A New Series of Antiallergic Agents. I. Synthesis and Activity of 11-(2-Aminoethyl)thio-6,11-dihydrodibenz[*b*,*e*]oxepin Derivatives

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A new series of 11-substituted 6,11-dihydrodibenz[*b*,*e*]oxepin derivatives was synthesized and evaluated for antiallergic activity. Convenient methods for the preparation of sulfides from alcohols were developed. Structure–activity relationships are described. Compound 7, 11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid hydrochloride, was the most potent in the rat passive cutaneous anaphylaxis test (ED_{50} = 0.92 mg/kg *p.o.*). It had a potent inhibitory effect on anaphylactic bronchoconstriction in guinea pigs (ED_{50} = 0.029 mg/kg *p.o.*) and H_1 receptor antagonistic effect (K_i = 14 nM) with few central nervous system side effects. Additionally, an antagonistic effect against prostagrandin D_2-induced contraction of isolated guinea pig trachea (pA_2 = 5.73) was an attractive mechanism of action of the new antiallergic agent. Compound 7 was selected for further evaluation as KW-4994.

Keywords antiallergic agent; antiasthmatic agent; H_1-antihistaminic activity; receptor antagonist; anti-passive cutaneous anaphylaxis activity; structure–activity relationship; prostagrandin D_2; 6,11-dihydrodibenz[*b*,*e*]oxepin

Effective and orally active antiallergic agents with fewer side effects have been attractive targets for drug research in recent years.[1] Our research has been focused on syntheses of some new series of benzoxepin derivatives and their pharmacological properties.[2] From our efforts, we had found that compound **1**,[3] one of the 11-substituted-dibenz[*b*,*e*]oxepin derivatives, showed highly potent antiallergic activity. However, **1** was accompanied by undesirable central nervous system (CNS) side effects (*e.g.* inhibition of locomotor activity in mice). We thus attempted to introduce a hydrophilic substituent instead of a methyl group at the 2-position of **1** in the hope that the decrease in lipophilicity of the molecule might lead to a reduction of CNS side effects. We finally found **7**, 11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid hydrochloride, which had potent antiallergic activity and was devoid of undesirable CNS side effects.

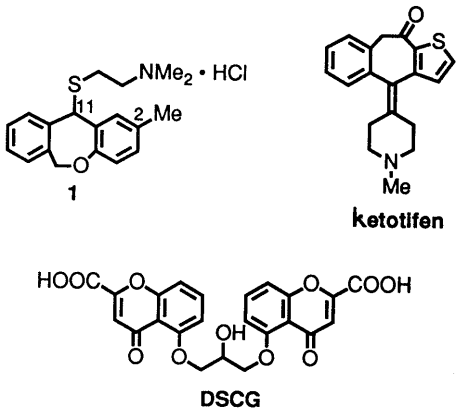


Fig. 1

Known antiallergic agents might be classified into two groups according to their chemical structures.[4] The basic agents such as ketotifen elicit their antiallergic effects by mainly antagonizing against histamine (H_1) and the acidic agents such as disodium cromoglycate (DSCG) by mainly inhibiting release of chemical mediators. From the viewpoint of the classification described above, **7** represents a new class of antiallergic agent having both acidic and basic moieties in one molecule. To our knowledge, only a few agents have been reported as such type of compound.[5] We expected such a new class of compounds to exhibit their

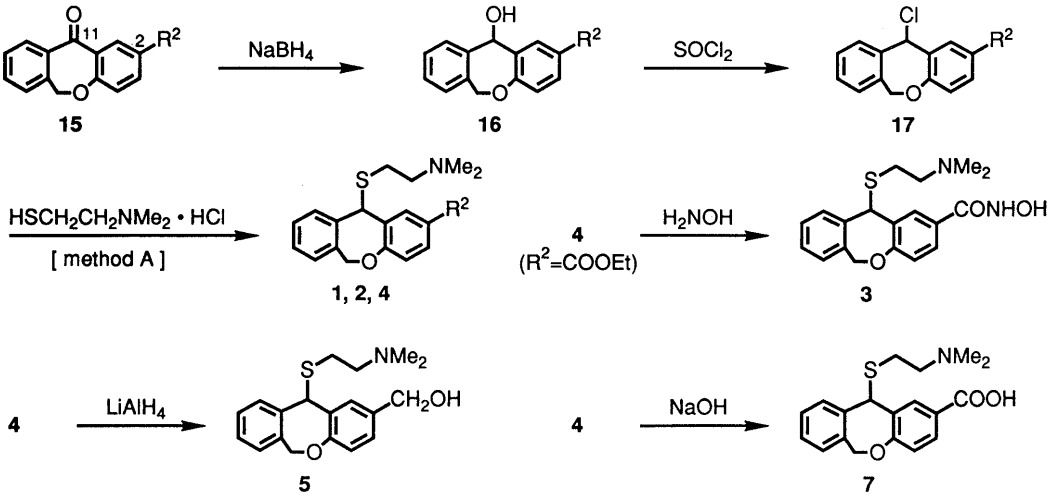
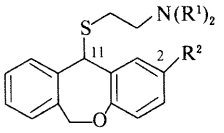


Chart 1

TABLE I. Substituted 6,11-Dihydrodibenz[*b*,*e*]oxepin Derivatives



Compd.[a] No.	R^1	R^2	mp (°C)	Recrystn.[b] solvent	H_1 % inhibn. 0.1 μM	M_1 % inhibn. 1 μM	PCA % inhibn. 10	PCA (mg/kg *p.o.*) 1
1	Me	Me	166—169	ET	93	24	97	66
2	Me	$CONH_2$	135—140 (dec.)	IP	91	79	59	20
3	Me	CONHOH	176—177	IP	91	24	51	61
4	Me	COOEt	169—171	IP	89	65	78	70
5	Me	CH_2OH	132—142	AC	93	23	92	41
6	H	COOH	250—253	IP	44	2	26	27
7	Me	COOH	233 (dec.)	IP	59	7	87	70
8	Et	COOH	128—130	IP	56	1	40	47
9	iso-Pr	COOH	250—252	IP	40	−2	66	58
10	Me	CH_2COOH	174—179	IP	84	−1	60	51
11	Me	CH(Me)COOH	123—124	EE	71	0	65	45
12	Me	$C(Me)_2COOH$	129—130	MT	74	16	66	69
13	Me	CH_2CH_2COOH	213—215	IE	61	1	78	58
14	Me	$CH_2CH_2CH_2COOH$	101—103	IE	75	3	57	21
Ketotifen					99	9	75	48

a) All compounds were obtained as HCl salts, except **2** (free base), **5** (fumaric acid salt), and **12** (free base). *b*) ET, ethanol; EE, diethyl ether; AC, acetone; MT, methanol; IE, diisopropyl ether; IP, isopropanol.

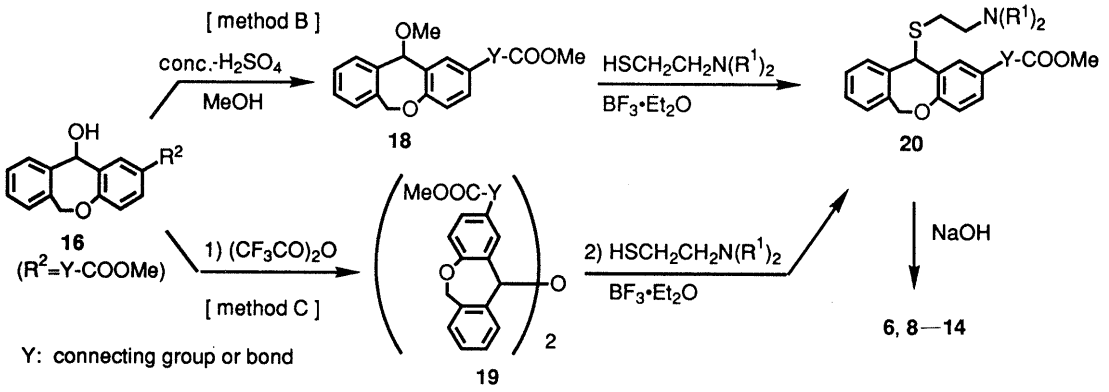


Chart 2

acitivity through new mechanisms of action.

In this paper, we describe the synthesis and structure–activity relationships of 11-substituted 6,11-dihydrodibenz[*b*,*e*]oxepin derivatives. Ketotifen, whose structure is also tricyclic, was used as a reference compound in our series of experiments.

Chemistry The 11-substituted dihydrodibenz[*b*,*e*]oxepin derivatives listed in Table I were prepared from appropriate aminoethanethiols and 11-alcohols **16** which were prepared by the $NaBH_4$ reduction of the corresponding ketones **15**[6,7] (Chart 1). In the initial stage of this study, we prepared the compounds having a varied substituent at the 2-position (**1**—**5**, and **7**). The chlorides **17** prepared by the reaction of **16** and $SOCl_2$ were extremely moisture-sensitive and immediately treated with 2-(dimethylamino)-ethanethiol in dimethylformamide (DMF) [method A]. The carboxylic acid **7** was prepared by the saponification of the ester **4**. The hydroxamic acid **3** was prepared by the treatment of **4** with hydroxylamine. The alcohol **5** was prepared by the reduction of **4** with lithium aluminum hydride ($LiAlH_4$).

Since **7**, which has a carboxyl group at C-2, was found to be the most favorable of the early cmpounds (**1**—**5**, **7**), a series of compounds having a carboxyl group as the terminal substituent of the dibenz[*b*,*e*]oxepin ring system (**6** and **8**—**14**) was prepared. These compounds were prepared *via* a methyl ether **18** [method B], or a dimeric ether **19** [method C] instead of an unstable chloride **17** (Chart 2). The sulfide formation in methods B and C can be explained in terms of a push-pull mechanism. A similar synthetic method for sulfides using zinc iodide has been reported.[8] In method C, the sequential treatments were performed in one-flask operation under very mild conditions: trifluoroacetic anhydride acted as a dehydrating agent to give **19**, which was converted to **20** in the presence of $BF_3 \cdot Et_2O$.

Results and Discussion

The compounds were tested for their inhibitory effects on the specific binding of [^{3}H]pyrilamine to guinea pig cerebellum histamine-1 (H_1) receptors,[9] the specific [^{3}H]-quinuclidinyl benzilate binding to rat striatum muscarinic acetylcholine (M_1) receptors,[10] and 48 h homologous

passive cutaneous anaphylaxis (PCA) in rats. These biological methods are described in the experimental section. The results are summarized and represented by percent inhibition in Table I. The H_1 receptor antagonistic effect was one of the mechanisms of antiallergic action,[11] whereas the M_1 receptor antagonistic was one of the indices of side effects such as suppression of salivary secretion and mydriasis.[12]

In the initial stage of this study, we focused on diminishing the undesirable CNS side effects of **1**. Our research began with replacement of the methyl group at the 2-position of **1** by a hydrophilic substituent (**2**—**5** and **7**). The results showed that inhibitory effects on both the H_1 receptor binding and rat PCA were retained, irrespective of a substituent at C-2, whereas affinity for the M_1 receptor was sensitive to the nature of the substituent. The carboxylic acid (**7**), which showed negligible M_1 receptor binding activity, turned out to be suitable for our purpose. Compound **7** was almost equipotent to **1** on the PCA test. Furthermore, it did not show any significant CNS effects up to a dose of 300 mg/kg *p.o.* These results encouraged us to pursue a series of compounds possessing a carboxyl group as the terminal of the substituent of the dibenzoxepin ring system (**6** and **8**—**14**). The effect of a substitution pattern of an amino group in the side chain was examined. From the data of several examples (**6**—**9**) in the 2-carboxyl series, dimethylamino group (**7**) was the most potent in the PCA test. We next examined the influence of the introduction of the connecting group between a carboxyl group and the dibenz[*b*,*e*]oxepin skeleton (C-2), fixing 2-[(2-dimethylamino)ethyl]thio side chain of **7**. Compounds **10**—**14** having a connecting group, as well as **7**, turned out to show significant inhibitory effects on both the PCA and H_1 receptor binding tests, and negligible M_1 receptor affinity. Although compounds **10**—**14** were somewhat more potent than **7** in the H_1 receptor binding assay, none of these compounds exhibited a significant increase in the PCA inhibitory activity.

Overall, **7** was the most potent in the rat PCA test with an ED_{50} value of 0.92 mg/kg *p.o.* and about 5 times more potent than ketotifen (ED_{50} = 5.1 mg/kg *p.o.*). Compound **7** exhibited a H_1 receptor antagonistic effect with a K_i value of 14 nM, whereas ketotifen had a K_i value of 0.31 nM. Observed H_1 receptor antagonistic activity alone could not explain the PCA inhibitory effect of **7**. Therefore, the mechanism of action of **7** might be different from that of ketotifen. Detailed analysis of the mechanism of action of **7** is now under investigation. From these results described above, compound **7** was selected for further pharmacological studies.

In order to elucidate efficacy on bronchial asthma, we examined the effect of **7** on immunoglobulin G_1 (IgG_1)-mediated bronchoconstriction in guinea pigs using the modified method reported by Konzett and Rössler.[13] Compound **7** inhibited the bronchoconstriction dose-dependently (0.003—0.3 mg/kg) with an ED_{50} value of 0.029 mg/kg *p.o.* Similarly ketotifen was also effective with an ED_{50} value of 0.009 mg/kg *p.o.*

Prostagrandin D_2 (PGD_2) has been identified as a potent bronchoconstrictor.[14] We therefore examined and found that **7** had an antagonistic effect against PGD_2-induced contraction of isolated guinea pig trachea (pA_2 = 5.73).[15] We deduced that the potent inhibitory effect of **7** on anaphylactic bronchoconstriction was based partly on the PGD_2 antagonistic effect.

In conclusion, we synthesized a new series of 11-(2-aminoethyl)thio-6,11-dihydrodibenz[*b*,*e*]oxepin derivatives and evaluated their antiallergic activity. Convenient methods for the preparation of sulfides were developed. Among the compounds synthesized, **7** had the most potent antiallergic activity with few CNS side effects. From the structural point of view, **7** represents the new class of antiallergic agent with both amino and carboxyl moieties in one molecule. It exhibited antihistaminic activity like a basic agent and a weak mediator release inhibitory effect[16] like an acidic agent. Additionally, it had an antagonistic effect against PGD_2, which was an attractive mechanism of action of the new antiallergic agents. It has a great safety margin (*e.g.* LD_{50} 771 mg/kg *p.o.*, mice) and a beneficial duration of action (6—9 h in rat PCA test). Compound **7** was seledted for further pharmacological evaluation as KW-4994. The detailed pharmacology and mechamisms of action of KW-4994 will be published elsewhere.

Experimental Section

Synthetic Procedures Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a JEOL PMX-60 (60 MHz), a Hitachi R-90H (90 MHz), or a JEOL GX-270 (270 MHz) spectrometer with Me_4Si as internal standard. Mass spectra (MS) were recorded on a JEOL D300 mass spectrometer. Elemental analyses were performed by the analytical department of our laboratories. For column chromatography, silica gel: Kieselgel 60 (Merck, 70—230 or 230—400 mesh) and highly porous synthetic resin: Diaion HP-10 (Mitsubishi Chem. Ind. Co., Ltd.) were used.

Methyl 11-Hydroxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (16c: R_2 = COOMe) To a suspension of methyl 11-oxo-6,11-dihydrodibenz-[*b*,*e*]oxepin-2-carboxylate[7] (200 g, 0.75 mol) in MeOH (1l), $NaBH_4$ (25 g, 0.66 mol) was added portionwise. After the addition was completed, the mixture was stirred at room temperature for 1 h. The mixture was treated with acetic acid (40 ml, 0.70 mol) at room temperature for 30 min. The resultant precipitate was filtered, washed successively with MeOH and H_2O, and dried. The crude product (136 g) was recrystallized from toluene to give 118 g (59%) of **16c**, mp 126—127 °C (lit.[6c] 85—87 °C). IR (KBr): 2950, 1710, 1240, 1015 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H), 5.01 and 6.05 (AB, J_{AB} = 12.4 Hz, 2H), 5.71 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 7.2—7.5 (m, 4H), 7.84 (dd, J = 2.1, 8.6 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.00; H, 5.41.

Compounds **16a** (R^2 = Me, mp 90—91 °C), **16b** (R^2 = $CONH_2$, mp 248 °C (dec.)), **16d** (R^2 = COOEt, oil), **16e** (R^2 = CH_2COOMe, mp 85—87 °C), **16f** (R^2 = CH(Me)COOMe, oil), **16g** (R^2 = $C(Me)_2$COOMe, oil), **16h** (R^2 = CH_2CH_2COOMe, oil), **16i** (R^2 = $CH_2CH_2CH_2$COOMe, oil) were prepared by a similar method as described above from the corresponding ketones.[6,7]

Method A. Ethyl 11-[2-(Dimethylamino)ethyl]thio-6,11-dihydrodibenz-[*b*,*e*]oxepin-2-carboxylate Hydrochloride (4) **16d** (R^2 = COOEt) (11.4 g, 40.1 mmol) was dissolved in dry CH_2Cl_2 (300 ml), to which was added $SOCl_2$ (4.0 ml, 55.1 mmol) dropwise at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to give crude **17** (R^2 = COOEt), which was used without purification in the next reaction. A mixture of **17** (R^2 = COOEt)(12.7 g, 39.9 mmol), 2-(dimethylamino)ethanethiol hydrochloride (90%, 9.5 g, 60.4 mmol), and DMF (200 ml) was stirred at 70 °C under nitrogen atmosphere for 5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (500 ml). The solution was acidified to pH 1.0 with 4 N HCl, washed twice with ether and subsequently adjusted to pH 10.0 with 10 N NaOH. The reaction mixture was extracted with ether. The extract was washed with brine, dried, and concentrated. The residue was chromatoraphed on silica gel (AcOEt–triethylamine, 10 : 1) to give 10.9 g (74%) of the free base of **4** as an oil. IR (neat): 2970, 2770, 1710,

1460, 1250, 1115 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (t, J=7.0 Hz, 3H), 2.15 (s, 6H), 2.3—2.9 (m, 4H), 4.32 (q, J=7.0 Hz, 2H), 4.85 and 6.45 (AB, J_{AB}=13.0 Hz, 2H), 5.04 (s, 1H), 6.7— 8.0 (m, 7H). MS m/z: 371 (M^+). This free base (8.0 g, 24.0 mmol) was dissolved in isopropanol (200 ml). To the solution was added 7 N HCl in isopropanol (10 ml, 70 mmol) and the mixture was stirred at room temperature for 1 h. The resultant precipitate was collected and recrystallized from isopropanol to give 7.5 g (84%) of **4** crystals. IR (KBr): 2930, 2670, 1720, 1610, 1240, 1130 cm^{-1}. *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot HCl$: C, 61.83; H, 6.42; N, 3.43. Found: C, 61.59; H, 6.70; N, 3.70.

Compounds **1** (R^2=Me) and **2** (R^2=$CONH_2$) were prepared by a similar method as described above from **16a** (R^2=Me) and **16b** (R^2=$CONH_2$), respectively. **1**: *Anal.* Calcd for $C_{19}H_{23}NOS \cdot HCl$: C, 65.22; H, 6.91; N, 4.00. Found: C, 65.20; H, 6.84; N, 3.84. **2**: *Anal.* Calcd for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.93; H, 6.25; N, 8.00.

Method B. Methyl 11-(2-Aminoethyl)thio-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylate (20a: R^1=H; Y=bond). A mixture of **16c** (R^2=COOMe)(190 g, 0.70 mol), conc-H_2SO_4 (15 ml), and MeOH (500 ml) was refluxed for 1 h. After being cooled, H_2O (500 ml) was added and the mixture was stirred at room temperature for 1 h. The resultant precipitate was collected, washed with H_2O, dried, and recrystallized from MeOH to give 180 g (91%) of **18** (Y= bond) as crystals, mp 112—113 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.27 (s, 3H), 3.82 (s, 3H), 4.84 and 6.08 (AB, J_{AB}= 12.1 Hz, 2H), 4.99 (s, 1H), 6.73—8.16 (m, 7H). To a mixture of **18** (Y= bond)(3.7 g, 13.0 mmol), 2-aminoethanethiol (1.2 g, 15.6 mmol) and dry CH_2Cl_2 (70 ml) was added $BF_3 \cdot Et_2O$ (3.9 ml, 31.7 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed successively with 1 N NaOH and brine, dried, and concentrated. The residue was chromatographed on silica gel (AcOEt–triethylamine, 20:1) to give 4.1 g (96%) of **20a** as an oil. IR (neat): 3370, 1710, 1240, 1115 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 2H), 2.23—2.97 (m, 4H), 3.79 (s, 3H), 4.79 and 6.32 (AB, J_{AB}=13 Hz, 2H), 4.93 (s, 1H), 6.72 (d, J= 8.5 Hz, 1H), 6.94—7.33 (m, 4H), 7.65 (dd, J=2.2, 8.5 Hz, 1H), 7.83 (d, J=2.2 Hz, 1H). *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.51; H, 5.62; N, 4.43.

Compounds **20c** (R^1=iso-Pr; Y=bond, oil) and **20e** (R^1=Me; Y= –CH(Me)–, oil) were prepared by a similar method as described above from the corresponding alcohols **16c** and **16f**, respectively. **20c**: ^{1}H-NMR ($CDCl_3$) δ: 0.90 (d, J=6.5 Hz, 12H), 2.46 (br s, 4H), 2.50—3.16 (m, 2H), 3.80 (s, 3H), 4.85 and 6.48 (AB, J_{AB}=12.5 Hz, 2H), 4.99 (s, 1H), 6.7—8.0 (m, 7H). High resolution MS m/z: Calcd for $C_{24}H_{31}NO_3S$ 413.2025. Found 413.2036 (M^+). **20e**: ^{1}H-NMR ($CDCl_3$) δ: 1.44 (d, 3H), 2.12 (s, 6H), 2.25—2.73 (m, 4H), 3.58 (s, 3H), 3.41—3.80 (m, 1H), 4.77 and 6.26 (AB, J_{AB}=13.0 Hz, 2H), 4.92 (s, 1H), 6.66—7.31 (m, 7H). High resolution MS m/z: Calcd for $C_{22}H_{27}NO_3S$ 385.1712. Found 385.1722 (M^+).

Method C. Methyl 11-[2-(Dimethylamino)ethyl]thio-6,11-dihydrodibenz-[*b,e*]oxepin-2-acetate (20d: R^1=Me; Y=–CH$_2$–) To a solution of **16e** (R^2=CH_2COOMe) (40 g, 0.14 mol) in dry CH_2Cl_2 (300 ml) was added trifluoroacetic anhydride (22 ml, 0.16 mol) dropwise and the mixture was stirred at room temperature for 2 h. The mixture was treated with 2-(dimethylamino)ethanethiol hydrochloride (25 g, 0.18 mol) and $BF_3 \cdot Et_2O$ (3 ml, 0.02 mol) at room temperature for 3 h. The reaction mixture was washed successively with 1 N NaOH and brine, dried, and concentrated. The residue was chromatographed on silica gel (AcOEt–triethylamine, 40:1) to give 32 g (61%) of **20d** as an oil. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (s, 6H), 2.30—2.76 (m, 4H), 3.50 (s, 2H), 3.63 (s, 3H), 4.77 and 6.25 (AB, J_{AB}=13 Hz, 2H), 4.92 (s, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.90—7.45 (m, 6H). *Anal.* Calcd for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77. Found: C. 67.85; H, 6.88; N, 3.59.

Compounds **20b** (R^1=Et, Y=bond, oil), **20f** (R^1=Me, Y=–C(Me)$_2$–, oil), **20g** (R^1=Me, Y=–CH_2CH_2–, oil) and **22h** (R^1=Me, Y=–CH_2CH_2–CH_2–, oil) were prepared by a similar method as described above from the corresponding materials. **20b**: ^{1}H-NMR ($CDCl_3$) δ: 0.84—1.14 (m, 6H), 2.28—2.77 (m, 8H), 3.80 (s, 3H), 4.84 and 6.44 (AB, J_{AB}=13.0 Hz, 2H), 5.03 (s, 1H), 6.7—8.0 (m, 7H). MS m/z: 385 (M^+). **20f**: ^{1}H-NMR ($CDCl_3$) δ: 1.55 (s, 6H), 2.16 (s, 6H), 2.1—2.7 (m, 4H), 3.63 (s, 3H), 4.83 and 6.31 (AB, J_{AB}=13.0 Hz, 2H), 6.7—7.4 (m, 7H). High resolution MS m/z: Calcd for $C_{23}H_{29}NO_3S$ 399.1868. Found 399.1875 (M^+). **20g**: ^{1}H-NMR ($CDCl_3$) δ: 2.14 (s, 6H), 2.14—2.97 (m, 8H), 3.61 (s, 3H), 4.79 and 6.24 (AB, J_{AB}=13.0 Hz, 2H), 4.92 (s, 1H), 6.63—7.31 (m, 7H). High resolution MS m/z: Calcd for $C_{22}H_{27}NO_3S$ 385.1712. Found 385.1733 (M^+). **20h**: ^{1}H-NMR ($CDCl_3$) δ: 2.15 (s, 6H), 1.75—2.78 (m, 10H), 3.62 (s, 3H), 4.81 and 6.25 (AB, J_{AB}=12.5 Hz, 2H), 4.93 (s, 1H), 6.66—7.36 (m, 7H). MS m/z: 399 (M^+).

11-[2-(Dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Hydrochloride (7) A mixture of the free base of **4** (57.3 g, 0.16 mol), 4 N NaOH (120 ml), and EtOH (800 ml) was refluxed for 2 h.The reaction mixute was concentrated and diluted with H_2O. The solution was acidified to pH 5.7 with 4 N HCl. After stirring for 1 h at room temperature, the resultant precipitate was filtered, washed with H_2O and dried to give 51.5 g (94%) of the crude free base of **7**. ^{1}H-NMR (DMSO-d_6) δ: 2.13 (s, 6H), 2.3—2.8 (m, 4H), 5.05 and 6.26 (AB, J_{AB}= 12.5 Hz, 2H), 5.43 (s, 1H), 6.87 (d, J=8.5 Hz, 1H), 7.36—7.46 (m, 4H), 7.71 (dd, J=2,2, 8.5 Hz, 1H), 7.97 (d, J=2.2 Hz, 1H). This was converted to the hydrochloride in a similar manner to that used for the preparation of **4** to give 53.0 g of **7** (91%), as crystals. IR (KBr): 3400, 2700, 1700, 1620, 1240, 1200 cm^{-1}. *Anal.* Calcd for $C_{19}H_{21}NO_3S \cdot HCl \cdot 0.5H_2O$: C, 58.68; H, 5.96; N, 3.60. Found: C, 58.45; H, 5.73; N, 3.52.

Compounds **6** and **8**—**14** were saponificated by a similar method as described above from the corresponding materials. **6**: *Anal.* Calcd for $C_{17}H_{17}NO_3S \cdot HCl$: C, 58.03; H, 5.16; N, 3.98. Found: C, 57.99; H, 5.29; N, 3.98. **8**: *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot HCl$: C, 61.83; H, 6.42; N, 3.43. Found: C, 61.54; H, 6.48; N, 3.66. **9**: *Anal.* Calcd for $C_{23}H_{29}NO_3S \cdot HCl$: C, 63.36; H, 6.94; N, 3.21. Found: C, 63.49; H, 7.28; N, 3.55. **10**: *Anal.* Calcd for $C_{20}H_{23}NO_3S \cdot HCl$: C, 60.98; H, 6.14; N, 3.56. Found: C, 61.32; H, 6.25; N, 3.73. **11**: *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot HCl \cdot 0.5H_2O$: C, 60.49; H, 6.53; N, 3.36. Found: C, 60.74; H, 6.51; N, 3.40. **12**: *Anal.* Calcd for $C_{22}H_{27}NO_3S \cdot H_2O$: C, 65.48; H, 7.24; N, 3.47. Found:C, 65.86; H, 7.61; N, 3.09. **13**: *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot HCl$: C, 61.83; H, 6.42; N, 3.43. Found: C, 62.02; H, 6.72; N, 3.37. **14**: *Anal.* Calcd for $C_{22}H_{27}NO_3S \cdot HCl \cdot 0.5H_2O$: C, 61.31; H, 6.78; N, 3.25. Found: C, 61.67; H, 6.94; N, 3.17.

11-[2-(Dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepin-2-hydroxamic Acid Hydrochloride (3) To a solution of hydroxylamine hydrochloride (1.67 g, 25.8 mmol) in H_2O (20 ml) was added a solution of NaOH (2.4 g, 60.2 mmol) in H_2O (10 ml) under nitrogen atmosphere. A solution of the free base of **4** (6.4 g, 17.2 mmol) in dioxane (10 ml) was added dropwise and the mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and then diluted with H_2O. The solution was washed with ether and subsequently acidified to pH 5.5 with 4 N HCl. Insoluble material was removed by filtration and the filtrate was concentrated. The precipitated material was filtered, washed with H_2O and dried to give 2.02 g (33%) of the crude free base of **3**. IR (KBr): 3200, 1640, 1260, 1010 cm^{-1}. MS m/z: 358 (M^+). This crude product was converted to the hydrochloride and purified in a similar manner to that used for the preparation of **4** to give 1.5 g of **3** (67%). IR (KBr): 1640, 1260, 1010 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}N_2O_3S \cdot HCl$: C, 57.79; H, 5.87; N, 7.09. Found: C, 57.96; H, 5.71; N, 7.43.

11-[2-(Dimethylamino)ethyl]thio-2-hydroxymethyl-6,11-dihydrodibenz-[*b,e*]oxepin Fumarate (5) To a solution of the free base of **4** (10.9 g, 29.4 mmol) in tetrahydrofuran (THF 300 ml) was added $LiAlH_4$ (0.8 g, 21.1 mmol) portionwise at 0 °C. After the addition was completed, the mixture was stirred at room temperature for 3.5 h. The excess reagent was quenched with H_2O and the resultant inorganic salts were removed by filtration. The filtrate was evaporated to give 9.6 g of the crude free base of **5** as an oil. IR (neat): 3400, 1500, 1460, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (s, 6H), 2.38—2.84 (m, 2H), 3.52—3.93 (m, 2H), 4.49 (s, 2H), 4.81 and 6.24 (AB, J_{AB}=13.5 Hz, 2H), 4.96 (s, 1H), 6.61—7.47 (m, 7H). MS m/z: 329 (M^+). The oil (1.5 g, *ca.* 4.5 mmol) and fumaric acid (0.6 g, 5.17 mmol) was dissolved in hot acetone (500 ml, 50 °C). After being cooled to room temperature, the resultant precipitate was filtered, washed with acetone, and dried to give 1.28 g (64%) of **5**. *Anal.* Calcd for $C_{19}H_{23}NO_2S \cdot C_4H_4O_4$: C, 62.00; H, 6.11; N, 3.14. Found: C, 62.02; H, 6.09; N, 2.88.

Biological Evaluation Procedures. Histamine-1 (H_1) Receptor Binding Assay H_1 binding assay was performed according to the previously reported method[10] with minor modification. The cerebellum of male Hartley guinea pig was homogenized in 40 volumes (w/v) of ice cold 50 mM sodium–potassium phosphate buffer, pH 7.5, (abbreviated as buffer) by a polytron homogenizer (Kinematica). The homogenate was centrifuged at 35500 × *g* for 10 min at 4 °C and the precipitate was homogenized again in the same volumes of buffer by the polytron homogenizer and centrifuged at 35000 × *g* for 10 min. The resulting precipitate was resuspended in 100 volumes of buffer by a teflon homogenizer. Tissue homogenates (10 mg wet weight), 3.8 nM of [^{3}H]pyrilamine and 0.1 μM of drugs in the total volume of 1.1 ml were added to a polypropylene tube

and incubated for 30 min at 25 °C. Ice cold buffer (4 ml) was added to a reaction tube and the reaction was stopped by rapid vacuum filtration (cell harvester Brandel M-24-R) through a Whatman GF/C glass fiber filter. The filter was washed 3 times with 5 ml of ice cold buffer. The filter was transferred to a scintillation vial, to which 0.5 ml of MeOH and 8 ml of scintisol EX-H (Wako Pure Chemicals) were added to determine radioactivity by a liquid scintillation counter (Packard 4530). Nonspecific binding was determined in the presence of 1 μM astemizole.

Muscarinic Acetylcholine (M_1) Receptor Binding Assay The binding assay was carried out as in the previously described method[11] with minor modification. The striatum of the rat was homogenized in 10 volumes of distilled water with a Potter-El-vehjem homogenizer. This homogenate preparation was diluted to 200 volumes of the wet tissue with 50 mM sodium–potassium phosphate buffer, pH 7.4. The homogenate (5 mg wet weight), 1.26 nM of [^{3}H]quinuclidinyl benzilate, and 1 μM of drugs in the total volume of 1.1 ml were incubated at 37 °C for 60 min. Nonspecific binding was determined by the addition of 1 μM unlabeled dexetimide. The assay was terminated by rapid filration under reduced pressure over a Whatman GF/B filter. The filters were washed three times with 5 ml of ice-cold 50 mM sodium–potassium phosphate buffer, pH 7.4 and the radioactivity was counted by a liquid scintillation counter.

Effects on 48 h Homologous Passive Cutaneous Anaphylaxis (PCA) in Rats Rat reaginic antibody (IgE) raised to ovalbumin (OA) was prepared by the method of Stotland and Share.[17] Briefly, Wistar strain male rats were immunized by giving a subcutaneous injection of 1 ml of a suspension containing 1 mg OA, 20 mg aluminum hydroxide gel and 10^{10} killed Bordetella pertussis organisms and then bled 14 d after this sensitization. The antiserum was separated and kept at −80 °C. Groups of 3 Wistar male rats were used and 0.05 ml of anti-OA rat serum, diluted 1 : 8 with 0.9% saline, was injected intradermally at two points on the dorsum. After 48 h, the PCA reaction was induced by intravenous administration of an aqueous solution containing 2 mg of OA and 5 mg of Evans blue. Test compounds were administered orally 1 h before injection of the antigen. After 30 min, the animals were anesthetized with ethyl ether and the dorsal skin was removed to determine the extravasated dye at each reaction site. The amount of dye was extracted by the method of Katayama[18] and was quantified by spectrometry. The percent of inhibition of the PCA reaction was then calculated.

Effects on Anaphylactic Bronchoconstriction in Passively Sensitized Guinea Pigs The experiment was performed according to the method of Konzett and Rössler.[14] Groups of 8 to 12 Hartley strain male guinea pigs were sensitized passively by giving intraperitoneally 1 ml of IgG-like guinea pig antiserum against OA. After 24 h, the animals were anesthetized with urethane (1.2 g/kg i.p.) and tracheotomised and ventilated by means of a respiratory pump (75 strokes/min, stroke volume 6 ml). After eliminating the spontaneous respiration by injection of gallamine triethiodide (10 mg/kg i.v.), initial airway resistance was kept constant at 8 cm H_2O pressure by means of a water valve. The airway was connected to a bronchospasm transducer (type 7020, Ugo Basile, Milan, Italy). The animals were challenged with OA (1 mg/kg i.v.) and anaphylactic bronchoconstriction was recorded as the % of maximal overflow obtained by clamping off the trachea. Test drugs were administered orally 1 h before the OA challenge. The preventive effect of the test drugs was expressed as present inhibition as compared to the increase of overflow volume determined at a 5 min later antigen challenge in control animals. ED_{50} value, *i.e.*, the dose required for 50% inhibition of the anaphylactic bronchoconstriction, was calculated from the relation between the logarithmic dose and the percent of inhibition by the method of least squares.

Effect on PGD_2-Induced Contraction of Isolated Guinea Pig Tracheal Preparations The zig-zag tracheal strip preparations from guinea pigs were made according to the method of Emmerson and Mackay.[19] The preparations were suspended in organ baths containing 10 ml of Krebs–Henseleit's solution with indomethacin (1×10^{-6} M) in order to antagonize the compensatory release of dilator PG product during tracheal contraction. The bath fluid was kept at 37 °C and gassed with 5% O_2 in CO_2. The contractile responses to PGD_2 were measured using an isotonic transducer (TD-112S, Nihon Kohden). PGD_2 was cumulatively added to the bath to obtain a concentration–response curve. Each test drug was added 10 min before the addition of PGD_2. The pA_2 value of the test drug was calculated by the method of Takayanagi.[20]

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