Syntheses of the Metabolites of 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole Difumarate (KG-2413) and Related Compounds

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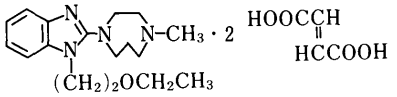
The metabolites of 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole difumarate (KG-2413), which has a potent H_1-antihistaminic activity, were predicted on the basis of metabolic studies of related compounds and were synthesized to aid in identification of the actual metabolites and for examination of their antihistaminic activity. Among the twelve compounds prepared, nine compounds were actually found as the metabolites of KG-2413 in rat urine. The antihistaminic activities of these metabolites were found to be lower than that of KG-2413.

Keywords 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole; benzimidazole; metabolite; H_1-antihistaminic activity

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole difumarate (KG-2413) is a new antiallergic and antiasthmatic agent,[1,2] which is now under clinical trial. The structure of KG-2413 consists of benzimidazole, *N*-methylhomopiperazine and ethoxyethyl moieties. Based on the metabolism of these substructures described in the literature, we predicted the metabolites of KG-2413 and synthesized them in order to elucidate the metabolism of KG-2413 efficiently.

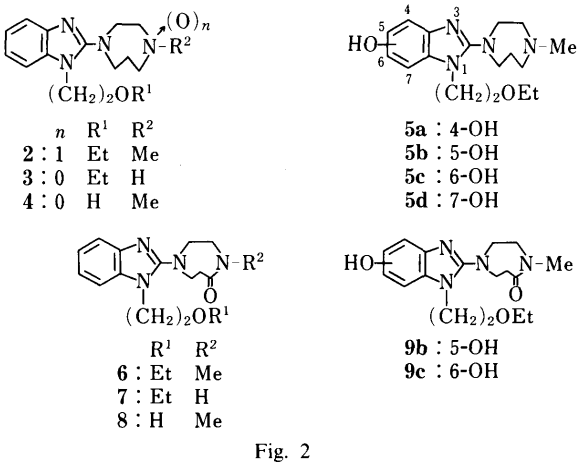


KG-2413

Fig. 1

In the metabolism studies of piperazine derivatives such as diethylcarbamazine,[3] pipemidic acid[4] and ofloxacin,[5] *N*-oxidation, *N*-dealkylation and ring oxidation of the piperazine moiety have been reported. As for the metabolism of benzimidazole derivatives, such as benzimidazole itself,[6] oxapadol,[7] oxatomide[8] and 5,6-dichloro-2-trifluoromethylbenzimidazole,[9] ring hydroxylation has been reported. And in case of the ether compounds, *O*-dealkylation has frequently been reported.

From these results we first designed eight compounds as candidate metabolites of KG-2413: that is, the *N*-oxide (**2**), *N*-demethylated (**3**), *O*-deethylated (**4**), ring hydroxylated (**5a—d**) and oxo (**6**) analogues of KG-2413. Next, by the combination of the above-mentioned metabolic conversions, four additional compounds (**7**, **8**, **9b**, **c**) were designed (Fig. 2).



n	R^1	R^2
2 : 1	Et	Me
3 : 0	Et	H
4 : 0	H	Me

5a : 4-OH
5b : 5-OH
5c : 6-OH
5d : 7-OH

	R^1	R^2
6 :	Et	Me
7 :	Et	H
8 :	H	Me

9b : 5-OH
9c : 6-OH

Fig. 2

Here, we describe the syntheses of these twelve compounds and their antihistaminic activity.

Synthesis Compounds **2**—**4** were synthesized as follows (Chart 1). Oxidation of compound **1** (free base of KG-2413) with hydrogen peroxide gave the *N*-oxide (**2**). The reaction of **1** with ethyl chloroformate, followed by hydrolysis with potassium hydroxide afforded demethylated KG-2413 (**3**). The reaction of **1** with 47% hydrobromic acid gave deethylated KG-2413 (**4**).

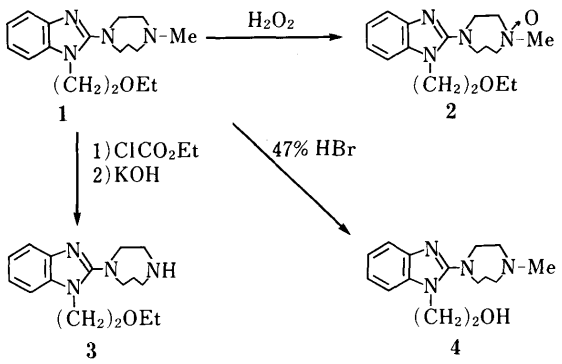


Chart 1

We chose the phenylmethoxy derivatives **15b—d** as precursors of 5-, 6- and 7-hydroxy-KG-2413 (**5b—d**) (Chart 2). Ethoxyethylamination of the starting materials **10b—d**[10] with 2-ethoxyethylamine, followed by reduction with zinc dust in the presence of hydrochloric acid, afforded the *o*-phenylenediamines (**12b—d**). Condensation of **12b—d** with urea gave the benzimidazolones (**13b—d**), which were chlorinated with phosphorus oxychloride. Reaction of the 2-chlorobenzimidazoles (**14b—d**) with *N*-methylhomopiperazine, followed by hydrogenolysis using 5% palladium charcoal gave the desired compounds **5b—d**.

As for the synthesis of 4-hydroxy-KG-2413 (**5a**), a synthetic route similar to that used to obtain **5b—d** was not suitable because 1-chloro-2-nitro-3-phenylmethoxybenzene did not react with 2-ethoxyethylamine. Thus, compound **16**[11] was chosen as a starting material (Chart 3). Ethoxyethylation of **16** with 2-bromoethyl ethyl ether in the presence of sodium hydride afforded a mixture of the 4-

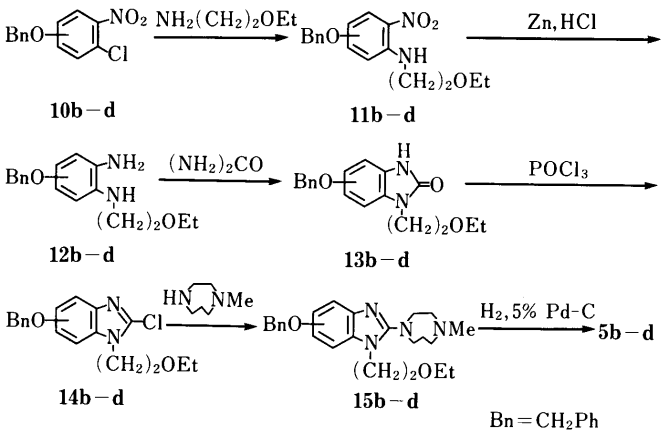
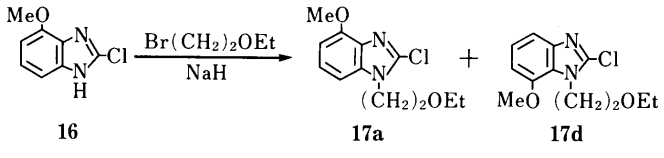


Chart 2



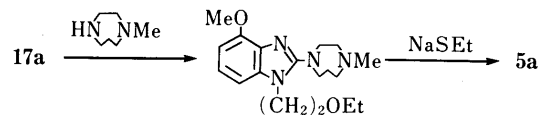


Chart 3

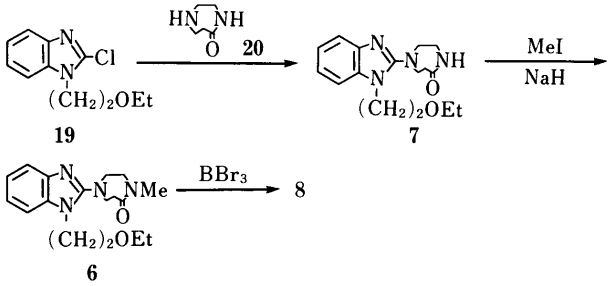


Chart 4

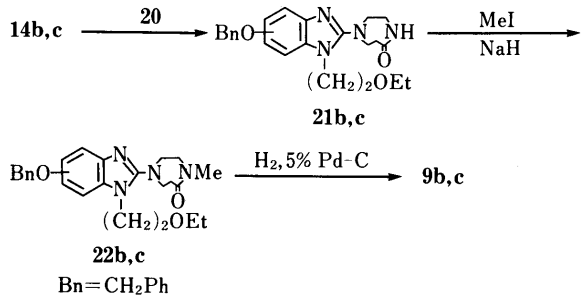


Chart 5

methoxy derivative (**17a**) and 7-methoxy derivative (**17d**), which were separated by silica gel column chromatography. The structure of **17d** was identified on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, which is similar to that of **14d**. Reaction of **17a** with *N*-methylhomopiperazine, followed by treatment with sodium ethyl mercaptide gave the desired compound **5a**.

Compounds **6**—**8** were synthesized as follows (Chart 4). Reaction of the starting material **19** with hexahydro-1*H*-1,4-diazepin-5-one[12] (**20**) gave the *N*-demethylated oxo analogue of KG-2413 (**7**). Methylation of **7** with methyl iodide in the presence of sodium hydride afforded the oxo analogue (**6**). Reaction of **6** with boron tribromide gave the *O*-deethylated oxo analogue (**8**).

Compounds **9b, c** were synthesized by reference to the syntheses of **5b, c** and **6** (Chart 5). Reaction of the starting materials **14b, c** with **20**, followed by treatment with methyl iodide in the presence of sodium hydride gave the phenylmethoxy oxo derivatives (**22b, c**). Hydrogenation of **22b, c** using 5% palladium charcoal afforded hydroxylated oxo analogues of KG-2413 (**9b, c**).

Results

Among the twelve compounds prepared, nine compounds (**2**—**4**, **5b, c**, **7**, **8**, **9b, c**) were actually found as the metabolites of KG-2413 in rat urine.[13]

The antihistaminic activities of the nine metabolites of KG-2413 and the other three related compounds were measured by the same method as described in the previous paper,[1] and the results are summarized in Table I. All the compounds tested were found to exhibit lower activity than KG-2413. However, compounds **3**, **5b** and **5c**, which are rat urinary metabolites, showed considerable antihistaminic activity.

In conclusion, predicting the metabolites of KG-2413 and synthesizing them in advance was found to be a useful methodology to speed up the metabolism study.

Experimental

Melting points were measured with a capillary melting point apparatus (Yamato MP-21) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-50 spectrometer. ^{1}H-NMR spectra were run on a Bruker AM-300 or a Hitachi R-24B NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer. Elemental analyses were performed by the Analytical Department of Kanebo Research Center.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole *N*-oxide (2) A solution of **1** (2.70 g, 8.9 mmol) in ethanol (15 ml) was treated with 10% H_2O_2 (15 ml) and the mixture was stirred for 2 d. The reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$–MeOH (4 : 1) gave 1.80 g (63%) of **2** as a yellow oil. IR (Nujol): 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz), 1.94—2.00 (1H, m), 3.05—3.13 (1H, m), 3.35 (3H, s), 3.41—3.51 (4H, m), 3.66—3.83 (6H, m), 3.94—4.01 (1H, m), 4.15—4.23 (3H, m), 7.12—7.28 (3H, m), 7.52—7.55 (1H, m). Compound **2** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-hexahydro-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole (3) A solution of ethyl chloroformate (16.3 g, 150 mmol) in benzene (10 ml) was added dropwise to a gently refluxing solution of **1** (43.0 g, 142 mmol) in benzene (100 ml), and the mixture was refluxed for 3 h. The reaction mixture was concentrated to dryness. The residue was column chromatographed on silica gel. Elution with $CHCl_3$–MeOH (10 : 1) gave 22.0 g of 2-(4-ethoxycarbonylhexahydro-1*H*-1,4-diazepin-1-yl)-1-(2-ethoxyethyl)-1*H*-benzimidazole as an oil. This oil was dissolved in EtOH (30 ml), and KOH (20.0 g, 360 mmol) was added to the solution. After being refluxed for 3 h, the reaction mixture was poured into water, neutralized with 3 N HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (4 : 1)) to give 12.1 g (30% from **1**) of **3** as a yellow oil. IR (Nujol): 3370, 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz), 1.90—1.98 (2H, m), 2.11 (1H, br), 3.03—3.13 (4H, m), 3.47 (2H, q, J=7 Hz), 3.60—3.64 (4H, m), 3.79 (2H, t,

TABLE I. Physicochemical and Pharmacological Data for the Metabolites of KG-2413 and Related Compounds

Compd. No.	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Analysis (%) Calcd (Found) C	H	N	Antihistaminic activity IC_{50} (M)[d]	Ratio[e]
2	63	87—193	A	$C_{17}H_{26}N_4O_2 \cdot 2C_6H_3N_3O_7$	44.85 (44.86)	4.15 4.13	18.04 18.06)	6.26×10^{-7} (4.70×10^{-7}—8.46×10^{-7})	0.0050
3	70	183—187	B	$C_{16}H_{24}N_4O \cdot 2C_6H_3N_3O_7$	45.04 (45.13)	4.05 3.80	18.76 18.75)	6.07×10^{-9} (4.37×10^{-9}—8.87×10^{-9})	0.51
4	54	205—209	A	$C_{15}H_{22}N_4O \cdot 2C_6H_3N_3O_7$	44.27 (44.39)	3.85 3.80	19.12 19.02)	2.39×10^{-7} (1.91×10^{-7}—3.05×10^{-7})	0.013
5a	70	111—114	D	$C_{17}H_{26}N_4O_2 \cdot 2C_6H_3N_3O_7$ $1/3\,C_3H_6O \cdot H_2O$	44.27 (44.15	4.46 4.33	17.21 17.40)	2.91×10^{-8} (2.16×10^{-8}—3.89×10^{-8})	0.11
5b	70	224—226	A	$C_{17}H_{26}N_4O_2 \cdot 2C_6H_3N_3O_7$	44.85 (44.85	4.15 4.11	18.04 18.04)	4.58×10^{-9} (3.62×10^{-9}—5.75×10^{-9})	0.68
5c	61	121—123	C	$C_{17}H_{26}N_4O_2$	64.13 (64.06	8.23 8.21	17.60 17.54)	1.05×10^{-8} (8.26×10^{-9}—1.31×10^{-8})	0.30
5d	79	191—194	A	$C_{17}H_{26}N_4O_2 \cdot 2C_6H_3N_3O_7$	44.85 (44.82	4.15 4.02	18.04 18.01)	1.32×10^{-8} (9.78×10^{-9}—1.83×10^{-8})	0.23
6	64	65—70	E	$C_{17}H_{24}N_4O_2 \cdot HCl \cdot 3H_2O$	50.18 (49.97	7.68 7.57	13.77 13.79)	$>10^{-6}$	<0.003
7	55	185—189	E	$C_{16}H_{22}N_4O_2 \cdot HCl \cdot 1/4\,H_2O$	55.97 (55.74	6.90 7.03	16.32 16.35)	$>10^{-6}$	<0.003
8	81	158—161	E	$C_{15}H_{20}N_4O_2 \cdot HCl \cdot 5/4\,H_2O$	51.87 (52.02	6.82 6.72	16.13 16.21)	$>10^{-6}$	<0.003
9b	78	201—204	E	$C_{17}H_{24}N_4O_3 \cdot HCl$	55.36 (55.20	6.83 6.96	15.19 15.29)	$>10^{-6}$	<0.003
9c	60	218—219	E	$C_{17}H_{24}N_4O_3 \cdot HCl$ $1/10\,C_4H_8O_2$	55.34 (54.95	6.89 6.86	14.83 14.45)	$>10^{-6}$	<0.003
KG-2413								3.10×10^{-9} (2.47×10^{-9}—3.82×10^{-9})	1

a) Yield of free base. *b*) Solvents: A, DMF–EtOH; B, MeOH; C, AcOEt; D, acetone–H_2O; E, AcOEt–EtOH. *c*) Formula: $C_6H_3N_3O_7$, picric acid; C_3H_6O, acetone; $C_4H_8O_2$, ethyl acetate. *d*) The 95% confidence limits are included in parentheses. *e*) Potency relative to KG-2413.

$J=6$ Hz), 4.20 (2H, t, $J=6$ Hz), 7.09—7.19 (2H, m), 7.25—7.28 (1H, m), 7.53—7.56 (1H, m). MS *m/z*: 288 (M^+). Compound **3** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

2-(Hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1-(2-hydroxyethyl)-1*H*-benzimidazole (4) A solution of **1** (10.0 g, 33 mmol) in 47% HBr (50 ml) was refluxed for 3 h. The reaction mixture was made basic with NaOH and extracted with *n*-BuOH. The extract was washed with water and concentrated *in vacuo* to give 4.89 g (54%) of **4** as a pale yellow oil. IR (Nujol): 3400, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.92—1.99 (2H, m), 2.37 (3H, s), 2.66—2.70 (4H, m), 3.54—3.59 (4H, m), 3.99 (2H, t, $J=6$ Hz), 4.19 (2H, t, $J=6$ Hz), 7.09—7.18 (2H, m), 7.22—7.26 (1H, m), 7.50—7.53 (1H, m). MS *m/z*: 274 (M^+). Compound **4** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

1-Chloro-2-nitro-4-phenylmethoxybenzene (10b) A mixture of 4-chloro-3-nitrophenol (2.89 g, 17 mmol), benzyl chloride (2.20 g, 17 mmol) and K_2CO_3 (2.30 g, 17 mmol) in *N,N*-dimethylformamide (DMF) (10 ml) was stirred at 90 °C for 5 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The resulting solid was recrystallized from MeOH to give 2.83 g (64%) of **10b** as pale yellow plates, mp 50—52 °C. IR (KBr): 1625, 1545, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.08 (2H, s), 7.10 (1H, dd, $J=3$, 9 Hz), 7.32—7.41 (6H, m), 7.45 (1H, d, $J=3$ Hz). *Anal.* Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.18; H, 3.80; N, 5.29.

2-Chloro-1-nitro-4-phenylmethoxybenzene (10c) and 2-Chloro-1-nitro-3-phenylmethoxybenzene (10d) Compounds **10c** and **10d** were prepared in the same manner as described for **10b**. **10c**: mp 82—85 °C (pale yellow plates from hexane–AcOEt). IR (KBr): 1610, 1535, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.11 (2H, s), 6.91 (1H, dd, $J=3$, 9 Hz), 7.07 (1H, d, $J=3$ Hz), 7.34—7.41 (5H, m), 7.95 (1H, d, $J=9$ Hz). *Anal.* Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.38; H, 3.79; N, 5.37. **10d**: mp 74—76 °C (colorless needles from MeOH–H_2O). IR (KBr): 1610, 1550, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.20 (2H, s), 7.14 (1H, dd, $J=2$, 8 Hz), 7.24—7.46 (7H, m). *Anal.* Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 58.63; H, 3.83; N, 5.28.

1-(2-Ethoxyethyl)-1,3-dihydro-5-phenylmethoxy-2*H*-benzimidazol-2-one (13b) A mixture of **10b** (34.9 g, 132 mmol) and 2-ethoxyethylamine (35.7 g, 400 mmol) was refluxed for 11 h. The reaction mixture was dissolved in AcOEt, and the AcOEt layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford *N*-(2-ethoxyethyl)-2-nitro-4-phenylmethoxybenzenamine (**11b**) as an orange oil (47.8 g). This oil was dissolved in EtOH (280 ml)–HCl (140 ml) and zinc dust (33.2 g, 508 mmol) was added portionwise to the solution at 10—35 °C. The reaction mixture was made basic with NH_4OH and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give N^1-(2-ethoxyethyl)-4-phenylmethoxy-1,2-benzenediamine (**12b**) as a brown oil (43.1 g). This oil was subjected to the next reaction without purification. A mixture of this oil and urea (24.0 g, 400 mmol) was stirred at 160 °C for 6 h. The reaction mixture was diluted with 1 N HCl (400 ml) and extracted with AcOEt. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was column chromatographed on silica gel. Elution with $CHCl_3$–MeOH (20 : 1) gave 11.9 g (29% from **10b**) of **13b** as a pale brown solid. **13b**: mp 130—133 °C (pale brown crystals from hexane–AcOEt). IR (KBr): 3130, 1710, 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, $J=7$ Hz), 3.48 (2H, q, $J=7$ Hz), 3.71 (2H, t, $J=6$ Hz), 4.04 (2H, t, $J=6$ Hz), 5.02 (2H, s), 6.72 (1H, dd, $J=2$, 9 Hz), 6.81 (1H, d, $J=2$ Hz), 7.01 (1H, d, $J=9$ Hz), 7.28—7.44 (5H, m), 10.67 (1H, br). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.10; H, 6.38; N, 8.96.

1-(2-Ethoxyethyl)-1,3-dihydro-6-phenylmethoxy-2*H*-benzimidazol-2-one (13c) and 1-(2-Ethoxyethyl)-1,3-dihydro-7-phenylmethoxy-2*H*-benzimidazol-2-one (13d) Compounds **13c** and **13d** were prepared in the same manner as described above for the synthesis of compound **13b**. **13c**: mp 145—147 °C (pale brown crystals from EtOH). IR (KBr): 3180, 1700, 1645, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, $J=7$ Hz), 3.48 (2H, q, $J=7$ Hz), 3.71 (2H, t, $J=6$ Hz), 4.03 (2H, t, $J=6$ Hz), 5.05 (2H, s), 6.70 (1H, dd, $J=2$, 9 Hz), 6.84 (1H, d, $J=2$ Hz), 6.98 (1H, d, $J=9$ Hz), 7.29—7.46 (5H, m), 10.29 (1H, br). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.18; H, 6.44; N, 9.05. **13d**: mp 153—155 °C (colorless needles from hexane–AcOEt). IR (KBr): 3120, 1730, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, $J=7$ Hz), 3.39 (2H, q, $J=7$ Hz), 3.68 (2H, t, $J=6$ Hz), 4.28 (2H, t, $J=6$ Hz), 5.16 (2H, s), 6.70 (1H, d, $J=8$ Hz), 6.79 (1H, d, $J=8$ Hz), 6.97 (1H, t, $J=8$ Hz), 7.32—7.47 (5H, m), 10.27 (1H, br). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.24; H, 6.42; N, 8.98.

2-Chloro-1-(2-ethoxyethyl)-5-phenylmethoxy-1*H*-benzimidazole (14b)

A mixture of **13b** (7.60 g, 27 mmol) and phosphorus oxychloride (11.1 g, 72 mmol) was refluxed for 1 h. The reaction mixture was poured into ice-water (100 g) and made basic with 5 N NaOH. The mixture was extracted with AcOEt, and the extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was recrystallized from ligroin to give 5.80 g (66%) of **14b** as colorless needles, mp 66—68 °C. IR (KBr): 1630, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 3.42 (2H, q, J=7 Hz), 3.72 (2H, t, J=6 Hz), 4.31 (2H, t, J=6 Hz), 5.10 (2H, s), 7.00 (1H, dd, J=2, 9 Hz), 7.23 (1H, d, J=2 Hz), 7.27 (1H, d, J=9 Hz), 7.29—7.47 (5H, m). *Anal.* Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.38; H, 5.79; N, 8.51.

2-Chloro-1-(2-ethoxyethyl)-6-phenylmethoxy-1*H*-benzimidazole (14c) and 2-Chloro-1-(2-ethoxyethyl)-7-phenylmethoxy-1*H*-benzimidazole (14d) Compounds **14c** and **14d** were prepared in the same manner as described for the synthesis of compound **14b**. **14c**: mp 62—65 °C (colorless scales from ligroin). IR (KBr): 1640, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 3.42 (2H, q, J=7 Hz), 3.70 (2H, t, J=6 Hz), 4.28 (2H, t, J=6 Hz), 5.10 (2H, s), 6.95 (1H, d, J=2 Hz), 6.97 (1H, dd, J=2, 9 Hz), 7.30—7.47 (5H, m), 7.55 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.38; H, 5.85; N, 8.46. **14d**: mp 66—68 °C (pale brown needles from ligroin). IR (KBr): 1620, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7 Hz), 3.31 (2H, q, J=7 Hz), 3.68 (2H, t, J=6 Hz), 4.55 (2H, t, J=6 Hz), 5.18 (2H, s), 6.80 (1H, d, J=8 Hz), 7.15 (1H, t, J=8 Hz), 7.31 (1H, d, J=8 Hz), 7.36—7.47 (5H, m). *Anal.* Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.39; H, 5.82; N, 8.50.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-5-phenylmethoxy-1*H*-benzimidazole (15b) A mixture of **14b** (5.00 g, 15 mmol) and *N*-methylhomopiperazine (5.10 g, 45 mmol) was stirred at 140 °C for 4 h. The reaction mixture was diluted with 5 N NaOH (20 ml) and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (20 : 1)) to give 3.70 g (60%) of **15b** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz), 1.97—2.05 (2H, m), 2.41 (3H, s), 2.67—2.79 (4H, m), 3.46 (2H, q, J=7 Hz), 3.60—3.71 (4H, m), 3.75 (2H, t, J=6 Hz), 4.13 (2H, t, J=6 Hz), 5.08 (2H, s), 6.81 (1H, dd, J=2, 9 Hz), 7.13 (1H, d, J=9 Hz), 7.15 (1H, d, J=2 Hz), 7.25—7.46 (5H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-6-phenylmethoxy-1*H*-benzimidazole (15c) and 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-7-phenylmethoxy-1*H*-benzimidazole (15d) Compounds **15c** and **15d** were prepared in the same manner as described for the synthesis of compound **15b**. **15c**: a viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz), 1.97—2.05 (2H, m), 2.42 (3H, s), 2.71—2.79 (4H, m), 3.45 (2H, q, J=7 Hz), 3.57—3.64 (4H, m), 3.74 (2H, t, J=6 Hz), 4.13 (2H, t, J=6 Hz), 5.09 (2H, s), 6.86 (1H, dd, J=2, 9 Hz), 6.91 (1H, d, J=2 Hz), 7.27—7.47 (6H, m). **15d**: a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz), 2.00—2.06 (2H, m), 2.43 (3H, s), 2.74—2.81 (4H, m), 3.23 (2H, q, J=7 Hz), 3.57—3.66 (6H, m), 4.33 (2H, t, J=6 Hz), 5.16 (2H, s), 6.71 (1H, d, J=8 Hz), 7.06 (1H, t, J=8 Hz), 7.21 (1H, d, J=8 Hz), 7.35—7.47 (5H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-5-hydroxy-1*H*-benzimidazole (5b) A solution of **15b** (10.0 g, 24 mmol) in EtOH (100 ml) was hydrogenolyzed over 5% Pd–C (4 g) at 60 °C (3 atm) for 5.5 h. After removal of the catalyst and evaporation to dryness, the residue was diluted with 2.5 N NaOH and extracted with $CHCl_3$. The resulting oil was purified by column chromatography on silica gel. Elution with the upper layer of AcOEt–cyclohexane–MeOH–NH_4OH (10 : 4 : 2 : 1) gave 5.43 g (70%) of **5b** as a brown oil. IR (Nujol): 3220, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz), 1.99—2.05 (2H, m), 2.42 (3H, s), 2.74—2.81 (4H, m), 3.44 (2H, q, J=7 Hz), 3.60—3.68 (4H, m), 3.74 (2H, t, J=6 Hz), 4.11 (2H, t, J=6 Hz), 6.64 (1H, dd, J=2, 8 Hz), 6.98 (1H, d, J=2 Hz), 7.06 (1H, d, J=8 Hz). MS *m/z*: 318 (M^+). Compound **5b** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-6-hydroxy-1*H*-benzimidazole (5c) and 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl-7-hydroxy-1*H*-benzimidazole (5d) Compounds **5c** and **5d** were prepared in the same manner as described for the synthesis of compound **5b**. **5c**: mp 121—123 °C (pale yellow scales from AcOEt). IR (KBr): 3400, 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz), 2.04 (2H, br), 2.45 (3H, s), 2.80 (2H, br), 2.83 (2H, br), 3.44 (2H, q, J=7 Hz), 3.56—3.60 (2H, m), 3.63—3.65 (2H, m), 3.73 (2H, t, J=6 Hz), 4.09 (2H, t, J=6 Hz), 6.65 (1H, dd, J=2, 8 Hz), 6.76 (1H, d, J=2 Hz), 7.32 (1H, d, J=8 Hz). **5d**: a colorless oil. IR (Nujol): 3400, 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.99—2.05 (2H, m), 2.43 (3H, s), 2.73—2.81 (4H, m), 3.55—3.64 (6H, m), 3.89 (2H, t, J=5 Hz), 4.38 (2H, t, J=5 Hz), 6.66 (1H, dd, J=1, 8 Hz), 6.99 (1H, t, J=8 Hz), 7.13 (1H, dd, J=1, 8 Hz). MS *m/z*: 318 (M^+). Compound **5d** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

2-Chloro-1-(2-ethoxyethyl)-4-methoxy-1*H*-benzimidazole (17a) and 2-Chloro-1-(2-ethoxyethyl)-7-methoxy-1*H*-benzimidazole (17d) A solution of 2-chloro-4-methoxy-1*H*-benzimidazole (**16**) (4.50 g, 25 mmol) and 2-bromoethyl ethyl ether (5.00 g, 33 mmol) in DMF (40 ml) was treated with NaH (in oil, 60%) (1.00 g, 25 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was column chromatographed on silica gel. Elution with hexane–AcOEt (3 : 1) gave 1.71 g (27%) of **17a** and 1.15 g (18%) of **17d**. **17a**: a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 3.41 (2H, q, J=7 Hz), 3.73 (2H, t, J=6 Hz), 4.00 (3H, s), 4.32 (2H, t, J=6 Hz), 6.69 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 7.19 (1H, t, J=8 Hz). **17d**: a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz), 3.45 (2H, q, J=7 Hz), 3.74 (2H, t, J=6 Hz), 3.94 (3H, s), 4.57 (2H, t, J=6 Hz), 6.71 (1H, d, J=8 Hz), 7.15 (1H, t, J=8 Hz), 7.28 (1H, d, J=8 Hz).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-4-methoxy-1*H*-benzimidazole (18) A mixture of **17a** (0.80 g, 3.1 mmol) and *N*-methylhomopiperazine (1.10 g, 9.6 mmol) was stirred at 150 °C for 4 h. The reaction mixture was diluted with 2 N NaOH and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (4 : 1)) to yield 0.90 g (86%) of **18** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7 Hz), 1.96—2.04 (2H, m), 2.42 (3H, s), 2.72—2.79 (4H, m), 3.45 (2H, q, J=7 Hz), 3.60—3.69 (4H, m), 3.77 (2H, t, J=6 Hz), 3.98 (3H, s), 4.16 (2H, t, J=6 Hz), 6.64 (1H, d, J=8 Hz), 6.89 (1H, d, J=8 Hz), 7.05 (1H, t, J=8 Hz).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-4-hydroxy-1*H*-benzimidazole (5a) Ethyl mercaptan (1.00 g, 16 mmol) and NaH (in oil, 60%) (0.60 g, 15 mmol) were added to a solution of **18** (0.90 g, 2.7 mmol) in DMF (5 ml) and the mixture was refluxed for 2 h. The reaction mixture was poured into water and extracted with *n*-BuOH. The extract was concentrated to dryness *in vacuo* and the residue was column chromatographed on silica gel. Elution with $CHCl_3$–MeOH–NEt_3 (20 : 1 : 1) gave 0.60 g (63%) of **5a** as a brown oil. IR (Nujol): 3560, 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz), 1.95—2.03 (2H, m), 2.40 (3H, s), 2.71—2.78 (4H, m), 3.46 (2H, q, J=7 Hz), 3.57—3.65 (4H, m), 3.78 (2H, t, J=6 Hz), 4.17 (2H, t, J=6 Hz), 6.70 (1H, dd, J=1, 8 Hz), 6.79 (1H, dd, J=1, 8 Hz), 7.00 (1H, t, J=8 Hz). MS *m/z*: 318 (M^+). Compound **5a** was crystallized as the dipicrate, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-(hexahydro-5-oxo-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole (7) A mixture of 2-chloro-1-(2-ethoxyethyl)-1*H*-benzimidazole (**19**) (8.79 g, 39 mmol) and hexahydro-1*H*-1,4-diazepin-5-one (**20**) (9.27 g, 81 mmol) was stirred at 170 °C for 6 h. The reaction mixture was diluted with 1 N NaOH (80 ml) and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (10 : 1)) to give 6.47 g (55%) of **7** as a pale yellow oil. IR (Nujol): 3300, 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.82—2.85 (2H, m), 3.42 (2H, q, J=7 Hz), 3.50—3.56 (6H, m), 3.81 (2H, t, J=6 Hz), 4.18 (2H, t, J=6 Hz), 6.35 (1H, br), 7.16—7.20 (2H, m), 7.25—7.27 (1H, m), 7.57—7.60 (1H, m). MS *m/z*: 302 (M^+). Compound **7** was crystallized as the hydrochloride, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole (6) Methyl iodide (2.80 g, 20 mmol) was added to a mixture of **7** (4.51 g, 15 mmol) and NaH (60%, in oil) (0.80 g, 20 mmol) in DMF (35 ml) and the whole was stirred at room temperature for 2.5 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel. Elution with $CHCl_3$–MeOH (20 : 1) gave 3.03 g (64%) of **6** as a pale yellow oil. IR (Nujol): 1665, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.84—2.87 (2H, m), 3.03 (3H, s), 3.42 (2H, q, J=7 Hz), 3.48—3.51 (4H, m), 3.64—3.66 (2H, m), 3.80 (2H, t, J=6 Hz), 4.17 (2H, t, J=6 Hz), 7.13—7.20 (2H, m), 7.24—7.27 (1H, m), 7.56—7.59 (1H, m). MS *m/z*: 316 (M^+). Compound **6** was crystallized as the hydrochloride, whose physicochemical data are listed in Table I.

2-(Hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-1-(2-hydroxyethyl)-

1*H*-benzimidazole (8) A solution of BBr_3 (1.50 g, 6.0 mmol) in CH_2Cl_2 (6 ml) was added to a solution of **6**·hydrochloride (1.44 g, 3.5 mmol) in CH_2Cl_2 (24 ml), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with MeOH (20 ml) and concentrated *in vacuo*. The residue was made basic with 2 N NaOH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness. The resulting oil was purified by column chromatography ($CHCl_3$–MeOH (20 : 1)) to yield 0.95 g (81%) of **8** as a colorless oil. IR (Nujol): 3400, 1645, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.68—2.71 (2H, m), 2.95 (3H, s), 3.33—3.40 (4H, m), 3.53—3.55 (2H, m), 3.97 (2H, t, J=6 Hz), 4.12 (2H, t, J=6 Hz), 7.14—7.17 (2H, m), 7.23—7.26 (1H, m), 7.50—7.52 (1H, m). MS m/z: 288 (M^+). Compound **8** was crystallized as the hydrochloride, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-(hexahydro-5-oxo-1*H*-1,4-diazepin-1-yl)-5-phenylmethoxy-1*H*-benzimidazole (21b) A mixture of **14b** (8.60 g, 26 mmol) and **20** (6.00 g, 53 mmol) was stirred at 170 °C for 6 h. The reaction mixture was diluted with water (70 ml) and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel. Elution with $CHCl_3$–MeOH–NEt_3 (25 : 1 : 1) gave 3.04 g (29%) of **21b** as a pale yellow oil. IR (Nujol): 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7 Hz), 2.70—2.96 (2H, m), 3.44 (2H, q, J=7 Hz), 3.41—3.66 (6H, m), 3.77 (2H, t, J=5 Hz), 4.15 (2H, t, J=5 Hz), 5.07 (2H, s), 6.76 (1H, br), 6.85 (1H, dd, J=2, 9 Hz), 7.05—7.55 (7H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-5-oxo-1*H*-1,4-diazepin-1-yl)-6-phenylmethoxy-1*H*-benzimidazole (21c) Compound **21c** was prepared in the same manner as described for the synthesis of **21b**. **21c**: a colorless oil. IR (Nujol): 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 2.70—2.93 (2H, m), 3.42 (2H, q, J=7 Hz), 3.40—3.63 (6H, m), 3.75 (2H, t, J=5 Hz), 4.14 (2H, t, J=5 Hz), 5.11 (2H, s), 6.83 (1H, br), 6.85—7.03 (2H, m), 7.28—7.57 (6H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-5-phenylmethoxy-1*H*-benzimidazole (22b) Methyl iodide (1.80 g, 13 mmol) was added to a mixture of **21b** (3.00 g, 7.3 mmol) and NaH (in oil, 60%) (0.50 g, 13 mmol) in DMF (24 ml), and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (50 : 1)) to give 2.51 g (81%) of **22b** as a pale yellow oil. IR (Nujol): 1645, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz), 2.76—3.04 (2H, m), 3.06 (3H, s), 3.25—3.77 (8H, m), 3.81 (2H, t, J=5 Hz), 4.17 (2H, t, J=5 Hz), 5.11 (2H, s), 6.91 (1H, dd, J=2, 9 Hz), 7.14—7.66 (7H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-6-phenylmethoxy-1*H*-benzimidazole (22c) Compound **22c** was prepared in the same manner as described for the synthesis of **22b**. **22c**: a colorless oil. IR (Nujol): 1650, 1620 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.74—2.97 (2H, m), 3.03 (3H, s), 3.25—3.76 (8H, m), 3.75 (2H, t, J=5 Hz), 4.13 (2H, t, J=5 Hz), 5.07 (2H, s), 6.76—6.99 (2H, m), 7.25—7.58 (6H, m).

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-5-hydroxy-1*H*-benzimidazole (9b) A solution of **22b** (1.00 g, 3.0 mmol) in EtOH (20 ml) was hydrogenolyzed over 5% Pd–C (0.4 g) at 60 °C (3 atm) for 3.5 h. After removal of the catalyst and evaporation to dryness, the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (15 : 1)) to give 0.56 g (71%) of **9b** as a pale yellow oil. IR (Nujol): 3250, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 2.83—2.85 (2H, m), 3.03 (3H, s), 3.43 (2H, q, J=7 Hz), 3.45—3.49 (4H, m), 3.62—3.64 (2H, m), 3.78 (2H, t, J=5 Hz), 4.13 (2H, t, J=5 Hz), 6.73 (1H, dd, J=2, 9 Hz), 7.06 (1H, d, J=2 Hz), 7.10 (1H, d, J=9 Hz). MS m/z: 332 (M^+). Compound **9b** was crystallized as the hydrochloride, whose physicochemical data are listed in Table I.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-5-oxo-1*H*-1,4-diazepin-1-yl)-6-hydroxy-1*H*-benzimidazole (9c) Compound **9c** was prepared in the same manner as described for the synthesis of compound **9b**. **9c**: a pale yellow oil. IR (Nujol): 3350, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 2.83—2.86 (2H, m), 3.03 (3H, s), 3.42 (2H, q, J=7 Hz), 3.43—3.46 (4H, m), 3.63—3.65 (2H, m), 3.77 (2H, t, J=6 Hz), 4.12 (2H, t, J=6 Hz), 5.96 (1H, br), 6.71 (1H, dd, J=2, 9 Hz), 6.77 (1H, d, J=2 Hz), 7.39 (1H, d, J=9 Hz). MS m/z: 332 (M^+). Compound **9c** was crystallized as the hydrochloride, whose physicochemical data are listed in Table I.

Pharmacological Method H_1-Antihistaminic activity (*in vitro*) was measured by the reported method,[1] against histamine-induced contraction of isolated ileum from guinea pigs. IC_{50} values of the test compounds were calculated by the probit method.

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