Bioisosteric Transformation of H_1-Antihistaminic Benzimidazole Derivatives

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With the aim of obtaining new H_1-antihistaminic agents, transformations of previously reported antihistaminic benzimidazoles were performed on the basis of the concept of bioisosterism. Among the compounds prepared, imidazo[4,5-*b*]pyridine (8) and 4(3*H*)-quinazolinone (11) exhibited significant H_1-antihistaminic activity.

Keywords H_1-antihistaminic activity; bioisosterism; synthesis; piperazine; benzimidazole; imidazo[4,5-*b*]pyridine; 4,5-diphenylimidazole; 4(3*H*)-quinazolinone

In the previous paper, we reported the synthesis and H_1-antihistaminic activity of benzimidazole derivatives.[1] The study revealed that compounds **1** exhibited potent antihistaminic activity. We planned to modify the structure of compounds **1** in order to find new H_1-antihistaminic agents. In the process of seeking new drugs, we employed the concept of "bioisosterism".[2-4] Bioisosteres are groups or molecules which have similarities of chemical and physical properties producing broadly similar biological profiles. The replacement of the 1-piperazinyl group in **1** was already reported,[5] and it was found that compounds **2** exhibited potent H_1-antihistaminic activity comparable to that of **1**.

In this paper we describe mainly the replacement of the benzimidazole ring of compounds **1a**, **1b** and **2a**, which are representatives of **1** and **2**, on the basis of the concept of bioisosterism.

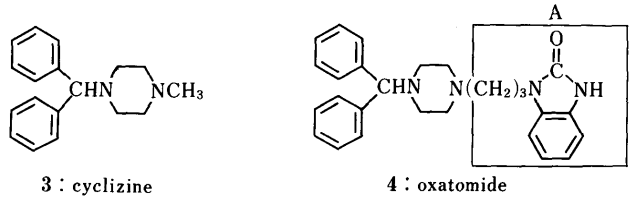
The methyl group in cyclizine (**3**) (an antihistaminic) can be considered to be a bioisostere for the A moiety in oxatomide (**4**) (an antihistaminic). On the other hand, the diphenylmethylpiperazine moiety in **3** and 1-(2-ethoxyethyl)-2-benzimidazolylpiperazine moiety in **1a** are also regarded as bioisosteres. So we designed compound **7**, where the methyl group in **1a** is replaced by the A moiety in **4**. The heterocyclic-aromatic nitrogen (–N=) and the –CH= group have been interchanged in a bioisosteric system. Such a relationship is not new among antihistaminic drugs, for example, phenbenzamine (**5**) and tripelennamine (**6**). In order to confirm whether this bioisosterism is applicable to compound **1b**, we designed the imidazo[4,5-*b*]pyridine **8**. The idea of using a phenyl substituent attached to a ring system to mimic the benzo analog has often been explored in medicinal chemistry.[3] On the basis of this idea we designed compound **9**, where the benzimidazole moiety in **1a** is replaced by diphenylimidazole. Bioisosterism between benzene, pyridine and thiophene has been commonly observed, and these are regarded as ring equivalents. The same relationship has also been observed between pyridine and thiazole.[2] In the expectation of ring equivalence between benzimidazole and quinazoline, we finally designed the 4(3*H*)-quinazolinones **10** and **11**, where the benzimidazole ring in **1a** and **2a** is replaced by a quinazoline ring.

Synthesis Compound **7** was synthesized by the condensation of 2-(1-piperazinyl)-1*H*-benzimidazole **12** with 1-(3-chloropropyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**13**).

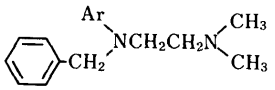
Compound **8** was synthesized as follows (Chart 1).

1 : $m=0$ (**1a** : $n=2$, R^1=Et, R^2=Me)
(**1b** : $n=3$, R^1=Et, R^2=Me)
2 : $m=1$ (**2a** : $n=2$, R^1=Et, R^2=Me)

Fig. 1

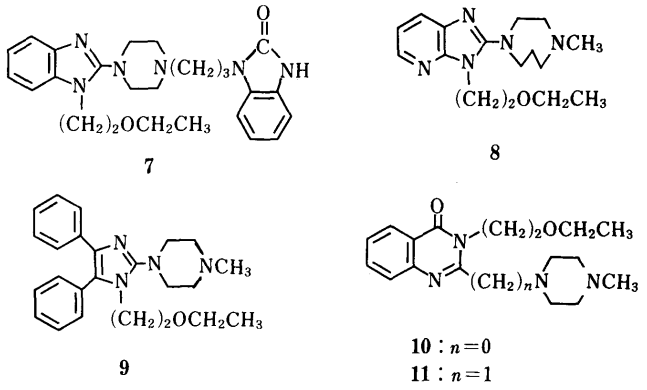


3 : cyclizine
4 : oxatomide



5 : phenbenzamine Ar=phenyl
6 : tripelennamine Ar=2-pyridyl

Fig. 2



7 **8** **9** **10** : $n=0$ **11** : $n=1$

Fig. 3

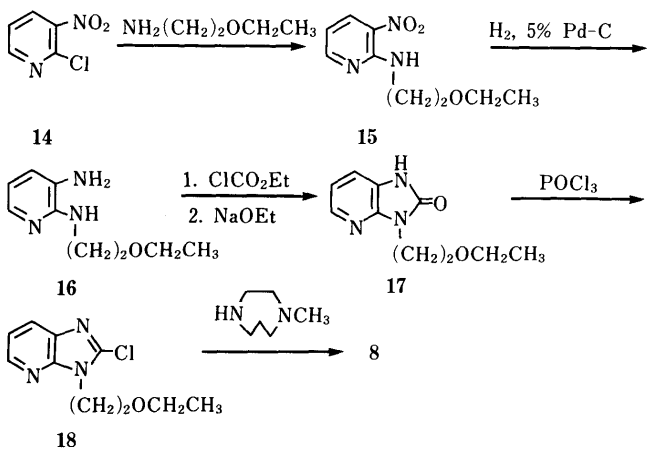


Chart 1

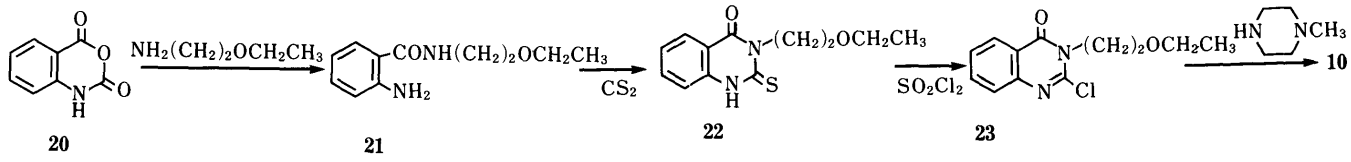


Chart 2

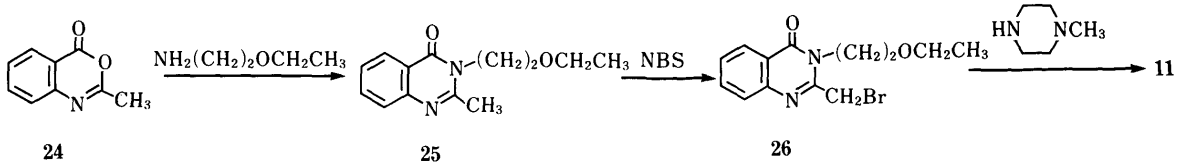


Chart 3

TABLE I. Physicochemical and Pharmacological Data for the Compounds Prepared

Compd. No.	mp (°C)	Recrystn. solvent[a]	Formula[b]	Analysis (%) Calcd (Found) C	H	N	Antihistaminic activity IC_{50} (M)[c]	Ratio[d]
7	157—161	A	$C_{25}H_{32}N_6O_2$	66.94 (66.78)	7.19 7.10	18.74 18.57)	9.5×10^{-8} [e]	0.11
8	145—147.5	B	$C_{16}H_{25}N_5O\cdot2.5C_4H_4O_4$	52.61 (52.11	5.94 5.99	11.80 11.60)	2.0×10^{-8} (4.7×10^{-9}—1.4×10^{-7})	0.50
9	204.5—206.5	A	$C_{24}H_{30}N_4O\cdot C_4H_4O_4$	66.38 (66.46	6.76 6.83	11.06 11.05)	$>3.0\times10^{-6}$	<0.003
10	184.5—186.5	A	$C_{17}H_{24}N_4O_2\cdot C_4H_4O_4$	58.32 (58.29	6.53 6.64	12.95 13.00)	1.2×10^{-6} (8.8×10^{-7}—1.7×10^{-6})	0.008
11	177—177.5	A	$C_{18}H_{26}N_4O_2\cdot2C_4H_4O_4$	55.51 (55.39	6.09 6.09	9.96 10.11)	3.1×10^{-8} (2.7×10^{-8}—3.8×10^{-8})	0.32
1a							1.0×10^{-8} (7.9×10^{-9}—1.3×10^{-8})	1.0
1b							6.1×10^{-9} (4.3×10^{-9}—8.6×10^{-9})	1.64
2a							2.1×10^{-8} (1.4×10^{-8}—3.8×10^{-8})	0.48

a) Solvents: A, AcOEt–EtOH; B, hexane–EtOH. *b*) Formula: $C_4H_4O_4$, fumaric acid. *c*) The 95% confidence limits are included in parentheses. *d*) Potency relative to compound **1a**. *e*) Estimated IC_{50}. The 95% confidence limits are not given because of poor dose dependency.

Ethoxyethylamination of 2-chloro-3-nitropyridine (**14**) with 2-ethoxyethylamine, followed by catalytic reduction using 5% palladium charcoal, afforded the 2,3-pyridinediamine **16**. Reaction of **16** with ethyl chloroformate, followed by treatment of sodium ethoxide, gave the 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one **17**. Chlorination of **17** with phosphorus oxychloride gave the 2-chloro-3*H*-imidazo[4,5-*b*]pyridine **18**, which was reacted with *N*-methylhomopiperazine to afford the desired compound **8**.

Compound **9** was synthesized by the reaction of 1-(4,5-diphenyl-1*H*-imidazol-2-yl)-4-methylpiperazine (**19**)[6] with 2-bromoethyl ethyl ether in the presence of sodium hydride.

Treatment of isatoic anhydride (**20**) with 2-ethoxyethylamine, followed by cyclization with carbon disulfide, afforded the 2,3-dihydro-2-thioxo-4(1*H*)-quinazolinone **22**. Chlorination of **22** with sulfuryl chloride gave the 2-chloro-4(3*H*)-quinazolinone **23**, which was reacted with *N*-methylpiperazine to afford compound **10** (Chart 2).

Compound **11** was synthesized as follows (Chart 3). Reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one (**24**) with 2-ethoxyethylamine afforded the 2-methyl-4(3*H*)-quinazolinone **25**. Bromination of **25** with *N*-bromosuccinimide (NBS), followed by reaction with *N*-methylpiperazine gave the desired compound **11**.

Results and Discussion

The H_1-antihistaminic activities of five newly synthesized compounds (**7**—**11**) were measured by the same method as described in the previous papers,[1,5] and the results are summarized in Table I.

The activity of **7** is about a tenth of that of compound **1a**. In other words, replacement of the methyl group in **1a** by the sterically large moiety A in oxatomide slightly decreased the activity. This result is consistent with the result of quantitative structure–activity relationship (QSAR) analysis for 2-(1-piperazinyl)benzimidazoles (**1**).[7] The result of QSAR study suggested that the antihistaminic activity depends on the steric parameter (STERIMOL parameters) of the substituent at the 1-position of the benzimidazole nucleus, and the substituent at the 4-position of piperazine or homopiperazine in **1** has little effect on the activity.

As mentioned previously, in bioisosteric systems the pyridine ring and the benzene ring have been interchanged successfully.[2] As the activities of **8** and **1b** are about the same, in this case also bioisosterism between pyridine ring and benzene ring was found. Replacement of the benzimidazole moiety in **1a** by diphenylimidazole resulted in loss of activity. Therefore, in the case of the relationship between **9** and **1a**, bioisosterism was not observed. Different results

were obtained when the benzimidazole moiety in **1a** and **2a** was replaced by 4(3*H*)-quinazolinone (**10** and **11**). That is, replacing the benzimidazole moiety in **1a** with 4(3*H*)-quinazolinone (**10**) led to loss of antihistaminic activity. On the other hand, replacement of the benzimidazole moiety in **2a** with 4(3*H*)-quinazolinone (**11**) led to the retention of activity.

In conclusion, bioisosteric transformations from **1b** to **8** and from **2a** to **11** were successfully performed.

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. Proton nuclear magnetic resonance (^{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. Elemental analyses were performed by the Analytical Department of Kanebo Research Center.

1-[3-[4-[1-(2-Ethoxyethyl)-1*H*-benzimidazol-2-yl]-1-piperazinyl]propyl]-1,3-dihydro-2*H*-benzimidazol-2-one (7) A mixture of 1-(2-ethoxyethyl)-2-(1-piperazinyl)-1*H*-benzimidazole (**12**) (6.18 g, 23 mmol), 1-(3-chloropropyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**13**) (4.74 g, 23 mmol) and K_2CO_3 (3.11 g, 23 mmol) in toluene (50 ml) was heated under reflux for 14 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was treated with water and extracted with AcOEt. The extract was washed with water and dried over $MgSO_4$. After evaporation of the solvent, purification by column chromatography on silica gel eluting with $CHCl_3$–MeOH (30 : 1) gave 5.36 g (53%) of **7** as a pale yellow solid, which was recrystallized from EtOH–AcOEt to give colorless prisms, mp 157—161 °C. IR (KBr): 1695, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7 Hz), 2.03—2.07 (2H, m), 2.55 (2H, br), 2.67 (4H, br), 3.42—3.49 (6H, m), 3.81 (2H, t, J=6 Hz), 4.00 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 7.02—7.31 (7H, m), 7.59—7.63 (1H, m), 9.10 (1H, s).

***N*-(2-Ethoxyethyl)-3-nitro-2-pyridinamine (15)** A mixture of 2-chloro-3-nitropyridine (**14**) (9.50 g, 60 mmol) and 2-ethoxyethylamine (16.0 g, 180 mmol) was stirred at 80 °C for 10 min. The reaction mixture was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (hexane–AcOEt (3 : 2)) to give 12.0 g (95%) of **15** as an orange oil. IR (neat): 3390, 1605, 1570, 1500, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 3.36—3.90 (6H, m), 6.47—6.70 (1H, m), 8.20—8.45 (2H, m).

***N*^{2}-(2-Ethoxyethyl)-2,3-pyridinediamine (16)** A solution of **15** (5.00 g, 24 mmol) in EtOH (100 ml) was hydrogenated over 5% Pd–C (0.25 g) at 40 °C (45 psi) for 3.5 h. After removal of the catalyst and evaporation to dryness, the residue was column chromatographed on silica gel. Elution with hexane–acetone (2 : 3) gave 4.00 g (93%) of **16** as a brown oil. IR (neat): 3350, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7 Hz), 3.22 (2H, br), 3.30—3.70 (6H, m), 4.50 (1H, br), 6.40 (1H, dd, J=5, 7 Hz), 6.75 (1H, dd, J=2, 7 Hz), 7.64 (1H, dd, J=2, 5 Hz).

3-(2-Ethoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (17) Ethyl chloroformate (8.00 g, 74 mmol) was added to a solution of **16** (6.10 g, 34 mmol) in $CHCl_3$ (150 ml), and the mixture was refluxed for 1 h. The reaction mixture was washed with aqueous $NaHCO_3$ and water, and evaporated to dryness. The residue was subjected to column chromatography on silica gel. Elution with $CHCl_3$–AcOEt (1 : 1) gave 8.00 g of a brown oil (a mixture of mono-ethoxycarbonylated and bis-ethoxycarbonylated compounds). A solution of this oil in absolute EtOH (30 ml) was added to a solution of sodium ethoxide (35 mmol) in absolute EtOH (20 ml), and the mixture was refluxed for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with water, neutralized with 2 N HCl and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The resulting solid was recrystallized from AcOEt–ether to give 2.20 g (32% from **16**) of **17** as colorless prisms, mp 121—122 °C. IR (KBr): 3090, 1735, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz), 3.54 (2H, q, J=7 Hz), 3.84 (2H, t, J=6 Hz), 4.23 (2H, t, J=6 Hz), 7.00 (1H, dd, J=5, 8 Hz), 7.33 (1H, dd, J=1, 8 Hz), 8.06 (1H, dd, J=1, 5 Hz), 10.76 (1H, br). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.09; H, 6.35; N, 20.39.

2-Chloro-3-(2-ethoxyethyl)-3*H*-imidazo[4,5-*b*]pyridine (18) A mixture of **17** (3.00 g, 14 mmol) and phosphorus oxychloride (30.0 g, 20 mmol) was refluxed for 4 h under bubbling of HCl gas. The reaction mixture was concentrated *in vacuo*, and the residue was poured into ice water. The mixture was neutralized with $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was washed with water, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was column chromatographed on silica gel ($CHCl_3$–AcOEt (4 : 3)) to give 0.90 g (28%) of **18** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7 Hz), 3.45 (2H, q, J=7 Hz), 3.79 (2H, t, J=6 Hz), 4.48 (2H, t, J=6 Hz), 7.15 (1H, dd, J=5, 8 Hz), 7.87 (1H, dd, J=2, 8 Hz), 8.27 (1H, dd, J=2, 5 Hz).

3-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (8) A mixture of **18** (0.85 g, 3.8 mmol) and *N*-methylhomopiperazine (3.50 g, 31 mmol) was stirred at 130 °C for 2 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* to give 0.90 g (79%) of **8** as a brown oil. IR (neat): 1610, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.02—2.11 (2H, m), 2.43 (3H, s), 2.70—2.74 (2H, m), 2.80—2.84 (2H, m), 3.45 (2H, q, J=7 Hz), 3.76—3.85 (4H, m), 3.90 (2H, t, J=6 Hz), 4.35 (2H, t, J=6 Hz), 7.06 (1H, dd, J=5, 8 Hz), 7.67 (1H, dd, J=1, 8 Hz), 8.08 (1H, dd, J=1, 5 Hz). Compound **8** was crystallized as the fumarate, whose physicochemical data are listed in Table I.

1-[1-(2-Ethoxyethyl)-4,5-diphenyl-1*H*-imidazol-2-yl]-4-methylpiperazine (9) Sodium hydride (in oil, 60%) (0.70 g, 18 mmol) was added to a solution of 1-(4,5-diphenyl-1*H*-imidazol-2-yl)-4-methylpiperazine (**19**) (3.00 g, 9.4 mmol) and 2-bromoethyl ethyl ether (2.00 g, 13 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml), and the mixture was stirred at 60 °C for 2 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and dried $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2–MeOH (20 : 1) to give 1.50 g (41%) of **9** as a pale yellow oil. IR (neat): 1605, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 2.37 (3H, s), 2.60 (4H, br), 3.24—3.33 (6H, m), 3.37 (2H, q, J=6 Hz), 3.93 (2H, q, J=6 Hz), 7.05—7.44 (10H, m). Compound **9** was crystallized as the fumarate, whose physicochemical data are listed in Table I.

2-Amino-*N*-(2-ethoxyethyl)benzamide (21) A mixture of isatoic anhydride (**20**) (38.4 g, 240 mmol) and 2-ethoxyethylamine (25.0 g, 280 mmol) in dioxane (450 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography. Elution with $CHCl_3$ gave a yellow solid, which was recrystallized from hexane–AcOEt to give 40.6 g (83%) of **21** as colorless scales, mp 52—53 °C. IR (KBr): 3420, 3310, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 3.53 (2H, q, J=7 Hz), 3.59 (4H, s), 5.51 (2H, br), 6.48 (1H, br), 6.62—6.69 (2H, m), 7.17—7.23 (1H, m), 7.33 (1H, dd, J=1, 8 Hz). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.21; H, 7.79; N, 13.46.

3-(2-Ethoxyethyl)-2,3-dihydro-2-thioxo-4(1*H*)-quinazolinone (22) Sodium hydroxide (6.00 g, 150 mmol) and CS_2 (11.4 g, 150 mmol) were added to a solution of **21** (20.8 g, 100 mmol) in EtOH (100 ml), and the whole was refluxed for 4 h. The reaction mixture was poured into dilute HCl. The precipitate was filtered off and recrystallized from AcOEt to give 10.0 g (40%) of **22** as colorless needles, mp 186—187 °C. IR (KBr): 3260, 3140, 1650, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7 Hz), 3.61 (2H, q, J=7 Hz), 3.85 (2H, t, J=6 Hz), 4.80 (2H, t, J=6 Hz), 7.23—7.34 (2H, m), 7.62—7.68 (1H, m), 8.11—8.14 (1H, m), 11.16 (1H, br). *Anal.* Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.77; H, 5.61; N, 11.24.

2-Chloro-3-(2-ethoxyethyl)-4(3*H*)-quinazolinone (23) Sulfuryl chloride (2.70 g, 20 mmol) was added to a solution of **22** (5.00 g, 20 mmol) in $CHCl_3$ (35 ml), and the mixture was heated under reflux for 1.5 h. After cooling, the reaction mixture was filtered. The filtrate was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a pale yellow oil. This oil was column chromatographed on silica gel ($CHCl_3$) to afford 3.00 g (59%) of **23** as a colorless oil. IR (neat): 1700, 1600, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=6 Hz), 3.53 (2H, q, J=6 Hz), 3.76 (2H, t, J=5 Hz), 4.52 (2H, t, J=5 Hz), 7.35—7.95 (3H, m), 8.15—8.40 (1H, m).

3-(2-Ethoxyethyl)-2-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (10) A mixture of **23** (5.00 g, 20 mmol) and *N*-methylpiperazine (4.00 g, 40 mmol) was stirred at 120 °C for 30 min. 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 ($CHCl_3$–MeOH (5 : 1)) to afford 4.00 g (64%) of **10** as a pale yellow oil. IR (neat): 1685, 1610, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 2.38 (3H, s), 2.55—2.70 (4H,

m), 3.21—3.33 (4H, m), 3.47 (2H, q, $J=7$ Hz), 3.77 (2H, t, $J=6$ Hz), 4.32 (2H, t, $J=6$ Hz), 7.28—7.34 (1H, m), 7.50—7.54 (1H, m), 7.60—7.67 (1H, m), 8.14—8.18 (1H, m). Compound **10** was crystallized as the fumarate, whose physicochemical data are listed in Table I.

3-(2-Ethoxyethyl)-2-methyl-4(3*H*)-quinazolinone (25) A mixture of 2-methyl-4*H*-3,1-benzoxazin-4-one (**24**) (5.98 g, 37 mmol) and 2-ethoxyethylamine (6.00 g, 67 mmol) was heated under reflux for 3 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 purified by column chromatography on silica gel. Elution with $CHCl_3$ gave 5.36 g (62%) of **25** as a pale yellow solid, which was recrystallized from hexane to give colorless needles, mp 74.5—76.5 °C. IR (KBr): 1680, 1610, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, $J=7$ Hz), 2.73 (3H, s), 3.44 (2H, q, $J=7$ Hz), 3.75 (2H, t, $J=5$ Hz), 4.31 (2H, t, $J=5$ Hz), 7.40—7.46 (1H, m), 7.60—7.63 (1H, m), 7.69—7.75 (1H, m), 8.23—8.26 (1H, m). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.43; H, 7.07; N, 12.02.

2-Bromomethyl-3-(2-ethoxyethyl)-4(3*H*)-quinazolinone (26) A mixture of **25** (12.0 g, 52 mmol) and NBS (9.20 g, 52 mmol) in DMF (200 ml) was stirred at 80 °C for 5.5 h. The reaction mixture was diluted with 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 ($CHCl_3$) to give 8.15 g (51%) of **26** as a pale yellow solid, which was recrystallized from hexane to afford colorless prisms, mp 60.5—62.5 °C. IR (KBr): 1680, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, $J=7$ Hz), 3.42 (2H, q, $J=7$ Hz), 3.75 (2H, t, $J=5$ Hz), 4.47 (2H, t, $J=5$ Hz), 4.74 (2H, s), 7.47—7.53 (1H, m), 7.67—7.71 (1H, m), 7.73—7.79 (1H, m), 8.26—8.30 (1H, m). *Anal.* Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.34; H, 4.81; N, 9.10.

3-(2-Ethoxyethyl)-2-[(4-methyl-1-piperazinyl)methyl)]-4(3*H*)-quinazolinone (11) A mixture of **26** (3.00 g, 9.6 mmol) and *N*-methylpiperazine (2.00 g, 20 mmol) was stirred at 120 °C for 1 h. The reaction mixture was diluted with 5% NaOH (20 ml) and extracted with AcOEt. The AcOEt layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel ($CHCl_3$–MeOH (10 : 1)) to give 2.23 g (70%) of **11** as a brown oil. IR (neat): 1670, 1600, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, $J=7$ Hz), 2.31 (3H, s), 2.47 (4H, br), 2.64 (4H, br), 3.43 (2H, q, $J=7$ Hz), 3.74 (2H, t, $J=5$ Hz), 3.85 (2H, s), 4.62 (2H, t, $J=5$ Hz), 7.43—7.49 (1H, m), 7.67—7.77 (2H, m), 8.25—8.29 (1H, m). Compound **11** was crystallized as the fumarate, whose physicochemical data are listed in Table I.

Pharmacological Method The H_1-antihistaminic activity (*in vitro*) was measured by the reported method,[1,5] 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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