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1-Substituted 2-benzylaminobenzimidazole derivatives: compounds with H_1-antihistaminic activity

A Da Settimo[1], G Primofiore[1], F Da Settimo[1], L Calzolari[1], P Cazzulani[2], A Passoni[2], O Tofanetti[2]

[1]*Istituto di Chimica Farmaceutica dell'Università di Pisa, Via Bonanno 6, 56100, Pisa;*
[2]*Boehringer Mannheim Italia SpA, Research Laboratories, Viale della Libertà, 20052, Monza, Milan, Italy*

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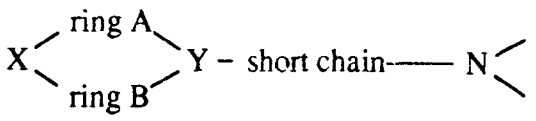
Summary — The preparation of 1-substituted 2-benzylaminobenzimidazole derivatives **13–24** is described. Although these compounds have a different structure from the general structure **I** of antihistamines, they showed some antihistaminic activity (pA_2: 5–7) when tested *in vitro* on guinea pig ileum. The introduction of an additional basic centre as in the Mannich bases **25–27** did not cause any improvement of activity. All the compounds tested proved to be inactive in *in vivo* induced passive cutaneous anaphylaxis (PCA) and cutaneous vasopermeability in rats.

2-benzylaminobenzimidazole / H_1-antihistaminic activity / *in vitro* histamine, metacholine and serotonin antagonism / *in vivo* PCA and histamine-induced vasopermeability inhibition

Introduction

Compounds with H_1-antihistaminic activity can find a useful therapeutic application in the treatment of various allergic and inflammatory conditions due to histamine release. Although antihistamines belong to several different chemical classes, such as ethylenediamines, aminoethylethers, propyl- and propenylamines, phenothiazines, piperidines and piperazines, they show remarkable chemical similarities. Indeed, at least the most potent antihistamines can be defined by the following general structure I.



I

where ring A is aryl or heteroaryl, ring B is aryl or arylmethyl, X= -S-, $-CH_2-$, -CH=CH- groups sometimes bridging the *ortho* positions of rings A and B, Y= -N<, >CH-, >C= and the short chain can be a linear chain or part of a piperidine or piperazine group. Generally, the mean Y-N distance is approximately 4 Å [1].

In view of the significant biological activities shown by various substituted 2-aminobenzimidazoles, such as antiviral [2], anthelmintic [3] and mostly antihistaminic [1, 4–7], we have been interested for several years in this field [8–10]. The development of drugs such as astemizole [11–13] (fig 1), a long-lasting, non-sedative, antihistaminic antiallergic compound, prompted us to search for new 2-aminobenzimidazole derivatives having antihistaminic activity.

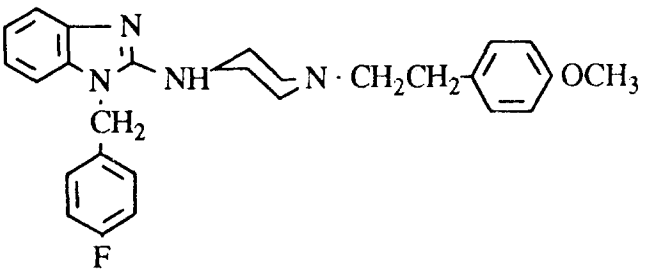


Fig 1. Astemizole.

The present paper reports the synthesis and the evaluation of the antihistaminic activity of a series of new 1-substituted 2-benzylaminobenzimidazoles **13–24**, which are unrelated to antihistamines of general structure I.

Chemistry

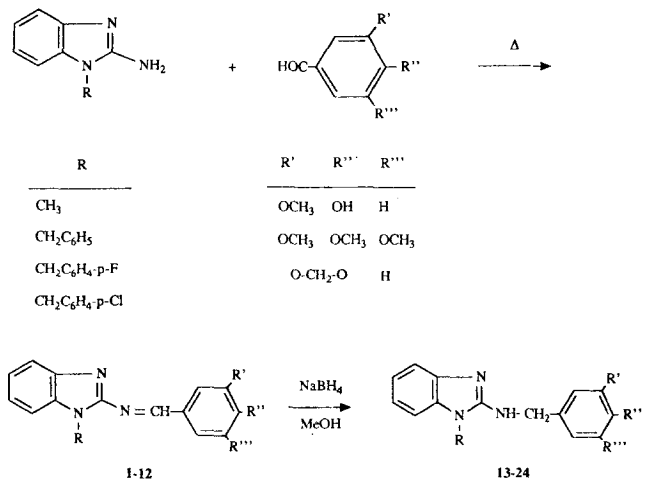
The general synthetic procedure (scheme 1) employed for the preparation of the target compounds involved condensation of the appropriate 1-substituted 2-aminobenzimidazole [8, 14, 15, 16] with vanilline, trimethoxybenzaldehyde and piperonale to give the Schiff bases **1–4**, **5–8** and **9–12** respectively (table I). The reduction [17] of these compounds with $NaBH_4$ in methanolic solution afforded the amino derivatives **13–16**, **17–20** and **21–24** (table II).

The Mannich bases **25–27** were prepared by reaction of compounds **14–16** with formalin (formaldehyde solution) and morpholine in ethanolic solution [18] (scheme 2) (table II).

Pharmacological results

The compounds were tested for antispasmodic activity *in vitro* against histamine-, metacholine- or serotonin-induced contractions on isolated organs, and *in vivo* against histamine-induced cutaneous vasopermeability and passive cutaneous anaphylaxis (PCA) in rats. Acute toxicity was detected in mice.

The results obtained in different tests performed on isolated organs are summarized in table III.



Scheme 1.

All compounds tested, with the exception of **24**, inhibited histamine-induced contractions on guinea pig ileum; compounds **13**, **17**, **18**, **20**, **21** and **25** showed a non-competitive activity, while the others competitively interacted with the H_1 receptors, **15**, **27**, **23**, **16**, **26** and **14** being the most potent compounds. Only compounds **15** and **26** inhibited metacholine-induced contractions on guinea pig ileum, whereas none of the compounds revealed any activity against serotonin-induced contractions on rat stomach fundus (data not shown). All reference drugs appeared to be more effective than the compounds tested.

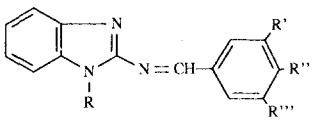
As shown in table IV, compounds **14–16**, **23**, **26** and **27** did not inhibit histamine-induced vasopermeability in rats, when administered up to 50 mg/kg *po*. Some antianaphylactic properties were shown only by compound **16**, which was effective in inhibiting PCA in rats, even if it appeared to be less active than astemizole and oxatomide.

Discussion

Compounds **13–24** differ markedly from the antihistaminic general structure **I**. They represent a structural simplification with respect to **I**, since they lack the short chain and the tertiary amine group bound to it. Instead, a substituted benzylic group is present in their position.

In the structure of all antihistaminic drugs, the presence is thought to be indispensable of a basic centre, protonated at physiological pH, which, by interacting with an anionic group on the receptor site, should have the function of binding the molecule to the receptor itself. It is therefore plausible to conclude that in our compounds **13–24** the cationic centre consists of the pyridine-like nitrogen at position 3 of the 2-aminobenzimidazole nucleus, as this atom is the one predominantly protonated in the acid-base equilibria of the parent compounds 2-aminobenzimidazole and 2-aminoimidazole [19, 20]. By interacting with a lipophilic planar area on the receptor site, the two benzylic groups could make the bond with the receptor stronger. This should be in accordance with the hypothesis of Borea *et al* [21] regarding pharmacophore geometry for optimum antihistaminic activity. According to these authors, the presence is necessary for a cationic centre, protonated amino nitrogen, and an aromatic system, a planar lipophilic area, at a distance of about 6.20 Å. Moreover, a second aromatic ring, though not indispensable, at a distance of about 4.90 Å from the first one, greatly increases the antihistaminic activity, because it can probably act as a new point of interaction with a hydrophobic accessory binding site, located at the receptor. Approximately the same distances can also

Table I. Preparation and physical properties of compounds **1–12**. All compounds were analyzed for C, H, N.



Compd No	*R*	*R'*	*R''*	*R'''*	*Reaction time (h)*	*Yield (%)*	*Recryst solvent*	*Mp °C*	*Formula*
1	CH_3	OCH_3	OH	H	6	56	Ethanol	182–183	$C_{16}H_{15}N_3O_2$
2	$CH_2C_6H_5$	OCH_3	OH	H	7	35	Ethanol	184–185	$C_{22}H_{19}N_3O_2$
3	$CH_2C_6H_4pF$	OCH_3	OH	H	15	49	Ethanol	187–189	$C_{22}H_{18}N_3O_2F$
4	$CH_2C_6H_4pCl$	OCH_3	OH	H	15	63	Ethanol	206–207	$C_{22}H_{18}N_3O_2Cl$
5	CH_3	OCH_3	OCH_3	OCH_3	90	84	Pet ether 100–140°	164–166	$C_{18}H_{19}N_3O_3$
6	$CH_2C_6H_5$	OCH_3	OCH_3	OCH_3	72	53	Pet ether 60–80°	114–116	$C_{24}H_{23}N_3O_3$
7	$CH_2C_6H_4pF$	OCH_3	OCH_3	OCH_3	160	81	Pet ether 100–140°	138–140	$C_{24}H_{22}N_3O_3F$
8	$CH_2C_6H_4pCl$	OCH_3	OCH_3	OCH_3	15	76	Pet ether 100–140°	130–131	$C_{24}H_{22}N_3O_3Cl$
9	CH_3	O-CH_2-O		H	24	85	Pet ether 100–140°	165–167	$C_{16}H_{13}N_3O_2$
10	$CH_2C_6H_5$	O-CH_2-O		H	23	74	Pet ether 100–140°	156–158	$C_{22}H_{17}N_3O_2$
11	$CH_2C_6H_4pF$	O-CH_2-O	H		24	85	Benzene-pet ether 60–80°	158–160	$C_{22}H_{16}N_3O_2F$
12	$CH_2C_6H_4pCl$	O-CH_2-O	H		17	80	Pet ether 100–140°	185–186	$C_{22}H_{16}N_3O_2Cl$

be observed in one of the possible conformations assumed by our compounds (Dreiding models). Indeed, the centre of gravity of the benzene ring of the benzyl group at position 1 of benzimidazole in one of the possible conformations is at a distance of approximately 5.9 Å from the protonable nitrogen atom at position 3. Moreover, in our compounds, the second aromatic ring, thought not to be indispensable for antihistaminic activity, should be the benzylamine group at position 2. This group can assume a distance of 4.9 Å from the first aromatic ring due to free rotation around the C(2)-N-C bonds. Therefore the aromatic ring at position 1 is of fundamental importance for antihistaminic activity, as supported by the lack of potency of 1-methyl substituted compounds (table III). Moreover, when an additional basic group is present (Mannich bases **25–27**) the *in vitro* activity remains substantially unchanged, since a second basic group is not necessary for binding at the receptor site. However, compounds **25–27** have no significant *in vivo* activity, although these molecules incorporate, even if in a different sequence, the principal structural moieties of astemizole.

Experimental protocols

Chemistry

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. IR spectra were recorded with a Pye Unicam Infracord Model PU 9516 in Nujol mulls. ^1H NMR spectra were determined in $CDCl_3$ (in DMSO-d_6 for compounds **13–16**) with tetramethylsilane (TMS) as an internal standard on a Varian EM 360 A spectrometer and were consistent with assigned structures. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Elemental analyses were performed by our analytical laboratory in Pisa and agreed with theoretical values to within ±0.4%.

The structures of all compounds were confirmed by elemental analysis and IR and NMR data.

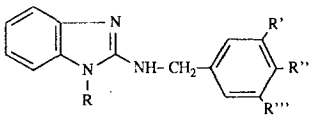
General procedure for the preparation of 1-substituted 2-[N-(substituted phenyl)methylene]amino-1H-benzimidazoles ***1–12***

Compounds **1–12** (table I) were synthesized from the appropriate 1-substituted-2-aminobenzimidazole by the representative procedure illustrated for compound **8**.

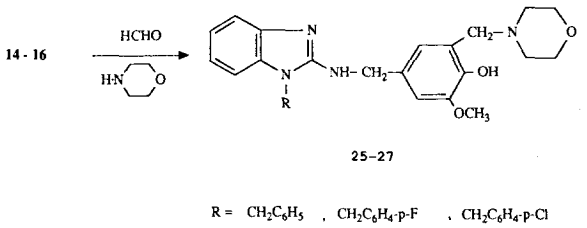
1-[(4-chlorophenyl)methyl]-2-[N-(3,4,5-trimethoxyphenyl) methylene]amino-1H-benzimidazole ***8***

A mixture of 2.575 g (0.01 mol) of 2-amino-1-(4-chlorobenzyl)benzimidazole and 1.960 g (0.01 mol) of trimethoxybenzal-

Table II. Preparation and physical properties of compounds **13–27**. All compounds were analyzed for C, H, N.



Compd No	*R*	*R'*	*R''*	*R'''*	*Yield (%)*	*Recryst solvent*	*Mp °C*	*Formula*
13	CH_3	OCH_3	OH	H	77	Ethanol	196–198	$C_{16}H_{17}N_3O_2$
14	$CH_2C_6H_5$	OCH_3	OH	H	85	Ethanol	170–172	$C_{22}H_{21}N_3O_2$
15	$CH_2C_6H_4pF$	OCH_3	OH	H	90	Ethanol	105–108	$C_{22}H_{20}N_3O_2F$
16	$CH_2C_6H_4pCl$	OCH_3	OH	H	71	Ethanol	115–118	$C_{22}H_{20}N_3O_2Cl$
17	CH_3	OCH_3	OCH_3	OCH_3	87	Benzene	179–181	$C_{18}H_{21}N_3O_3$
18	$CH_2C_6H_5$	OCH_3	OCH_3	OCH_3	59	Benzene-pet ether 60–80°	72–74	$C_{24}H_{25}N_3O_3$
19	$CH_2C_6H_4pF$	OCH_3	OCH_3	OCH_3	76	Pet ether 100–140°	143–145	$C_{24}H_{24}N_3O_3F$
20	$CH_2C_6H_4pCl$	OCH_3	OCH_3	OCH_3	81	Benzene	132–134	$C_{24}H_{24}N_3O_3Cl$
21	CH_3	O-CH_2-O		H	52	Benzene	174–175	$C_{16}H_{15}N_3O_2$
22	$CH_2C_6H_5$	O-CH_2-O		H	65	Benzene	150–151	$C_{22}H_{19}N_3O_2$
23	$CH_2C_6H_4pF$	O-CH_2-O		H	48	Benzene	140–142	$C_{22}H_{18}N_3O_2F$
24	$CH_2C_6H_4pCl$	O-CH_2-O		H	74	Benzene-pet ether 60–80°	127–129	$C_{22}H_{18}N_3O_2Cl$
25	$CH_2C_6H_5$	CH_2-Morph	OH	OCH_3	80	Pet ether 100–140°	93–95	$C_{27}H_{30}N_4O_3$
26	$CH_2C_6H_4pF$	CH_2-Morph	OH	OCH_3	86	Pet ether 100–140°	96–98	$C_{27}H_{29}N_4O_3F$
27	$CH_2C_6H_4pCl$	CH_2-Morph	OH	OCH_3	80	Pet ether 100–140°	111–113	$C_{27}H_{29}N_4O_3Cl$



Scheme 2.

dehyde in 30 ml of toluene was refluxed for 15 h until the disappearance of the starting materials (TLC analysis). The solution obtained was concentrated to dryness under reduced pressure and the residue was recrystallized from petroleum ether 100–140°C to yield a yellow solid (3.310 g, 76%, mp = 130–131°C). IR (nujol mull, cm^{-1}): 1615, 1590, 1330, 1235, 1135, 760; ^1H NMR ($CDCl_3$): δ 3.90 (s, 9H, $-OCH_3$); 5.55 (s, 2H, $-CH_2C_6H_4Cl$); 7.05–7.85 (m, 10H, ArH); 9.45 (s, 1H, -N=CH-).

General procedure for the preparation of 1-substituted 2-[N-(substituted phenyl)methyl]amino-1H-benzimidazoles ***13–24***

Compounds **13–24** (table II) were synthesized from the appropriate imines **1–12** by the representative procedure illustrated for compound **21**.

1-methyl-2-[N-(3,4-methylenedioxyphenyl)methyl]amino-1H-benzimidazole ***21***

A quantity of 0.567 g (0.015 mol) of $NaBH_4$ was added in small portions to a stirred solution of 2.794 g (0.01 mol) of **9** in 50 ml of methanol, cooled at 0°C. After stirring at 0°C for 1 h, then at room temperature for 3 h, the mixture was concentrated to dryness under reduced pressure. The residue was treated with water (neutralized with diluted HCl only for compounds **13–16**), then collected and recrystallized from benzene to yield a white solid (1.460 g, 52%, mp = 174–175°C). IR (nujol mull, cm^{-1}): 3200, 1600, 1560, 1440, 1235,

Table III. *In vitro* effects of 1-substituted 2-benzylamino-1H-benzimidazole derivatives and reference drugs on contractions induced by histamine and metacholine on guinea pig ileum. NA = not active up to 10^{-6} M.

Compd No	*Histamine*	*Methacholine*
13	$pD_2' = 4.02 \pm 0.21$	NA
14	$pA_2 = 6.17 \pm 0.03$	NA
15	$pA_2 = 6.89 \pm 0.14$	$pD_2' = 5.11 \pm 0.20$
16	$pA_2 = 6.59 \pm 0.05$	NA
17	$pD_2' = 3.97 \pm 0.22$	NA
18	$pD_2' = 4.88 \pm 0.08$	NA
19	$pA_2 = 5.81 \pm 0.05$	NA
20	$pD_2' = 5.16 \pm 0.06$	NA
21	$pD_2' = 3.94 \pm 0.16$	NA
22	$pA_2 = 5.97 \pm 0.07$	NA
23	$pA_2 = 6.72 \pm 0.09$	NA
24	NA	NA
25	$pD_2' = 5.44 \pm 0.24$	NA
26	$pA_2 = 6.38 \pm 0.04$	$pA_2 = 5.99 \pm 0.05$
27	$pA_2 = 6.89 \pm 0.05$	NA
Diphenhydramine	$pA_2 = 7.40 \pm 0.07$	
Atropine		$pA_2 = 8.71 \pm 0.09$

1035, 930, 815, 735; ^{1}H NMR ($CDCl_3$): δ 3.4 (s, 3H, N-CH_3); 4.6 (s, 2H, -NH-CH_2-); 5.9 (s, 2H, -O-CH_2-O-); 6.5–7.7 (m, 7H, ArH).

General procedure for the preparation of 1-substituted 2-{N-[4-hydroxy-3-methoxy-5-(4'-morpholino)methylphenyl]-methyl}amino-1H-benzimidazoles ***25–27***

Compounds **25–27** (table II) were synthesized from the appropriate amine derivatives **14–16** by the representative procedure illustrated for compound **25**.

2-{N-[4-hydroxy-3-methoxy-5-(4'-morpholino)methylphenyl]-methyl}amino-1-[(phenyl)methyl]-1H-benzimidazole ***25***

A solution of 3.590 g (0.01 mol) of the amine **14**, 0.87 ml (0.01 mol) of morpholine and 1.53 ml (0.02 mol) of formaldehyde (36% solution in water) in 15 ml of ethanol was refluxed for 16 h. After cooling, the reaction mixture was poured into water and left to stand overnight in a refrigerator. The precipitated solid was collected and recrystallized from petroleum ether 100–140°C (3.664 g, 80%, mp = 93–95°C). IR (nujol mull, cm^{-1}): 1610, 1595, 1560, 1240, 1110, 740. ^{1}H NMR ($CDCl_3$): δ 2.4–2.7 (m, 4H, -CH_2-N-CH_2- Morph); 3.6–3.9 (m, 9H, -OCH_3, -CH_2-N< Morph, -CH_2-O-CH_2-); 4.6 (s broad, 2H, -NH-CH_2-); 5.15 (s, 2H, -$CH_2C_6H_5$); 6.55–7.75 (m, 12H, ArH, -NH-).

Pharmacology

Materials and methods

Experiments were carried out using male or female albino mice (Crl: CD-1 (ICR) BR), 20–30 g bw, Sprague Dawley rats, (Crl: CD (SD) BR), 180–200 g bw, supplied by Charles River (Calco, Italy) and albino guinea-pigs, 300–350 g bw, supplied by Rodentia (Torre Pallavicina, Italy). Reference compounds were obtained from Sigma Chemical Co, St Louis, MO, USA).

In vitro tests

Histamine H_1 and metacholine antagonism

Guinea pig ileum

According to Magnus [22], segments of pre-terminal ileum, about 2 cm long, were excised from guinea pigs of both sexes and rapidly suspended in a 50 ml organ bath containing Tyrode's solution, maintained at 37°C and gassed with a mixture of 95% O_2 and 5% CO_2, under an initial load of 500 mg. After 15 min stabilization, cumulative dose-response curves to histamine ($1.6\ 10^{-7}$–$2.6\ 10^{-6}$ M) or metacholine ($1.5\ 10^{-8}$–$5.5\ 10^{-7}$ M) were obtained by adding graded concentrations of agonists every minute to the bath.

Table IV. Acute toxicity in mice and effects of some compounds and reference drugs on passive cutaneous anaphylaxis (PCA) and cutaneous permeability in rats. NA = not active.

Compd No	*Acute toxicity* LD_{50}[a] *mg/kg*		*PCA*		*Cutaneous permeability*	
	po	*ip*	*% inhib*[b]	ED_{50}[c]	*% inhib*[d]	ED_{50}
14	> 1000	557	NA		NA	
15	> 1000	> 1000	NA		NA	
16	> 1000	> 1000	43		NA	
23	> 1000	> 1000	NA		NA	
26	> 1000	> 1000	NA		NA	
27	> 1000	> 1000	NA		NA	
Astemizole	> 1000	–	–	2.87 (2.69–3.05)	–	–
Oxatomide	> 1000	> 1000	–	4.79 (4.34–5.26)	–	3.84 (2.56–4.27)

[a]LD_{50} = lethal dose 50 (dose inducing the death of animals by 50%); [b]Percent of inhibition *vs* controls at 50 mg/kg *po*; [c]ED_{50} = effective dose 50 (dose reducing the effect by 50%). In brackets 95% confidence limits; [d]Effect of 50 mg/kg *po*.

The H_1-histamine or cholinergic antagonism was tested by repeating the cumulative dose-response curves by histamine or by metacholine 1 min after administration of diphenhydramine ($0.01–10^{-6}$ M) or atropine ($0.1–10^{-8}$ M) respectively and of the compound under evaluation ($0.01–10^{-6}$ M). The PA_2 (negative logarithm of the molar concentration of antagonist which causes a shift of agonist activity of a factor 2) or pD_2' (negative logarithm of the molar concentration of antagonist which causes a depression to 50% of the maximum responses of agonist) values, for competitive or non-competitive antagonism respectively, were calculated according to Van Rossum [23].

5-Hydroxytryptamine (5-HT_1) antagonism

Rat stomach fundus strip

Stomach fundus was excised from male or female rats and stripped according to Vane [24]. The resulting strips, approximately 2 mm wide and 3–4 cm long, were suspended in a 50 ml organ bath containing Krebs' solution, kept at 37°C and gassed with a mixture of 95% O_2 and 5% CO_2, under an initial load of 2 g.

Cumulative dose-response curves were obtained by adding graded concentrations of 5-HT ($2\ 10^{-9}$– $4\ 10^{-6}$ M) to the bath every 4 min. The 5-HT_1 receptor antagonism was detected by repeating the cumulative dose-response curve 4 min after administration of methysergide ($0.01–10^{-7}$ M) or the compounds under examination (10^{-6} or 10^{-5} M). The pD_2' values were calculated according to van Rossum [23].

In vivo tests

Acute toxicity

Acute toxicity was detected in male and female albino mice. Test compounds were suspended in 0.5% methylcellulose and administered in a vol of 5 ml/kg both intraperitoneally and orally. LD_{50} values and 95% confidence limits were calculated by a computerized Logit system.

Antianaphylactic activity

The test of antianaphylactic activity was carried out by a modification of the method of Goose and Blair [25]. Female rats were sensitized with 1% egg albumin in 0.9% NaCl (1 ml im) and with Haemophilus pertussis vaccine ($2\ 10^{10}$ organisms; 1 ml ip). Twelve days after treatment, the animals were bled and serum was collected, and then other rats were challenged at the ventral site by intradermal injection of the antialbumin antiserum. 24 h later, the rats were treated with the compounds under test, suspended in 0.5% methylcellulose (5 ml/kg *po*), 1 h before the challenge with egg albumin (2.5% in NaCl 0.9%, 0.1 ml iv) and Evans blue dye (1% in NaCl 0.9%, 0.5 ml iv). 30 min later, the animals were killed, ventral skin was reflected and blued areas were measured. Mean values for areas in control and drug-treated groups were determined. ED_{50} values were calculated by regression analysis.

Histamine-induced cutaneous vasopermeability

Cutaneous vasopermeability was induced in female rats by intradermal administration of 0.1 ml of histamine (100 μg/ml) and Evans blue dye (1% in NaCl 0.9%, 0.5 ml/kg). The compounds suspended in 0.5% methylcellulose (5 ml/kg) were administered *po* 1 h before inducing cutaneous reaction. The inhibitory effect was detected in the same way as the antianaphylactic activity.

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