in water (500 mL) and acidified by addition of 6 N HCl with stirring. The precipitates were collected and recrystallized from water–MeOH to afford 27 g of **20**: $[\alpha]^{24}_D = -18°$ (*c* 1.0, DMF); mp 274–275 °C dec. Anal. ($C_{10}H_{11}O_5NS$) C, H, N.

The first MeOH filtrate was concentrated by evaporation of the solvent in vacuo. The residue was suspended in water and acidified with concentrated HCl. The precipitates (106 g, 0.41 mol), collected by filtration, were suspended in MeOH (1 L). To this was added a mixture of cinchonine (121 g, 0.41 mol) and MeOH (0.8 L). After being dissolved by warming, the mixture was allowed to stand overnight at room temperature. The collected precipitates were recrystallized three times from water–MeOH to afford 60 g of the cinchonine salt of **21**: $[\alpha]^{24}_D = +77.5°$ (*c* 1.0, DMF); mp 238–239 °C dec. The salt was treated in a manner similar to the case of **20** to give 25 g of **21**: $[\alpha]^{24}_D = +18.5°$ (*c* 1.0, DMF); mp 274–275 °C dec. Anal. ($C_{10}H_{11}O_5NS$) C, H, N.

The absolute configuration of **21** was determined to be *R* by X-ray data of its cinchonine salt.[8] The opposite optical rotation of **20** to **21** indicated that the absolute configuration of **20** was *S*.

Optical Resolutions of 1-Alkyl-2-(aminomethyl)-pyrrolidine. Preparations of 24 and 25. To a solution of racemic 2-(aminomethyl)-1-*n*-butylpyrrolidine (676 g, 4.33 mol) in isopropyl alcohol (IPA, 2.7 L) was added a solution of L-tartaric acid (1.30 kg, 8.66 mol) in water (2.7 L). The mixture was then allowed to stand overnight. The precipitates, collected by filtration, were recrystallized twice from water–IPA (1:1) to give 630 g of **25**·di-L-tartrate: $[\alpha]^{24}_D = +44.1°$ (*c* 1.0, H_2O); mp 126–129 °C (91 °C sintering). Anal. ($C_9H_{20}ON_2 \cdot 2C_4H_6O_6 \cdot 3H_2O$) C, H, N. To the salt, dissolved in 830 mL of water, was added 40% aqueous NaOH (586 mL). The separated oil was extracted with AcOEt three times. After being dried over anhydrous $MgSO_4$, the organic phase was concentrated by evaporation of the solvent in vacuo. The resulting residue was distilled under reduced pressure to afford 160 g of **25**: bp 66–67 °C (0.6 mmHg). The first filtrate, which was obtained in the preparation of **25**·di-L-tartrate, was concentrated in vacuo. The residue was treated with aqueous NaOH and then with AcOEt to extract the base. After evaporation of the solvent, the residue was distilled under reduced pressure to give 157 g of the base. To a solution of the base in IPA (640 mL) was added a solution of D-tartaric acid (306 g, 2.0 mol) in water (640 mL), and this mixture was allowed to stand overnight at room temperature. The precipitates, collected by filtration, were recrystallized from water–IPA (2 L–2 L) to afford 362 g of the di-D-tartrate salt of **24**: $[\alpha]^{24}_D = -43.4°$ (*c* 1.0, H_2O); mp 126–129 °C (92 °C sintering). Anal. ($C_9H_{20}ON_2 \cdot 2C_4H_6O_6 \cdot 3H_2O$) C, H, N. The salt was treated in a manner similar to the preparation of **25** to give 104 g of **24**: bp 105 °C (6 mmHg). The absolute configurations of **24** and **25** were determined to be *S* and *R*, respectively, by X-ray analyses of **13** and **14**.

Preparations of 26 and 27. In a manner similar to the above, the *S* and *R* enantiomers of 2-(aminomethyl)-1-*n*-hexylpyrrolidine were obtained by resolution of their ditartrate salts of D- and L-tartaric acids, respectively. **26**·di-D-tartrate: $[\alpha]^{24}_D = -41.4°$ (*c* 1.0, H_2O); mp 162–164 °C. Anal. ($C_{11}H_{24}N_2 \cdot 2C_4H_6O_6$) C, H, N. **26**: $[\alpha]^{24}_D = -85.4°$ (*c* 1.0, MeOH); bp 101–103 °C (0.7 mmHg). **27**·di-L-tartrate: $[\alpha]^{24}_D = +41.2°$ (*c* 1.0, H_2O); mp 162–164 °C. Anal. ($C_{11}H_{24}N_2 \cdot 2C_4H_6O_6$) C, H, N. **27**: $[\alpha]^{24}_D = +86.7°$ (*c* 1.0, MeOH); bp 102–105 °C (0.7 mmHg). The absolute configuration of **26** was determined to be *S* as follows. Condensation of *n*-hexyl bromide (8.3 g) with L-prolinamide (5.7 g) derived from L-proline produced (*S*)-2-carbamoyl-1-*n*-hexylpyrrolidine (6.3 g), which was reduced by $LiAlH_4$, followed by distillation under reduced pressure to give (*S*)-2-(aminomethyl)-1-*n*-hexylpyrrolidine. The optical rotation ($[\alpha]^{24}_D$) of the reduced amine was −87.4° (*c* 1.0, MeOH) which was in accord with that of **26** described above.

Preparations of 22 and 23. Enantiomers **22** and **23** were resolved according to the procedure reported in ref 5b. **22**: $[\alpha]^{24}_D = -105°$ (*c* 1.0, MeOH). **23**: $[\alpha]^{24}_D = +108°$ (*c* 1.0, MeOH).

General Procedure for the Preparation of the Stereoisomers of Benzamides. (*S*)- and (*R*)-*N*-[(1-*n*-Butyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfamoylbenzamides (5 and 6). To a mixture of 2-methoxy-5-sulfamoylbenzoic acid (**19**; 1.23 g, 5.34 mmol), Et_3N (1.6 mL, 11.5 mmol), DMF (5 mL), and THF (5 mL) was added isobutyl chloroformate (0.74 mL, 5.7 mmol) dropwise at −10 °C. After stirring for 45 min, a solution of **24** (1.0 g, 6.4 mmol) in THF (10 mL) was added dropwise to the mixture at the same temperature. The resulting mixture was gradually warmed to room temperature over a period of 2 h and then concentrated by evaporation of the solvent in vacuo. To the resultant residue was added AcOEt and 5% aqueous $NaHCO_3$. The separated organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual solid was washed with *n*-hexane and recrystallized from a mixed solvent of diisopropyl ether (IPE) and IPA to afford 1.00 g (51%) of **5**: mp 130–132 °C; $[\alpha]^{24}_D = -79.1°$ (*c* 1.0, DMF); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.2–1.8 (7 H), 1.90 (m, 1 H), 2.15–2.24 (2 H), 2.65 (m, 1 H), 2.74 (m, 1 H), 3.20 (t, 1 H), 3.31 (m, 1 H), 3.75 (m, 1 H), 4.01 (s, 3 H), 7.05 (d, 1 H), 8.01 (dd, 1 H), 8.33 (m, 1 H), 8.76 (d, 1 H); MS *m/e* 370 ($M^+ + 1$). Anal. ($C_{17}H_{27}N_3O_4S$) C, H, N.

Replacement of **24** with **25** in the same procedure as described for **5** afforded 1.80 g (49%) of **6**: mp 130–132 °C; $[\alpha]^{24}_D = +82.0°$ (*c* 1.0, DMF); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.2–1.8 (7 H), 1.90 (m, 1 H), 2.15–2.24 (2 H), 2.65 (m, 1 H), 2.74 (m, 1 H), 3.20 (t, 1 H), 3.31 (m, 1 H), 3.75 (m, 1 H), 4.01 (s, 3 H), 7.05 (d, 1 H), 8.01 (dd, 1 H), 8.33 (m, 1 H), 8.76 (d, 1 H); MS *m/e* 370 ($M^+ + 1$). Anal. ($C_{17}H_{27}N_3O_4S$) C, H, N.

(S)- and (R)-N-[(1-n-Hexyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfamoylbenzamides (7 and 8). Isobutyl chloroformate (1.40 mL, 10.8 mmol) was added dropwise to a mixture of 2-methoxy-5-sulfamoylbenzoic acid (**19**; 2.34 g, 10.1 mmol) and Et_3N (3.0 mL, 21.4 mmol) in DMF (12 mL) and THF (20 mL) at −10 °C. After stirring for 1 h, a solution of **26** (2.25 g, 12.2 mmol) in THF (15 mL) was added dropwise to the mixture at the same temperature. The resulting mixture was gradually warmed to room temperature over a period of 4 h, and then a procedure similar to that described for **5** gave 2.30 g (57%) of **7**: mp 139–142 °C; $[\alpha]^{24}_D$ = −75.0° (*c* 1.0, DMF); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H), 1.2–1.8 (11 H), 1.88 (m, 1 H), 2.15–2.23 (2 H), 2.64 (m, 1 H), 2.73 (m, 1 H), 3.19 (t, 1 H), 3.31 (m, 1 H), 3.73 (m, 1 H), 4.0 (s, 3 H), 7.04 (d, 1 H), 8.01 (dd, 1 H), 8.34 (m, 1 H), 8.75 (d, 1 H); MS *m/e* 398 (M^+ + 1). Anal. ($C_{19}H_{31}N_3O_4S$) C, H, N.

With a similar procedure using **27** (2.25 g, 12.2 mmol) instead of **26**, **8** (2.40 g, 60%) was obtained: mp 139–142 °C; $[\alpha]^{24}_D$ = −74.5° (*c* 1.0, DMF); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H), 1.2–1.8 (11 H), 1.88 (m, 1 H), 2.15–2.23 (2 H), 2.64 (m, 1 H), 2.73 (m, 1 H), 3.19 (t, 1 H), 3.31 (m, 1 H), 3.73 (m, 1 H), 4.0 (s, 3 H), 7.04 (d, 1 H), 8.01 (dd, 1 H), 8.34 (m, 1 H), 8.75 (d, 1 H); MS *m/e* 398 (M^+ + 1). Anal. ($C_{19}H_{31}N_3O_4S$) C, H, N.

General Procedure for the Preparation of the Stereoisomers of Dihydrobenzofurancarboxamides. (2S,2S)- and (2S,2R)-N-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamides (9 and 10). Ethyl chloroformate (2.65 g, 24.4 mmol) was added dropwise to a stirring mixture of **20** (6.00 g, 23.4 mmol), Et_3N (8.2 mL, 59 mmol), acetone (55 mL), and DMF (55 mL) at 10 °C. After stirring at 10 °C to room temperature over a period of 1.5 h, **22** (3.90 g, 30.5 mmol) was added and the resultant mixture was stirred overnight. Concentration of the reaction mixture in vacuo gave the residue, which was washed with 750 mL of water to afford a solid. The crude product was recrystallized twice from AcOEt to provide 4.20 g (49%) of **9**: mp 155–156 °C; $[\alpha]^{24}_D$ = −64.7° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 3 H), 1.4–1.9 (4 H), 1.48 (d, 3 H), 2.14 (dd, 1 H), 2.21 (dq, 1 H), 2.61 (m, 1 H), 2.82 (dq, 1 H), 2.93 (dd, 1 H), 3.12 (m, 1 H), 3.24 (m, 1 H), 3.47 (dd, 1 H), 3.49 (m, 1 H), 5.23 (m, 1 H), 7.26 (2 H), 7.76 (1 H), 8.06 (m, 1 H), 8.17 (1 H); MS *m/e* 368 (M^+ + 1). Anal. ($C_{17}H_{25}N_3O_4S$) C, H, N.

Replacement of **20** with **21** in the same procedure as described above afforded 4.60 g (54%) of **10**: mp 164–165 °C; $[\alpha]^{24}_D$ = −50.8° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 1.08 (t, 3 H), 1.4–1.9 (4 H), 1.48 (d, 3 H), 2.13 (dd, 1 H), 2.22 (dq, 1 H), 2.61 (m, 1 H), 2.82 (m, 1 H), 2.94 (dd, 1 H), 3.12 (m, 1 H), 3.20 (m, 1 H), 3.47 (dd, 1 H), 3.58 (m, 1 H), 5.24 (m, 1 H), 7.26 (2 H), 7.76 (1 H), 8.12 (m, 1 H), 8.18 (1 H); MS *m/e* 368 (M^+ + 1). Anal. ($C_{17}H_{25}N_3O_4S$) C, H, N.

(2R,2S)- and (2R,2R)-N-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamides (11 and 12). A reaction of **20** (6.00 g, 23.4 mmol) with **23** (3.90 g, 30.5 mmol) was carried out in a manner similar to that described for **9** to give 3.9 g (46%) of **11**: mp 163–164 °C; $[\alpha]^{24}_D$ = +50.8° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 1.08 (t, 3 H), 1.4–1.9 (4 H), 1.48 (d, 3 H), 2.13 (dd, 1 H), 2.22 (dq, 1 H), 2.61 (m, 1 H), 2.82 (m, 1 H), 2.94 (dd, 1 H), 3.12 (m, 1 H), 3.20 (m, 1 H), 3.47 (dd, 1 H), 3.58 (m, 1 H), 5.24 (m, 1 H), 7.26 (2 H), 7.76 (1 H), 8.12 (m, 1 H), 8.18 (1 H); MS *m/e* 368 (M^+ + 1). Anal. ($C_{17}H_{25}N_3O_4S$) C, H, N.

In a similar way, using **21** (6.00 g, 23.4 mmol) instead of **20**, 3.00 g (35%) of **12** was obtained: mp 156–157 °C; $[\alpha]^{24}_D$ = −64.6° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 3 H), 1.4–1.9 (4 H), 1.48 (d, 3 H), 2.14 (dd, 1 H), 2.21 (dq, 1 H), 2.61 (m, 1 H), 2.82 (dq, 1 H), 2.93 (dd, 1 H), 3.12 (m, 1 H), 3.24 (m, 1 H), 3.47 (dd, 1 H), 3.49 (m, 1 H), 5.23 (m, 1 H), 7.26 (2 H), 7.76 (1 H), 8.06 (m, 1 H), 8.17 (1 H); MS *m/e* 368 (M^+ + 1). Anal. ($C_{17}H_{25}N_3O_4S$) C, H, N.

(2S,2S)- and (2S,2R)-N-[(1-n-Butyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide Hydrochlorides (13 and 14). Isobutyl chloroformate (4.10 mL, 31.6 mmol) was added dropwise to a solution of **20** (7.70 g, 30.0 mmol) and Et_3N (9.30 mL, 66.6 mmol) in DMF (30 mL) and THF (30 mL) at −10 °C. After stirring at the same temperature for 1 h, a solution of **24** (5.60 g, 35.9 mmol) in THF (30 mL) was added dropwise over a period of 12 min. The resultant mixture was gradually warmed to room temperature with stirring for 8 h. Removal of the solvent from the reaction mixture in vacuo gave the residue. To it was added AcOEt and 5% aqueous $NaHCO_3$. The separated organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a solid (6.7 g). The solid was dissolved in acetone (67 mL). After the addition of concentrated HCl (1.8 mL), the mixture was left to stand at room temperature, which resulted in a precipitate. Recrystallization of it from water–acetone (2 mL–100 mL) afforded 5.12 g (40%) of **13**: mp 214–216 °C; $[\alpha]^{24}_D$ = −2.0° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, *J* = 7.3 Hz), 1.26 (m, 2 H), 1.52 (d, 3 H, *J* = 6.3 Hz), 1.55–1.86 (3 H), 1.86–2.05 (2 H), 2.14 (m, 1 H), 2.91 (dd, 1 H), 2.97–3.10 (2 H), 3.15 (m, 1 H), 3.47 (dd, 1 H), 3.55 (m, 1 H), 3.60–3.81 (3 H), 5.22 (m, 1 H), 7.29 (s, 2 H), 7.78 (1 H), 8.14 (1 H), 8.52 (m, 1 H), 10.96 (br s, 1 H); MS *m/e* 396 (M^+ − Cl). Anal. ($C_{19}H_{29}N_3O_4S$·HCl) C, H, N.

Replacement of **20** with **21** (5.57 g, 21.7 mmol) in the same procedure as described above provided 3.00 g (32%) of **14**: mp 222–225 °C; $[\alpha]^{24}_D$ = −5.2° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3 H, *J* = 7.3 Hz), 1.27 (m, 2 H), 1.52 (d, 3 H, *J* = 6.3 Hz), 1.55–1.85 (3 H), 1.85–2.05 (2 H), 2.14 (m, 1 H), 2.92 (dd, 1 H), 2.97–3.10 (2 H), 3.16 (m, 1 H), 3.46 (dd, 1 H), 3.55 (m, 1 H), 3.61–3.81 (3 H), 5.19 (m, 1 H), 7.30 (s, 2 H), 7.79 (1 H), 8.13 (1 H), 8.53 (m, 1 H), 11.06 (br s, 1 H); MS *m/e* 396 (M^+ − Cl). Anal. ($C_{19}H_{29}N_3O_4S$·HCl) C, H, N.

(2R,2S)- and (2R,2R)-N-[(1-n-Butyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamide Hydrochlorides (15 and 16). A similar reaction and treatment to that described for **13**, using **20** (7.70 g, 30.0 mmol) and **25** (5.60 g, 35.9 mmol) as starting materials, was carried out to yield 5.8 g (45%) of **15**: mp 222–225 °C; $[\alpha]^{24}_D$ = +5.8° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3 H, *J* = 7.3 Hz), 1.27 (m, 2 H), 1.52 (d, 3 H, *J* = 6.3 Hz), 1.55–1.85 (3 H), 1.85–2.05 (2 H), 2.14 (m, 1 H), 2.92 (dd, 1 H), 2.97–3.10 (2 H), 3.16 (m, 1 H), 3.46 (dd, 1 H), 3.55 (m, 1 H), 3.61–3.81 (3 H), 5.19 (m, 1 H), 7.30 (s, 2 H), 7.79 (1 H), 8.13 (1 H), 8.53 (m, 1 H), 11.06 (br s, 1 H); MS *m/e* 396 (M^+ − Cl). Anal. ($C_{19}H_{29}N_3O_4S$·HCl) C, H, N.

Starting from **21** (4.19 g, 16.3 mmol) and **25** (3.05 g, 19.6 mmol), the same procedure as described above provided 3.10 g (44%) of **16**: mp 212–215 °C; $[\alpha]^{24}_D$ = +2.4° (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, *J* = 7.3 Hz), 1.26 (m, 2 H), 1.52 (d, 3 H, *J* = 6.3 Hz), 1.55–1.86 (3 H), 1.86–2.05 (2 H), 2.14 (m, 1 H), 2.91 (dd, 1 H), 2.97–3.10 (2 H), 3.15 (m, 1 H), 3.47 (dd, 1 H), 3.55 (m, 1 H), 3.60–3.81 (3 H), 5.22 (m, 1 H), 7.29 (s, 2 H), 7.78 (1 H), 8.14 (1 H), 8.52 (m, 1 H), 10.96 (br s, 1 H); MS *m/e* 396 (M^+ − Cl). Anal. ($C_{19}H_{29}N_3O_4S$·HCl) C, H, N.

(2S,2S)- and (2R,2S)-N-[(1-n-Hexyl-2-pyrrolidinyl)methyl]-2-methyl-5-sulfamoyl-2,3-dihydrobenzofuran-7-carboxamides (17 and 18). To a solution of **20** (1.44 g, 5.60 mmol) and Et_3N (1.8 mL, 13 mmol) in DMF (10 mL) and THF (10 mL) was added dropwise isobutyl chloroformate (0.80 mL, 6.2 mmol) at −15 °C. After stirring for 0.5 h, a solution of **26** (1.30 g, 7.07 mmol) in THF (10 mL) was added to the mixture at the same temperature. The resultant mixture was gradually warmed to room temperature with stirring for 3.5 h, and then the solvent was removed under reduced pressure. To the residue was added AcOEt and 5% aqueous $NaHCO_3$. The separated organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated by evaporation of the solvent in vacuo. The residue was crystallized by addition of IPE. The crude product, obtained by filtration, was recrystallized from IPA–IPE to give 0.97 g (41%) of **17**: mp 117–118 °C; $[\alpha]^{24}_D$ = −75.1° (*c* 1.0, DMF); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 1.2–1.8 (11 H), 1.55 (d, 3 H), 1.90 (m, 1 H), 2.15–2.24 (2 H), 2.65 (m, 1 H), 2.72 (m, 1 H), 2.91 (dd, 1 H), 3.18 (m, 1 H), 3.31 (m, 1 H), 3.43 (dd, 1 H), 3.71 (m, 1 H), 5.17 (m, 1 H), 7.84 (1 H), 8.09 (m, 1 H), 8.54 (1 H); MS *m/e* 424 (M^+ + 1). Anal. ($C_{21}H_{33}N_3O_4S$) C, H, N.

In a similar manner to that described above, replacement of **26** with **27** [**20** (2.57 g, 10.0 mmol), **27** (2.40 g, 13.0 mmol)] yielded 2.30 g (54%) of **18**: mp 131–132 °C; $[\alpha]^{24}_D$ = +64.1° (*c* 1.0, DMF); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.2–1.8 (11 H), 1.55 (d, 3 H), 1.89 (m, 1 H), 2.15–2.24 (2 H), 2.65 (m, 1 H), 2.74 (m, 1 H), 2.92 (dd, 1 H), 3.19 (m, 1 H), 3.29 (m, 1 H), 3.43 (dd, 1 H), 3.76 (m, 1 H), 5.17 (m, 1 H), 7.84 (1 H), 8.19 (m, 1 H), 8.55 (1 H); MS *m/e* 424 (M^+ + 1). Anal. ($C_{21}H_{33}N_3O_4S$) C, H, N.

Antidopaminergic Activities. Inhibition of [^{3}H]Spiperone Binding. The assays were performed in the rat striatal membranes using a previously described method.[14] Briefly, rat striata were homogenized in 100 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.7) and centrifuged (500*g*, 10 min, 0 °C). The supernatant was centrifuged at 50000*g* for 15 min. The pellet was suspended in 100 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.7) and recentrifuged (50000*g*, 15 min, 0 °C). The final pellet was resuspended in 150 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.1) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1.1 mM ascorbic acid, and 10 μM pargyline and incubated at 37 °C for 10 min. A portion of this membrane suspension (900 μM) was placed in a tube, and 50 μL of either test compound or vehicle solution was added, followed by 50 μL of [^{3}H]spiperone (40 Ci/mmol) at a final concentration of 0.2 nM. The tubes were incubated at 37 °C for 20 min and filtered through Whatman GF/B glass filters, which were then washed three times with 3 mL of the Tris-HCl buffer (50 mM, pH 7.7). (±)-Sulpiride (100 μM) was used for the determination of nonspecific binding. The radioactivity trapped on the filters was measured by liquid-scintillation spectrometry. The IC_{50} values were determined from concentration–inhibition curves.

Inhibition of Apomorphine-Induced Hyperactivity in Mice. Motor activity was measured with Varimex (Columbus Instruments) in groups of three male mice. Apomorphine hydrochloride (0.5 mg/kg) was injected subcutaneously 1 h after the oral or intraperitoneal administration of test compounds. The motor activity was measured for 20 min immediately after the apomorphine injection.

Supplementary Material Available: Tables of final atomic positional parameters, atomic thermal parameters, and bond distances and angles of compound **9** and the cinchonine salt of compound **21** (10 pages). Ordering information is given on any current masthead page.

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Dual Inhibitors of Thromboxane A_2 Synthase and 5-Lipoxygenase with Scavenging Activity of Active Oxygen Species. Synthesis of a Novel Series of (3-Pyridylmethyl)benzoquinone Derivatives

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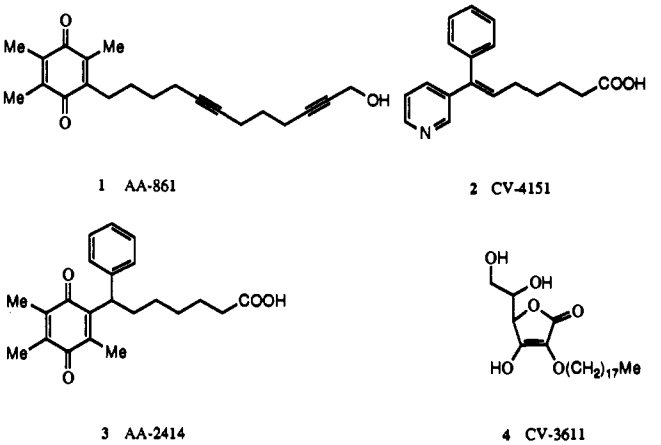
A novel series of (3-pyridylmethyl)benzoquinone derivatives was molecular designed and synthesized for the dual purpose of inhibiting thromboxane A_2 and leukotriene biosynthesis enzymes and scavenging active oxygen species (AOS). They were evaluated for inhibition of TXA_2 synthase, inhibition of 5-lipoxygenase, and for their scavenging activity of AOS using the thiobarbituric acid method. 2,3,5-Trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (**24**, CV-6504) was the most promising derivative since it showed efficient AOS scavenging activity (inhibition of lipid peroxidation in rat brain homogenates: $IC_{50} = 1.8 \times 10^{-6}$ M) as well as potent, specific, and well-balanced inhibitory effects on both enzymes (inhibitory effect on TXA_2 synthase in human blood, $IC_{50} = 3.3 \times 10^{-7}$ M; inhibitory effect on 5-lipoxygenase in human blood, $IC_{50} = 3.6 \times 10^{-7}$ M). In adriamycin-induced proteinuria in a rat model, compound **24** at 10 mg/kg per day (po) suppressed proteinuria by more than 50%. The proteinuria, however, could not be reduced by single administration of an inhibitor specific for thromboxane A_2 synthase [(*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**2**, CV-4151)] or for 5-lipoxygenase [2-(12-hydroxy-5,10-dodecadiynyl)-3,5,6-trimethyl-1,4-benzoquinone (**1**, AA-861)]. The proteinuria was also not reduced by administration of an AOS scavenger, 2-*O*-octadecylascorbic acid (**4**, CV-3611). Triple function compounds such as compound **24** that specifically inhibit both enzymes as well as scavenge AOS possess a variety of pharmacologically beneficial effects.

Arachidonic acid liberated from phospholipid by various stimuli can be metabolized by the cyclooxygenase (CO) pathway to prostaglandins (PGs) and thromboxane A_2 (TXA_2) or by lipoxygenase (LO) pathways to hydroxyeicosatetraenoic acid (HETEs) and leukotrienes (LTs). These oxidative metabolites of arachidonic acid have been implicated as important mediators in a variety of diseases including stroke, myocardial infarction, inflammation, ulcerative colitis, and rheumatoid arthritis.[1] In addition, recent reports suggest that active oxygen species (AOS), including superoxide (O_2^-), hydrogen peroxide, hydroxyl radical, and ferryl radical, mediate cell damage in a variety of pathological conditions.[2] Intensive research in the perturbation of the arachidonate cascade system resulted in the discovery of many interesting agents, some of which have found therapeutic application. Most of these compounds are selective enzyme inhibitors and specific receptor antagonists. For example, we have developed a potent and selective 5-lipoxygenase inhibitor, 2-(12-hydroxy-5,10-dodecadiynyl)-3,5,6-trimethyl-1,4-benzoquinone (**1**, AA-861),[3] a potent, selective, long-acting thromboxane A_2 synthase inhibitor, (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**2**, CV-4151),[4] a specific throm-

Chart I



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