Amphoteric Drugs. I. Synthesis and Antiallergic Activity of [4-(Diphenylmethoxy)piperidino]-, [4-(Diphenylmethyl)piperazinyl]- and [4-(Diphenylmethylene)piperidino]alkanoic Acid Derivatives

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A simple method of transforming classical antihistaminics into nonsedative antiallergic agents with strong effects in rat models is described. Various [4-(diphenylmethoxy)piperidino]- (series A), [4-(diphenylmethyl)piperazinyl]- (series B) and [4-(diphenylmethylene)piperidino]alkanoic acid derivatives (series C) were synthesized and examined for antiallergic activities and effects on the central nervous system (CNS), in comparison with the corresponding *N*-methyl derivatives (1a—c). *N*-Alkylcarboxylic acids (5a—c) showed stronger inhibitory effects on compound 48/80-induced lethality in rats than the corresponding *N*-methyl derivatives (1a—c). In particular, *N*-alkylcarboxylic acids (5a) in series A exhibited approximately 100-fold stronger inhibitory effects than 1a, and were the least effective in prolonging the sleeping time on hexobarbital-induced anesthesia in mice in all series. As a result of chemical modification in series A, it was found that introduction of a methyl group at the *para*-position on one benzene ring in the (diphenylmethoxy)piperidine system effectively reduced CNS side-effects without reducing antiallergic activity. (+)-3-[4-[(4-Methylphenyl)phenylmethoxy]piperidino]propionic acid ((+)-5l), an optically active isomer of 5l, exhibited a stronger antiallergic effect (ED_{50} = 0.17 mg/kg, *p.o.*) than ketotifen and terfenadine in the 48 h homologous passive cutaneous anaphylaxis (PCA) test, and moreover exhibited no CNS side-effects, such as prolongation of the sleeping time on hexobarbital-induced anesthesia, at an oral dose of 30 mg/kg. Compound (+)-5l was thus proved to be a promising candidate as a nonsedative antiallergic agent.

Keywords amphoteric drug; zwitter-ionization; antiallergic agent; classical antihistaminic; *N*-alkylcarboxylic acid; diphenylmethoxypiperidine

Many antiallergic agents have been developed and shown to be effective clinically in the treatment of allergic disorders such as bronchial asthma, allergic rhinitis, conjunctivitis, urticaria and atopic dermatitis.[1] These antiallergic agents could be classified into two groups on the basis of chemical structure.[2] One group consists of acidic antiallergic agents such as disodium cromoglycate (DSCG),[3] which show antiallergic activities by inhibiting release of various chemical mediators in rat models. The other consists of basic antiallergic agents such as ketotifen[4] and terfenadine.[5] These agents possess strong antihistaminic activities in mice and guinea-pigs, but relatively weak effects in rats. Recently, compounds of a new class bearing both acidic and basic moieties in their molecules have been reported (*e.g.*, acrivastine,[6] cetirizine,[7] KW-4679[8] and AHR-13268D[9]). Agents of this type could be referred to as amphoteric or zwitter-ionized antiallergic agents. Nevertheless, little is known about the changes of pharmacological profile and antiallergic activity caused by zwitter-ionization.

Zwitter-ionization of drugs by introducing simple *N*-alkylcarboxy groups instead of *N*-alkyl (especially *N*-methyl) groups and its influence on pharmacological activity have been studied in our laboratories. In our previous paper,[10] zwitter-ionized derivatives of tricyclic and tetracyclic antipsychotic agents were synthesized and examined for modification of the pharmacological activities. It was found that zwitter-ionization of these agents resulted in retention of H_1-antihistaminic activity, while greatly reducing other pharmacological activities on the central nervous system (CNS) *in vitro*. The zwitter-ionized derivatives showed strong inhibitory effects on 48 h homologous passive cutaneous anaphylaxis (PCA) in comparison with the corresponding *N*-methyl derivatives. These results encouraged us to examine the usefulness of this simple zwitter-ionization for the conversion of classical antihistaminics into nonsedative antiallergic agents with strong effects in rat models.

In this paper, we describe the synthesis and antiallergic activity of a series of amphoteric compounds derived from representative classical antihistaminics (**1a—c**).[11–13]

Synthesis

The compounds tested were prepared by the methods shown in Charts 2 and 3. *N*-Methylamines (**1**) obtained by the usual methods were treated with ethyl chloroformate in toluene to give the corresponding ethyl carbamates (**2**), which were subsequently hydrolyzed with alkali, yielding secondary amines (**3**). Compounds **3** were alkylated with ethyl bromoacetate, ethyl 3-bromopropionate (or ethyl acrylate), ethyl 4-bromobutyrate, ethyl 5-bromovalerate or methyl 6-bromohexanoate to give the corresponding *N*-alkylcarboxylates (**4**), subsequent hydrolysis of which with 2 N NaOH afforded the corresponding *N*-alkylcarboxylic acids (**5**) having various methylene chains (n = 1—5).

The optical isomers of **5l** were prepared from the enantiomers of **3l** by the same method. Optical resolution of racemic **3l** was achieved by fractional crystallization of the diastereomeric dibenzoyl tartrate. Enantiomeric excess

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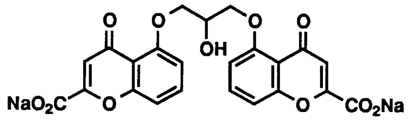
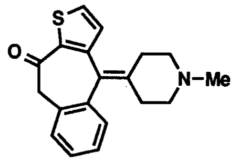
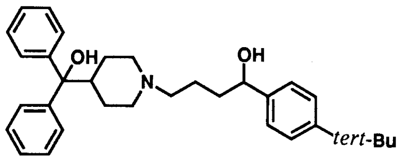


DSCG



ketotifen



terfenadine

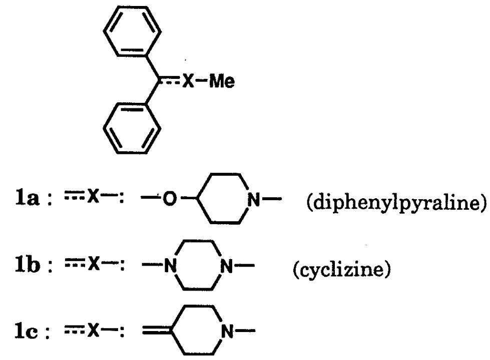
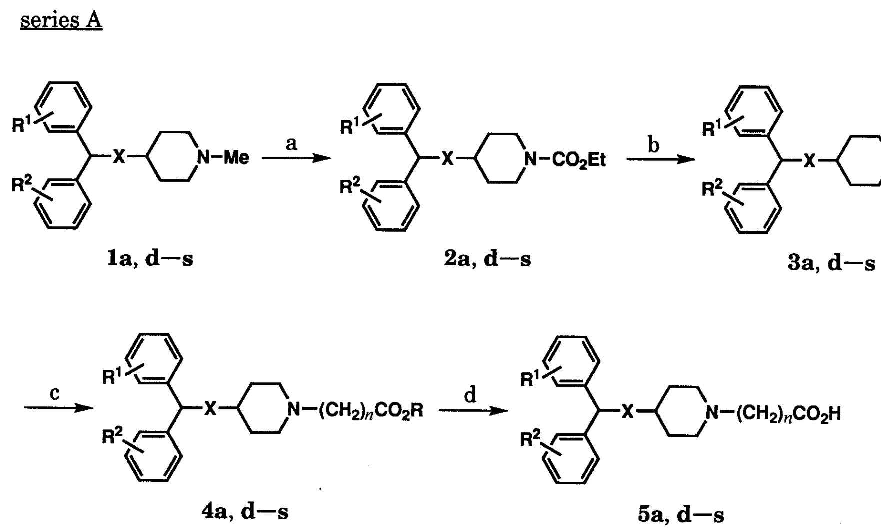


Chart 1



X = O, S

R^1 = H, F, Cl, Br, Me, Et, *n*-Pr, iso-Pr, *n*-Bu, OMe, OEt

R^2 = H,Me

R = Me, Et

n = 1 − 5

a) $ClCO_2Et$ in toluene b) NaOH in EtOH or *n*-BuOH

c) $Br(CH_2)_nCO_2R$, K_2CO_3 in DMF or $CH_2{=}CHCO_2Et$ in EtOH

d) 2 N NaOH in MeOH

Chart 2

(ee) of each enantiomer ((+)-**5l** and (−)-**5l**) was found to be >99% by HPLC analysis. Physicochemical data are summarized in Tables I and II.

Results and Discussion

We initially examined the changes of antiallergic activity and undesirable CNS side-effects caused by zwitterionization, by comparing **5a**—**c** with the corresponding *N*-methylamines (**1a**—**c**). Histamine (H_1) antagonism was measured in terms of the inhibitory effect on specific [^{3}H]mepyramine binding to guinea-pig cortex histamine receptors. Antiallergic activity was evaluated in terms of the inhibitory effect on compound 48/80-induced lethality in rats. The prolongation of sleeping time on hexobarbital-

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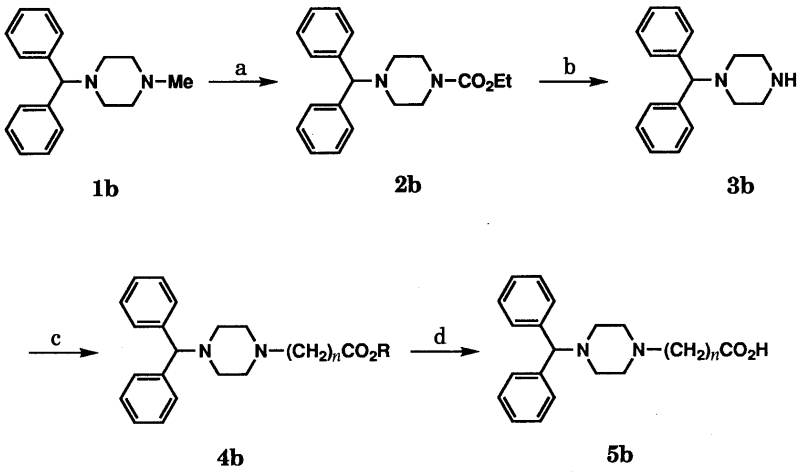
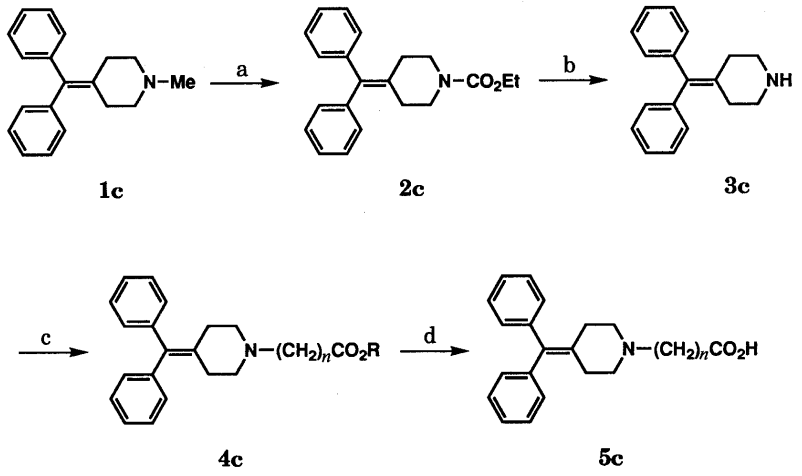
series B



series C



a) $ClCO_2Et$ in toluene b) NaOH in EtOH or *n*-BuOH

c) $Br(CH_2)_nCO_2R$, K_2CO_3 in DMF or $CH_2{=}CHCO_2Et$ in EtOH

d) 2 N NaOH in MeOH

Chart 3

induced anesthesia in mice was employed as an index of CNS side-effects. The results are summarized in Table III.

Except for the acetic acid derivatives ($n=1$), *N*-alkylcarboxylic acids (**5a**—**c**) showed stronger inhibitory effects on compound 48/80-induced lethality *in vivo* than the corresponding *N*-methylamines (**1a**—**c**), in spite of a slight reduction in H_1 binding affinity *in vitro*. Although the influence of difference in species should naturally be considered, zwitter-ionization may change the mechanism of action. As for activity to prolong sleeping time on hexobarbital-induced anesthesia, all *N*-alkylcarboxylic acids (**5a**—**c**) were a little weaker than the *N*-methylamines (**1a**—**c**). In particular, *N*-alkylcarboxylic acids (**5a**) in series A showed approximately 100-fold stronger inhibitory effects on compound 48/80-induced lethality than **1a**, and were the least effective in prolongation of the sleeping time on hexobarbital-induced anesthesia.

The influence of the methylene chain length (n) in **5a**—**c** was then examined. The *N*-propionic acids ($n=2$) in all series showed stronger antiallergic activities and weaker effects on hexobarbital-induced anesthesia than those of the other *N*-alkanoic acids. These results are in good accordance with those obtained previously in another system.[10] We selected the propionic acid derivative (**5a**-2) of the 4-(diphenylmethoxy)piperidine system (series A) as a lead compound because it possessed the strongest antihistaminic and antiallergic activity and the weakest CNS side-effect among all the series, and carried out optimization studies by chemical modification, including introduction of substituents on its benzene rings.

Several studies on the influence of substituents in classical antihistaminics have appeared. Two systematic studies on aryl-substituted diphenhydramines were reported by Harms and Nauta[15] and Ensor *et al.*[16] They found that: 1) *para*-substituted derivatives showed stronger antihistaminic activities than the *ortho*- and *meta*-

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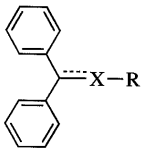
TABLE I. Physicochemical Data for *N*-Alkylcarboxylic Acids (**5a**—**c**)



No.	X	R	mp, °C (Recryst. solvent)	Yield (%)	Formula	Analysis Calcd (Found)		
						C	H	N
5a-1		CH_2CO_2H	193—194 ($MeOH–Et_2O$)	67	$C_{20}H_{23}NO_3 \cdot HCl$	66.38 (66.33)	6.68 6.71	3.87 3.84)
5a-2		$(CH_2)_2CO_2H$	183—185 (H_2O)	97	$C_{21}H_{25}NO_3 \cdot HCl \cdot 1/2H_2O$	65.53 (65.73)	7.07 6.87	3.64 3.80)
5a-3[a]	O—N	$(CH_2)_3CO_2H$	199—200 (H_2O)	91	$C_{22}H_{27}NO_3 \cdot HCl$	67.77 (67.78)	7.24 7.31	3.59 3.55)
5a-4		$(CH_2)_4CO_2H$	150—151 (H_2O)	94	$C_{23}H_{29}NO_3 \cdot HCl \cdot H_2O$	65.47 (65.50)	7.64 7.67	3.32 3.27)
5a-5		$(CH_2)_5CO_2H$	164—165 ($EtOH–Et_2O$)	92	$C_{24}H_{31}NO_3 \cdot HCl$	68.97 (68.89)	7.72 7.70	3.35 3.36)
5b-1		CH_2CO_2H	103—105 (H_2O)	93	$C_{19}H_{22}N_2O_2 \cdot 2H_2O$	65.88 (65.70)	7.56 7.37	8.09 7.85)
5b-2		$(CH_2)_2CO_2H$	201—203 (aq. acetone)	84	$C_{20}H_{24}N_2O_2$	74.05 (73.86	7.46 7.47	8.63 8.57)
5b-3	N N	$(CH_2)_3CO_2H$	182—185 ($EtOH–Et_2O–H_2O$)	58	$C_{21}H_{26}N_2O_2$	338.1994[b] (338.1986)		
5b-4		$(CH_2)_4CO_2H$	249—252 (aq. MeOH)	52	$C_{22}H_{28}N_2O_2 \cdot HCl \cdot 1/4H_2O$	67.16 (67.18	7.56 7.29	7.12 7.15)
5b-5		$(CH_2)_5CO_2H$	197.5—199 ($EtOH–Et_2O$)	47	$C_{23}H_{30}N_2O_2 \cdot HCl$	68.56 (68.43	7.75 7.53	6.95 6.78)
5c-1		CH_2CO_2H	227.5—228.5 ($MeOH–Et_2O$)	54	$C_{20}H_{21}NO_2 \cdot HCl$	69.86 (69.79	6.45 6.38	4.07 3.93)
5c-2		$(CH_2)_2CO_2H$	190—193 ($EtOH–Et_2O–H_2O$)	50	$C_{21}H_{23}NO_2 \cdot HCl \cdot 1/4H_2O$	69.60 (69.46	6.81 6.64	3.87 3.86)
5c-3	=N	$(CH_2)_3CO_2H$	226—229 ($EtOH–Et_2O$)	81	$C_{22}H_{25}NO_2 \cdot HCl$	71.05 (70.97	7.05 6.85	3.77 3.74)
5c-4		$(CH_2)_4CO_2H$	230—233 ($EtOH–Et_2O$)	60	$C_{23}H_{27}NO_2 \cdot HCl$	71.58 (71.60	7.31 7.14	3.63 3.55)
5c-5		$(CH_2)_5CO_2H$	175—176 ($EtOH–Et_2O$)	50	$C_{24}H_{29}NO_2 \cdot HCl$	72.07 (72.22	7.56 7.31	3.50 3.43)

a) See reference 14. *b*) High-resolution MS data. The upper value is calculated and the lower one is that found.

substituted derivatives, 2) a second *para* substituent appeared to have a deactivating effect, 3) introduction of a halogen atom enhanced antihistaminic activity and CNS effects, 4) alkyl substitution resulted in a decrease in CNS effects and toxicity. On the basis of the above criteria, we first undertook introduction of chlorine and a methyl group at various positions on the two benzene rings in the 4-(diphenylmethoxy)piperidine system. Further conversion of the ether moiety into thioether was also tried. The results are summarized in Table IV.

Substitution at the *para* position on a benzene ring slightly enhanced antiallergic activity, while *meta*- and *ortho*-substituted derivatives showed weaker activities than the unsubstituted compound (**5a**-2). Additional introduction of a methyl group at the *para* position on the other benzene ring of **5l** resulted in slight loss of activity (**5m**). On the other hand, the replacement of the ether moiety by the thioether (**5a**-2→**5d**) led to a great loss of activity.

Accordingly, we next introduced various substituents at the *para* position on one benzene ring to optimize the 4-(diphenylmethoxy)piperidine system. Antiallergic activity was evaluated in terms of the inhibitory effect on 48 h homologous PCA in rats and undesirable CNS side-effects were assessed in terms of effects on hexobarbital-induced anesthesia and locomotor activity in mice. Ketotifen and terfenadine were used as reference compounds. The results are summarized in Table V.

Introduction of a halogen atom caused an increase in antiallergic activity, and in particular, compound **5e** showed the strongest activity among all synthesized compounds; nevertheless, the 4-halogenation also caused prolongation of sleeping time on hexobarbital-induced anesthesia and a great decrease in locomotor activity. It could therefore be presumed that introduction of a halogen atom at the *para* position relatively enhanced the CNS side-effects.

As for the introduction of alkyl and alkoxy groups, the 4-methyl derivative (**5l**) showed similar antiallergic activity to that of the unsubstituted compound (**5a**-2), but introduction of bulkier substituents (**5n**—**q**) decreased the potency with increasing bulk. However, introduction of alkyl and alkoxy groups led to a substantial lowering of

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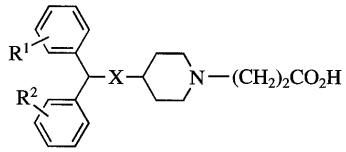
TABLE II. Physicochemical Data for *N*-Alkylcarboxylic Acids (**5d—s**)



No.	R^1	R^2	X	mp, °C (Recryst. solvent)	Yield (%)	Formula	Analysis Calcd (Found) C	H	N
5d	H	H	S	170—172 (EtOH–Et_2O)	92	$C_{21}H_{25}NO_2S \cdot HCl \cdot 1/2H_2O$	62.91 (63.03	6.79 7.03	3.49 3.31)
5e	4-F	H	O	170—171 (MeOH–acetone)	86	$C_{21}H_{24}FNO_3 \cdot HCl$	64.04 (63.80	6.40 6.39	3.56 3.59)
5f	2-Cl	H	O	164—166 (H_2O)	66	$C_{21}H_{24}ClNO_3 \cdot HCl$	61.47 (61.39	6.14 6.16	3.41 3.42)
5g	3-Cl	H	O	116—120 (H_2O)	89	$C_{21}H_{24}ClNO_3 \cdot HCl$	61.47 (61.70	6.14 6.25	3.41 3.42)
5h	4-Cl	H	O	179—181 (MeOH–Et_2O)	80	$C_{21}H_{24}ClNO_3 \cdot HCl$	61.47 (61.46	6.14 6.17	3.41 3.50)
5i	4-Br	H	O	163—165 (H_2O)	49	$C_{21}H_{24}BrNO_3 \cdot HCl$	55.46 (55.27	5.54 5.44	3.08 3.33)
5j	2-Me	H	O	99—103 (aq. EtOH)	56	$C_{22}H_{27}NO_3 \cdot HCl \cdot 1/4H_2O$	66.99 (67.17	7.28 7.28	3.55 3.64)
5k	3-Me	H	O	159—162 (aq. EtOH)	68	$C_{22}H_{27}NO_3 \cdot HCl$	67.77 (67.59	7.24 7.45	3.59 3.60)
5l	4-Me	H	O	157—159 (EtOH–Et_2O)	82	$C_{22}H_{27}NO_3 \cdot HCl$	67.77 (67.63	7.24 6.99	3.59 3.54)
(+)-**5l**	4-Me	H	O	170.5—172.5 (MeCN)	72	$C_{22}H_{27}NO_3 \cdot HCl$	67.77 (67.62	7.24 7.37	3.59 3.67)
(−)-**5l**	4-Me	H	O	126—129 (EtOH)	73	$C_{22}H_{27}NO_3 \cdot HCl$	67.77 (67.77	7.24 7.50	3.59 3.52)
5m	4-Me	4-Me	O	159—162 (H_2O)	99	$C_{23}H_{29}NO_3 \cdot HCl$	68.39 (68.43	7.49 7.49	3.47 3.39)
5n	4-Et	H	O	139.5—142.5 (Acetone–Et_2O)	90	$C_{23}H_{29}NO_3 \cdot HCl$	68.39 (68.29	7.49 7.65	3.47 3.52)
5o	4-*n*-Pr	H	O	140—143 (Acetone–Et_2O)	63	$C_{24}H_{31}NO_3 \cdot HCl$	68.97 (68.85	7.72 7.75	3.35 3.29)
5p	4-iso-Pr	H	O	153—155 (Acetone–Et_2O)	52	$C_{24}H_{31}NO_3 \cdot HCl$	68.97 (68.64	7.72 7.66	3.35 3.23)
5q	4-*n*-Bu	H	O	127—130 (Acetone–iso-Pr_2O)	89	$C_{25}H_{33}NO_3 \cdot HCl \cdot 1/4H_2O$	68.79 (68.69	7.97 7.98	3.21 3.24)
5r	4-OMe	H	O	146—148 (EtOH–AcOEt)	63	$C_{22}H_{27}NO_4 \cdot HCl$	65.10 (64.99	6.95 6.83	3.45 3.45)
5s	4-OEt	H	O	75—78 (AcOEt–Et_2O)	88	$C_{23}H_{29}NO_4 \cdot H_2O$	68.80 (69.05	7.78 7.83	3.49 3.52)

CNS side-effects irrespective of bulkiness. Our observations were essentially in accordance with the results reported by Harms and Nauta[15] and Ensor *et al.*[16]

We therefore chose compound **5l** bearing a methyl group and then examined pharmacological differences between the enantiomers, since Nauta *et al.*[17] reported that (+)-4-methyldiphenhydramine showed much stronger antihistaminic and anticholinergic activities than the (−)-isomer *in vitro*. In our case, the (+)-isomer ((+)-**5l**) exhibited much stronger antihistaminic and antiallergic activity than (−)-**5l**. In the PCA test (+)-**5l** was approximately 100-fold more potent than terfenadine and also approximately twice as potent as ketotifen. Moreover, (+)-**5l** exhibited weaker CNS side-effects than (−)-**5l**.

In conclusion, it was demonstrated that a simple zwitter-ionization was capable of transforming classical antihistaminics into new nonsedative antiallergic agents with excellent effects in rat models. Further biological evaluation of (+)-**5l** in various experimental models and further development of amphoteric drugs are in progress.

Experimental

All melting points were measured on a Yanagimoto melting point apparatus without correction. Spectral data were obtained as follows: ^{1}H-NMR spectra with JEOL FX-90Q (90 MHz) and JEOL A-500 (500 MHz) spectrometers, using tetramethylsilane (TMS) as an internal standard; mass spectra (MS) with a JEOL JMS-DX 300 mass spectrometer; IR spectra with a Hitachi 270-30 spectrometer. Elemental analyses were performed with a Yanagimoto MT-3 or MT-5 elemental analysis apparatus. Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC was performed with a JASCO BIP-1 pumping system and a JASCO UNIDEC-100-V ultraviolet detector. Column chromatography was carried out with silica gel [Kieselgel 60 (Merck)]. TLC was conducted on 0.25 mm pre-coated silica gel plates ($60F_{254}$, Merck).

The following known intermediates were prepared essentially accord-

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TABLE III. Pharmacological Data for *N*-Methylamines (**1a—c**) and *N*-Alkylcarboxylic Acids (**5a—c**)

No.	H_1-binding pIC_{50}	Compound 48/80-induced lethality in rats (mg/kg, *p.o.*) inhibition, % ($n=5$)				Hexobarbital-induced anesthesia in mice (*p.o.*)[a]
		0.01	0.1	1	10	
1a	8.7				0	+
5a-1	6.1				0	+
5a-2	7.5	0	40	80	80	+
5a-3	7.4		0	60	100	+
5a-4	7.4	0	20	80	80	+
5a-5	7.5		0	20	100	−
1b	7.9		0	40	20	++
5b-1	<5		0	20	60	+
5b-2	6.0	0	20	80	80	++
5b-3	5.4		0	20	100	++
5b-4	6.1		0	20	80	+
5b-5	6.0		0	20	80	+
1c	8.5				0	++++
5c-1	>5				0	++
5c-2	6.8		0	60	100	++
5c-3	6.4	0	20	40	60	+++
5c-4	6.8		0	40	100	+++
5c-5	6.6			0	60	++

a) The meanings of the symbols are as follows: ++++, percent increase of sleeping time at 3 mg/kg of test compound is 50% or above; +++, percent increase of sleeping time at 10 mg/kg of test compound is 50% or above; ++, percent increase of sleeping time at 30 mg/kg of test compound is 50% or above; +, percent increase of sleeping time at 100 mg/kg of test compound is 50% or above; −, percent increase of sleeping time at 100 mg/kg of test compound is less than 50%.

TABLE IV. Inhibitory Effects of *N*-Alkylcarboxylic Acids on Compound 48/80-Induced Lethality

No.	Compound 48/80-induced lethality in rats (mg/kg, *p.o.*) inhibition, % ($n=5$)			
	0.01	0.1	1	10
5a-2	0	40	80	80
5d	0	20	40	60
5f	0	20	40	60
5g		0	20	100
5h	20	40	80	100
5j	0	20	60	100
5k		0	60	100
5l	0	60	80	100
5m	0	20	20	20

ing to the literature: 4-diphenylmethoxy-1-methylpiperidine (**1a**),[11] 4-diphenylmethyl-1-methylpiperazine (**1b**),[12] 4-diphenylmethylene-1-methylpiperidine (**1c**)[13] and related compounds (**1d—s**).

Ethyl 4-Diphenylmethoxy-1-piperidinecarboxylate (2a) A solution of **1a** (89.0 g, 0.32 mol) and ethyl chloroformate (102.6 g, 0.95 mol) in toluene (400 ml) was refluxed for 5.5 h. After cooling, the reaction mixture was washed with diluted hydrochloric acid and water, dried over Na_2SO_4 and evaporated to afford **2a** as a pale yellow oil (93.7 g, 87%). IR (liq.): 1698 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, $J=7$ Hz, $CO_2CH_2C\underline{H}_3$), 1.44—2.00 (4H, m, $CH_2\times2$), 3.00—3.95 (5H, m, $CH_2\times2$ and CH), 4.11 (2H, q, $J=7$ Hz, $CO_2C\underline{H}_2CH_3$), 5.52 (1H, s, CH), 7.30 (10H, br s, Ar-H). MS *m/z*: 339 (M^+).

4-(Diphenylmethoxy)piperidine (3a) A solution of **2a** (93.7 g, 0.28 mol) and 40% NaOH (prepared from NaOH 66.2 g and H_2O 100 ml) in EtOH (600 ml) was refluxed for 16.5 h. After removal of the solvent under reduced pressure, the residue was diluted with water and extracted with Et_2O. The ethereal layer was extracted with diluted hydrochloric acid. The aqueous layer was made alkaline with K_2CO_3 and then extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to afford **3a** as a colorless oil (64.7 g, 88%). The free base was converted to the hydrochloride by the usual method.

Hydrochloride: Colorless prisms, mp 211—212 °C (EtOH) [lit.[18] 209.8 °C]. ^{1}H-NMR (DMSO-d_6) δ: 1.60—2.20 (4H, m, $CH_2\times2$), 2.70—3.30 (4H, m, $CH_2\times2$), 3.50—3.80 (1H, m, CH), 5.64 (1H, s, CH), 7.00—7.50 (10H, m, Ar-H), 9.10 (2H, br s, N^+H_2). MS *m/z*: 268 (M^+(free)+1). *Anal.* Calcd for $C_{18}H_{21}NO\cdot HCl$: C, 71.16; H, 7.30; N, 4.61. Found: C, 71.17; H, 7.25; N, 4.48.

TABLE V. Pharmacological Data for *N*-Alkylcarboxylic Acids

No.	H_1-binding pIC_{50}	PCA in rats ED_{50} (mg/kg, *p.o.*)	Hexobarbital-induced anesthesia in mice ID_{50} (mg/kg, *p.o.*)	Locomotor activity in mice MNED[a] (mg/kg, *p.o.*)
5a-2	7.5	0.27	74	3
5e	6.5	0.056	44	0.03
5h	7.1	0.11	48	1
5i	6.8	0.51	4	10
5l	7.0	0.27	>300	30
(+)-**5l**	7.0	0.17	>300	100
(−)-**5l**	6.3	7.7	300	30
5n	7.1	0.67	>300	30
5o	7.3	1.7	>300	30
5p	6.8	1.8	100	>100
5q	6.7	8.7	>300	>100
5r	6.4	1.1	135	30
5s	6.3	0.91	173	>100
Ketotifen	9.1	0.43	13	30
Terfenadine	6.8	9.0	76	>100

a) Maximum no-effect dose.

1-(Diphenylmethyl)piperazine (**3b**),[12] 4-(diphenylmethylene)piperidine (**3c**)[19] and related compounds **3d—s** were prepared similarly.

Ethyl [(4-Diphenylmethoxy)piperidino]acetate (4a-1) A mixture of **3a** (4.01 g, 15 mmol), ethyl bromoacetate (2.76 g, 17 mmol) and K_2CO_3 (2.07 g, 15 mmol) in *N*,*N*-dimethylformamide (DMF) (25 ml) was heated at 80 °C for 2 h. The reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The oily residue was purified by column chromatography [SiO_2, $CHCl_3$–MeOH (50:1)] to afford **4a**-1 as a pale yellow oil (3.70 g, 70%). IR (liq.): 1748 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, $CO_2CH_2C\underline{H}_3$), 1.56—2.10 (4H, m, $CH_2\times2$), 2.20—3.00 (4H, m, $CH_2\times2$), 3.20 (2H, s, $C\underline{H}_2CO_2Et$), 3.30—3.64 (1H, m, CH), 4.17 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 5.50 (1H, s, CH), 7.08—7.64 (10H, m, Ar-H). High-resolution MS *m/z*: Calcd for $C_{22}H_{27}NO_3$: 353.1991. Found: 353.1975.

Ethyl 3-[4-[(4-Ethylphenyl)phenylmethoxy]piperidino]propionate (4n) A solution of **3n** (3.25 g, 11 mmol) and ethyl acrylate (1.43 g, 14 mmol)

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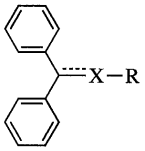
TABLE VI. Physicochemical Data for *N*-Alkylcarboxylates (**4a—c**)



No.	X	R	mp, °C (Recryst. solvent)	Yield (%)	Formula	Analysis Calcd (Found)		
						C	H	N
4a-1		CH_2CO_2Et	Oil	70	$C_{22}H_{27}NO_3$		353.1991[a] (353.1975)	
4a-2		$(CH_2)_2CO_2Et$	176—178 (EtOH)	68	$C_{23}H_{29}NO_3 \cdot HCl$	68.39 (68.29)	7.49 7.33	3.47 3.45)
4a-3[b]	O—N	$(CH_2)_3CO_2Et$	131—133 (AcOEt)	64	$C_{24}H_{31}NO_3 \cdot HCl$	68.97 (68.74)	7.72 7.57	3.35 3.33)
4a-4		$(CH_2)_4CO_2Et$	137—139 (AcOEt)	70	$C_{25}H_{33}NO_3 \cdot HCl$	69.51 (69.50)	7.93 7.86	3.24 3.33)
4a-5		$(CH_2)_5CO_2Me$	142.5—143.5 (H_2O)	79	$C_{25}H_{33}NO_3 \cdot HCl$	69.51 (69.31)	7.93 7.82	3.24 3.31)
4b-1[c]		CH_2CO_2Et	60—61 (*n*-Hexane)	66	$C_{21}H_{26}N_2O_2$	74.53 (74.51)	7.74 7.57	8.28 8.17)
4b-2[d]		$(CH_2)_2CO_2Et$	143—148 (EtOH–Et_2O)	81	$C_{22}H_{28}N_2O_2 \cdot 2HCl \cdot 3/2H_2O$	58.40 (58.28)	7.35 6.97	6.19 6.24)
4b-3	N N	$(CH_2)_3CO_2Et$	68—70 (*n*-Hexane)	52	$C_{23}H_{30}N_2O_2$	75.38 (75.43)	8.25 7.99	7.64 7.56)
4b-4		$(CH_2)_4CO_2Et$	187—189 (EtOH)	63	$C_{24}H_{32}N_2O_2 \cdot C_4H_4O_4 \cdot 1/2H_2O$	66.52 (66.47)	7.38 7.05	5.54 5.44)
4b-5		$(CH_2)_5CO_2Me$	176.5—178.5 (Acetone)	61	$C_{24}H_{32}N_2O_2 \cdot 2HCl \cdot 3/4H_2O$	61.73 (61.87)	7.66 7.57	6.00 5.83)
4c-1		CH_2CO_2Et	138—140 (H_2O)	78	$C_{22}H_{25}NO_2 \cdot C_4H_4O_4$	69.16 (69.14)	6.47 6.43	3.10 3.15)
4c-2		$(CH_2)_2CO_2Et$	156—158 (EtOH–Et_2O)	48	$C_{23}H_{27}NO_2 \cdot C_4H_4O_4$	69.66 (69.62)	6.71 6.59	3.01 3.08)
4c-3	N	$(CH_2)_3CO_2Et$	160.5—162.5 (EtOH)	87	$C_{24}H_{29}NO_2 \cdot C_4H_4O_4$	70.13 (69.82)	6.94 6.78	2.92 2.92)
4c-4		$(CH_2)_4CO_2Et$	170—173 (EtOH)	67	$C_{25}H_{31}NO_2 \cdot C_4H_4O_4 \cdot H_2O$	68.08 (68.28)	7.29 6.97	2.74 2.58)
4c-5		$(CH_2)_5CO_2Me$	158—160 (H_2O)	79	$C_{25}H_{31}NO_2 \cdot HCl$	72.53 (72.54)	7.79 7.54	3.38 3.37)

a) High-resolution MS data. The upper value is calculated and the lower one is that found. *b*) See reference 20. *c*) See reference 21. *d*) See reference 22.

in EtOH (20 ml) was refluxed for 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in Et_2O and treated with ethanolic HCl to give **4n** (hydrochloride) (4.47 g, 94%). Recrystallization from AcOEt afforded colorless prisms, mp 142—145 °C. IR (KBr): 1734 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.20 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.68—2.34 (4H, m, $CH_2 \times 2$), 2.34—2.75 (2H, m, CH_2), 2.75—3.81 (7H, m, $CH_2 \times 3$ and CH), 2.89 (2H, q, J=7.5 Hz, CH_2CH_3), 4.10 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.60 (1H, s, CH), 7.07—7.52 (9H, m, Ar-H). MS *m/z*: 395 (M^+(free)). *Anal.* Calcd for $C_{25}H_{33}NO_3 \cdot HCl$: C, 69.51; H, 7.93; N, 3.24. Found: C, 69.23; H, 7.91; N, 3.33.

Other *N*-alkylcarboxylates (**4**) were prepared in a manner similar to that described for **4a**-1 or **4n** from corresponding secondary amines (**3**). Physicochemical data for *N*-alkylcarboxylates (**4**) are summarized in Tables VI and VII.

[4-(Diphenylmethoxy)piperidino]acetic Acid (5a-1) A solution of **4a**-1 (3.00 g, 8.5 mmol), 2 N NaOH (8.5 ml, 17 mmol) in MeOH (30 ml) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was diluted with water, acidified to pH 2 with concentrated hydrochloric acid and then extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give the crude product. Recrystallization from MeOH–Et_2O afforded pure **5a**-1 hydrochloride as colorless crystals (2.05 g, 67%), mp 193—194 °C. IR (KBr): 1742 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.68—2.30 (4H, m, $CH_2 \times 2$), 3.00—3.80 (5H, m, $CH_2 \times 2$ and CH), 4.02 (2H, s, CH_2) 5.64 (1H, s, CH), 7.10—7.52 (10H, m, Ar-H). MS *m/z*: 325 (M^+(free)). *Anal.* Calcd for $C_{20}H_{23}NO_3 \cdot HCl$: C, 66.38; H, 6.68; N, 3.87. Found: C, 66.33; H, 6.71; N, 3.84.

Other *N*-alkylcarboxylic acids (**5**) were prepared similarly from corresponding *N*-alkylcarboxylates (**4**).

Resolution of Racemic 4-[(4-methylphenyl)phenylmethoxy]piperidine ((+)-3l and (−)-3l) (+)-Dibenzoyl-D-tartaric acid monohydrate (19.3 g, 51 mmol) was added to a solution of racemic **3l** (25.3 g, 90 mmol) in MeOH (330 ml) at room temperature. The deposited crystals were collected by filtration to give the crude (+)-**3l** (+)-dibenzoyl-D-tartrate (22.1 g). The filtrate was evaporated to dryness. The residue was made alkaline with 10% NaOH and extracted with Et_2O. The ethereal layer was washed with water, dried over Na_2SO_4 and evaporated. The residue (12.5 g, 44 mmol) was diluted with MeOH and (−)-dibenzoyl-L-tartaric acid monohydrate (8.3 g, 22 mmol) was added to the solution. The deposited crystals were collected by filtration to give (−)-**3l** (−)-dibenzoyl-L-tartrate (16.8 g). Each of these crude salts was recrystallized from MeOH twice to give an optically pure salt. Each of the pure salts was converted to the free base by the usual method to afford (+)-**3l** and (−)-**3l**. (+)-**3l** (free base): colorless oil, $[\alpha]_D$ +14.0° (c=0.5, $CHCl_3$). (−)-**3l** (free base): colorless oil, $[\alpha]_D$ −14.4° (c=0.5, $CHCl_3$).

Enantiomers of 3-[4-[(4-Methylphenyl)phenylmethoxy]piperidino]propionic Acid ((+)-5l and (−)-5l) Each enantiomer of **5l** was prepared from the corresponding optical isomer of **3l** by a similar method to that described above. (+)-**5l** (hydrochloride): colorless crystals (MeCN), mp 170.5—172.5 °C, $[\alpha]_D$ +11.3° (c=0.5, MeOH). Optical purity (by HPLC): >99% ee. (−)-5l (hydrochloride): colorless crystals (EtOH), mp 126—129 °C, $[\alpha]_D$ −10.8 (c=0.5, MeOH). Optical purity (by HPLC): >99% ee.

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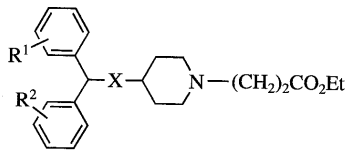
TABLE VII. Physicochemical Data for *N*-Alkylcarboxylic Acids (**4d—s**)



No.	R^1	R^2	X	mp, °C (Recryst. solvent)	Yield (%)	Formula	Analysis Calcd (Found) C	H	N
4d	H	H	S	149—150 (EtOH–Et_2O)	69	$C_{23}H_{29}NO_2S \cdot HCl$	65.77 (65.72	7.20 7.06	3.33 3.36)
4e	4-F	H	O	200—201 (EtOH–Et_2O)	85	$C_{23}H_{28}FNO_3 \cdot HCl$	65.47 (65.17	6.93 6.87	3.32 3.34)
4f	2-Cl	H	O	144—146 (Acetone–Et_2O)	83	$C_{23}H_{28}ClNO_3 \cdot HCl$	63.01 (62.93	6.67 6.75	3.20 3.12)
4g	3-Cl	H	O	170—172 (H_2O)	70	$C_{23}H_{28}ClNO_3 \cdot HCl$	63.01 (62.80	6.67 6.42	3.20 3.15)
4h	4-Cl	H	O	187—189 (EtOH–Et_2O)	56	$C_{23}H_{28}ClNO_3 \cdot HCl$	63.01 (62.77	6.67 6.63	3.20 3.24)
4i	4-Br	H	O	Oil	66	$C_{23}H_{28}BrNO_3$	445.1253, 447.1234[a] (445.1257, 447.1234)		
4j	2-Me	H	O	Oil	92	$C_{24}H_{31}NO_3$	381.2305[a] (381.2307)		
4k	3-Me	H	O	Oil	79	$C_{24}H_{31}NO_3$	381.2305[a] (381.2307)		
4l	4-Me	H	O	101—104 (EtOH–Et_2O)	74	$C_{24}H_{31}NO_3 \cdot C_4H_4O_4$	67.59 (67.29	7.09 7.15	2.81 2.83)
(+)-**4l**	4-Me	H	O	Oil	95	$C_{24}H_{31}NO_3$	381.2305[a] (381.2300)		
(−)-**4l**	4-Me	H	O	Oil	96	$C_{24}H_{31}NO_3$	381.2305[a] (381.2209)		
4m	4-Me	4-Me	O	153—156 (Acetone–Et_2O)	89	$C_{25}H_{33}NO_3 \cdot HCl$	69.51 (69.39	7.93 7.96	3.24 3.25)
4n	4-Et	H	O	142—145 (AcOEt)	94	$C_{25}H_{33}NO_3 \cdot HCl$	69.51 (69.23	7.93 7.91	3.24 3.33)
4o	4-*n*-Pr	H	O	154—156 (AcOEt)	96	$C_{26}H_{35}NO_3 \cdot HCl$	70.01 (70.00	8.14 8.13	3.14 3.21)
4p	4-iso-Pr	H	O	144—146 (EtOH–Et_2O)	76	$C_{26}H_{35}NO_3 \cdot C_4H_4O_4$	68.55 (68.50	7.48 7.58	2.66 2.71)
4q	4-*n*-Bu	H	O	167—170 (AcOEt)	94	$C_{27}H_{37}NO_3 \cdot HCl$	70.49 (70.49	8.33 8.27	3.04 3.08)
4r	4-OMe	H	O	109—111 (EtOH–Et_2O)	76	$C_{24}H_{31}NO_4 \cdot C_4H_4O_4$	65.48 (65.37	6.87 6.82	2.73 2.64)
4s	4-OEt	H	O	149—150.5 (AcOEt)	94	$C_{25}H_{33}NO_4 \cdot C_4H_4O_4$	66.02 (65.89	7.07 7.02	2.65 2.65)

a) High-resolution MS data. The upper values are calculated and the lower ones are those found.

HPLC Analysis Chromatographic conditions were as follows: column, ULTRON ES-OVM (4.6 i.d. × 150 mm); column temperature, 25 °C; mobile phase, 0.02 M phosphate buffer (pH 3.5)–CH_3CN (91 : 9); flow rate, 1.0 ml/min; detection, UV at 224 nm; retention time (t_R), (+)-**5l**, 9.3 min; (−)-**5l**, 7.9 min.

Pharmacological Evaluation Procedures. Histamine-1 (H_1) Receptor Binding Assay Male Hartley guinea-pigs (weighing 420 to 560 g) were decapitated and the brain cortex was isolated. The cortex was homogenized in 20 volumes of 50 mM Na/K phosphate buffer (pH 7.4) using a Polytron at setting 7 with two 10-s bursts separated by a 30-s pause. The homogenates were centrifuged at 50000 × *g* for 15 min at 4 °C. The pellets were washed twice and the final pellets were resuspended in cold 50 mM Na/K phosphate buffer. For the [^{3}H]mepyramine binding assay, each assay tube received 50 μl of radioligand ([^{3}H]mepyramine, 917.6 GBq/mmol, NEN), 50 μl of the test compound or buffer and 0.3 ml of the membrane suspension. The binding assay was initiated by the addition of the membrane suspension and assay tubes were kept at room temperature for 1 h. The reaction was terminated by rapid vacuum filtration over GF/B glass fiber filters (Whatman) using a cell harvester (M-24R, Brandel). The filters were transferred to vials to which 7 ml of Aquasol-2 had been added and the radioactivity was counted (Model 3385, Packard). The specific binding of [^{3}H]mepyramine was estimated as the difference between radioactivity bound in the absence and in the presence of 1 μM promethazine. The IC_{50} values (concentration which produced 50% inhibition of the specific binding of [^{3}H]mepyramine) were determined.

Effect on Compound 48/80-Induced Lethality in Rats[23] Male Wistar rats (starved for 24 h, 6 weeks of age) were used. Compound 48/80 (formaldehyde condensation product of *p*-methoxy-*N*-methylphenethylamine) was administered intravenously at a lethal dose of 1 mg/kg. Survival for more than 2 h was selected as an all-or-none criterion. Test compounds were given orally 1 h before compound 48/80 administration.

Effect on 48 h Homologous PCA in Rats The induction and evaluation of allergic reaction were done according to the method of Makino *et al.*[24] Male Wistar rats (starved for 20 h, 6 weeks of age) were passively sensitized by intracutaneous injection on the back of 0.1 ml of 20- or 40-fold-diluted anti-2,4-dinitrophenylated ascaris extract (DNP-As) rat serum. After 48 h, the animals were challenged by an intravenous injection of 0.5 ml of saline solution containing 1 mg of DNP-As and 5 mg of Evans blue. The animals were killed 30 min after the challenge and the extravasated dye was extracted with 1 N KOH and acetone, neutralized with 1 N H_3PO_4 and determined from the absorbance at 620 nm (U-2000,

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Hitachi). Test compounds were administered orally 1 h before antigen challenge. A suitable pretreatment time was determined in a preliminary test. The inhibitory activity of the test compound was expressed as percent inhibition of PCA as compared with the control group. The ED_{50} value (dose which produced 50% inhibition of the PCA) was calculated according to the probit method.

Effect on Hexobarbital-Induced Anesthesia in Mice Male ddY mice (starved for 20 to 24 h, weighing 19 to 27 g) were treated orally with test compounds or vehicle. Thirty minutes later, hexobarbital sodium (80 mg/kg, i.p.) was injected into the animals and the duration of loss of righting reflex was observed and taken as the sleeping time. The percent increase of sleeping time was calculated by using the following formula:

$$\text{percent increase} = \frac{\text{sleeping time of drug-treated} - \text{sleeping time of vehicle-treated}}{\text{sleeping time of vehicle-treated}} \times 100$$

The ID_{50} (mg/kg) value (dose which produced 50% increase of sleeping time relative to that of the vehicle-treated group) was determined for each compound.

Effect on Locomotor Activity in Mice Male ddY mice (starved for 24 h, weighing 20 to 30 g) were used. Locomotor activity was recorded with an Animex activity meter (MK-110, Muromachi Kikai) for 4 h after oral administration of each test compound. The maximum no-effect dose (MNED) was determined.

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