

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.

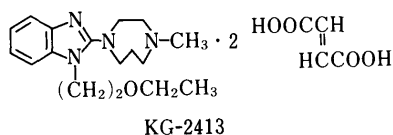


Fig. 1

In the metabolism studies of piperazine derivatives such as diethylcarbamazine,³⁾ pipemidic acid⁴⁾ 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⁾ oxatamide⁸⁾ 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

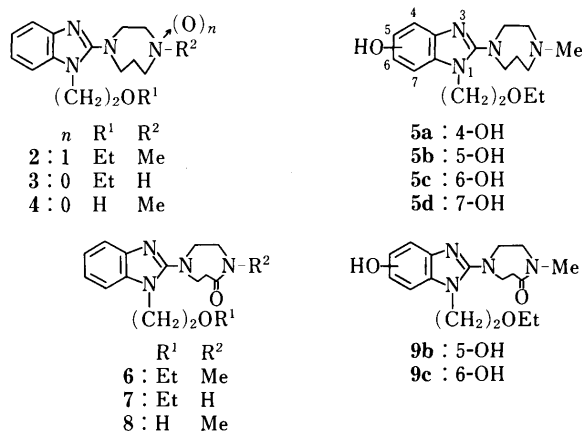


Fig. 2

combination of the above-mentioned metabolic conversions, four additional compounds (7, 8, 9b, c) were designed (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).

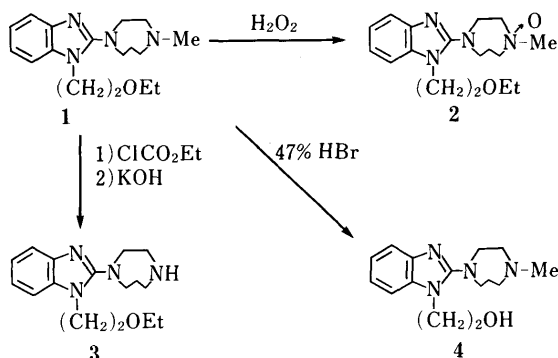
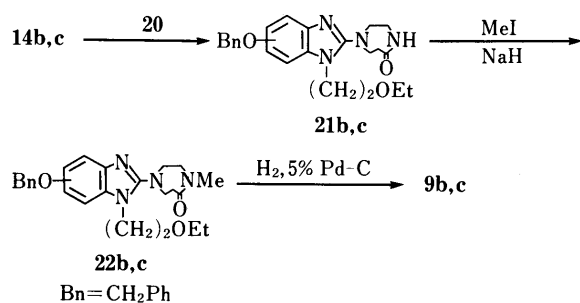
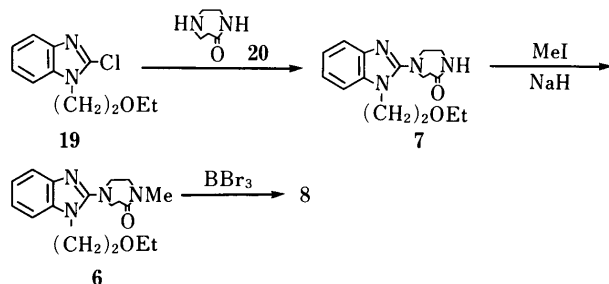
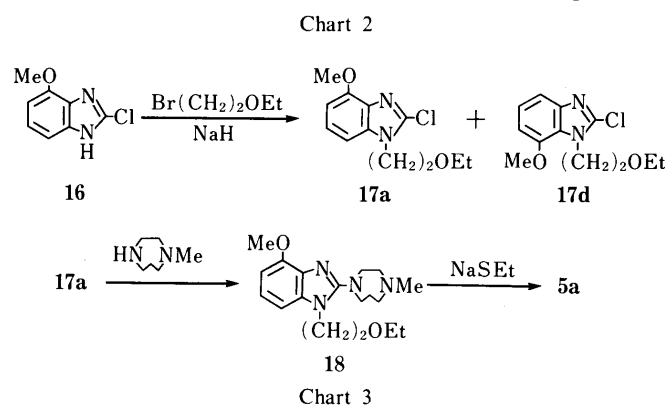
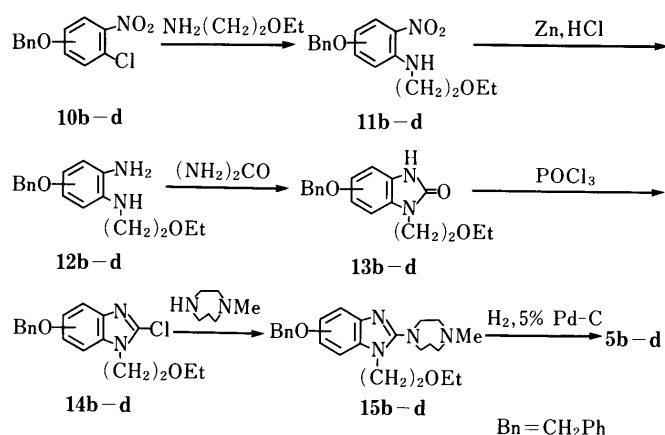


Chart 1

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-d¹⁰⁾ 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 16¹¹⁾ 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-



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 ($^1\text{H-NMR}$) 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-one¹²⁾ (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. $^1\text{H-NMR}$ 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} . $^1\text{H-NMR}$ (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} . $^1\text{H-NMR}$ (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 (%)			Antihistaminic activity	
					Calcd (Found)			IC ₅₀ (M) ^{d)}	Ratio ^{e)}
					C	H	N		
2	63	87—193	A	C ₁₇ H ₂₆ N ₄ O ₂ · 2C ₆ H ₃ N ₃ O 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 ₄ O ₂ · 2C ₆ H ₃ N ₃ O 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 ₄ O · 2C ₆ H ₃ N ₃ O 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 ₄ O ₂ · 2C ₆ H ₃ N ₃ O ₇ 1/3 C ₃ H ₆ O · H ₂ O	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 ₄ O ₂ · 2C ₆ H ₃ N ₃ O 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 ₄ O 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 ₄ O ₂ · 2C ₆ H ₃ N ₃ O 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 ₄ O ₂ · HCl · 3H ₂ O	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 ₄ O ₂ · HCl · 1/4 H ₂ O	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 ₄ O ₂ · HCl · 5/4 H ₂ O	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 ₄ O ₃ · 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 ₄ O ₃ · HCl 1/10 C ₄ H ₈ O 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-H₂O; E, AcOEt-EtOH. c) Formula: C₆H₃N₃O₇, picric acid; C₃H₆O, acetone; C₄H₈O₂, 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. ¹H-NMR (CDCl₃) 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 K₂CO₃ (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 MgSO₄ 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. ¹H-NMR (CDCl₃) 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 C₁₃H₁₀ClNO₃: 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. ¹H-NMR (CDCl₃) 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 C₁₃H₁₀ClNO₃: 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-H₂O). IR (KBr): 1610, 1550, 1375 cm⁻¹. ¹H-NMR (CDCl₃) δ: 5.20 (2H, s), 7.14 (1H, dd, *J* = 2, 8 Hz), 7.24—7.46 (7H, m). Anal. Calcd for C₁₃H₁₀ClNO₃: 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 MgSO₄ 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 NH₄OH and extracted with AcOEt. The extract was washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give *N*-(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 MgSO₄ and concentrated to dryness *in vacuo*. The residue was column chromatographed on silica gel. Elution with CHCl₃-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. ¹H-NMR (CDCl₃) 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 C₁₈H₂₀N₂O₃: 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. ¹H-NMR (CDCl₃) 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 C₁₈H₂₀N₂O₃: 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. ¹H-NMR (CDCl₃) 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 C₁₈H₂₀N₂O₃: 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 MgSO₄ 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. ¹H-NMR (CDCl₃) 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 C₁₈H₁₉ClN₂O₂: 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-1H-benzimidazole (14c) and **2-Chloro-1-(2-ethoxyethyl)-7-phenylmethoxy-1H-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. ¹H-NMR (CDCl₃) 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 C₁₈H₁₉ClN₂O₂: 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. ¹H-NMR (CDCl₃) 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 C₁₈H₁₉ClN₂O₂: 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-1H-1,4-diazepin-1-yl)-5-phenylmethoxy-1H-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 MgSO₄ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃–MeOH (20:1)) to give 3.70 g (60%) of **15b** as a brown oil. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-6-phenylmethoxy-1H-benzimidazole (15c) and **1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-7-phenylmethoxy-1H-benzimidazole (15d)** Compounds **15c** and **15d** were prepared in the same manner as described for the synthesis of compound **15b**. **15c**: a viscous oil. ¹H-NMR (CDCl₃) 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. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-5-hydroxy-1H-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 CHCl₃. The resulting oil was purified by column chromatography on silica gel. Elution with the upper layer of AcOEt–cyclohexane–MeOH–NH₄OH (10:4:2:1) gave 5.43 g (70%) of **5b** as a brown oil. IR (Nujol): 3220, 1640 cm⁻¹. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-6-hydroxy-1H-benzimidazole (5c) and **1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-7-hydroxy-1H-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. ¹H-NMR (CDCl₃) 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. ¹H-NMR (CDCl₃) 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-1H-benzimidazole (17a) and **2-Chloro-1-(2-ethoxyethyl)-7-methoxy-1H-benzimidazole (17d)** A solution of 2-chloro-4-methoxy-1H-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 MgSO₄ 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. ¹H-NMR (CDCl₃) 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. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-4-methoxy-1H-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 MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃–MeOH (4:1)) to yield 0.90 g (86%) of **18** as a brown oil. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-4-hydroxy-1H-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 CHCl₃–MeOH–NEt₃ (20:1:1) gave 0.60 g (63%) of **5a** as a brown oil. IR (Nujol): 3560, 1640, 1620 cm⁻¹. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-1H-benzimidazole (7) A mixture of 2-chloro-1-(2-ethoxyethyl)-1H-benzimidazole (**19**) (8.79 g, 39 mmol) and hexahydro-1H-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 CHCl₃. The extract was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃–MeOH (10:1)) to give 6.47 g (55%) of **7** as a pale yellow oil. IR (Nujol): 3300, 1660, 1620 cm⁻¹. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-1H-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 MgSO₄ and concentrated *in vacuo*. The residue was column chromatographed on silica gel. Elution with CHCl₃–MeOH (20:1) gave 3.03 g (64%) of **6** as a pale yellow oil. IR (Nujol): 1665, 1630 cm⁻¹. ¹H-NMR (CDCl₃) 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-1H-1,4-diazepin-1-yl)-1-(2-hydroxyethyl)-

1H-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 2N 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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-5-phenylmethoxy-1H-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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-6-phenylmethoxy-1H-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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-5-phenylmethoxy-1H-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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-6-phenylmethoxy-1H-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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-5-hydroxy-1H-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} . $^1\text{H-NMR}$ (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-1H-1,4-diazepin-1-yl)-6-hydroxy-1H-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} . $^1\text{H-NMR}$ (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,¹¹ 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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