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Synthesis of piperazine derivatives and evaluation of their antihistamine and antibradykinin effects

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Abstract: Piperazine derivatives were prepared as histamine antagonists. Some of the synthesized compounds showed dual antagonistic activity against bradykinin as well as histamine.

Histamine and bradykinin are autocoids that act locally to produce pain, vasodilation, increased vascular permeability and the release of prostaglandin.[1] Many potent histamine H_1-antagonists are introduced in the market for the treatment of allergic diseases. Antagonists of the bradykinin B_2 receptor also has the potential to become a drug for allergy and inflammation. However most of the bradykinin B_2 receptor antagonists developed are bradykinin-derived peptides such as Icatibant (HOE 140) and Bradycor (CP0127), and their therapeutic use is limited. Only a few non-peptide antagonists(FR173657, WIN64338) are disclosed to date by screening or systemic drug design.[2-9] The SAR for non-peptide B_2 antagonists has not been studied much yet but that of peptide antagonists is well established and used in designing the non-peptide antagonists.; (1) a requirement of an aromatic residue at position 8 or a D-aromatic residue in position 7 for high affinity binding, and (2) the 10Å separation of two positive charges.[10]

In our study for non-peptide bradykinin B_2 antagonists, we found some second generation antihistamines with piperazine moiety have weak B_2 antagonistic effects.[11] It would be reasonable to assume that the antihistamines are modified to have additional lipophilic groups which mimic the position 8 aromatic residue requirement of bradykinin antagonists could show antagonistic effect against both histamine and bradykinin. Therefore cetirizine, a piperazine containing potent second-generation antihistamine drug recently introduced in the market, was modified to have aryl or alkyl branch at carbon side chain and their antihistamine and antibradykinin effects were investigated. Compounds that block both histamine and bradykinin would be used as an efficient treatment for allergy.

Chemistry

The side chain next to piperazine was modified to introduce aryl or alkyl groups to cetirizine skeleton. These cetirizine analogues (**1-16**) were prepared according to the standard procedure .[12] (Scheme 1)

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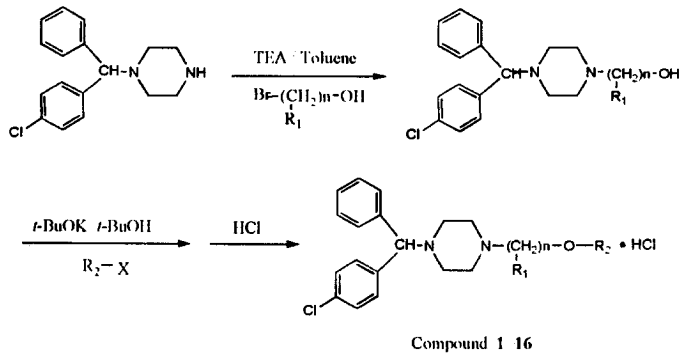


Scheme 1. Synthetic procedure for cetirizine analogues.

Results and discussion

The synthesized compounds were investigated *in vitro* for histamine H_1 receptor antagonist activity and for B_2 receptor antagonist activity. The inhibition of histamine-induced contractions of isolated guinea-pig ileum and inhibition of bradykinin-induced contractions of isolated rat ileum[2] were measured. All analogues synthesized demonstrated antagonistic effect on histamine. But the antibradykinin effect was observed only in the selected compounds (Table 1).

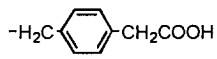
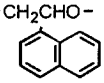
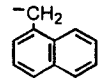
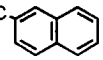
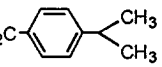
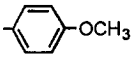
Compounds with dimethyl, phenyl or naphthyl groups at the carbon next to ether oxygen (**5-8**) showed high inhibition activity on histamine and bradykinin. High histamine antagonistic effect was observed at compounds having a terminal *p*-methoxyphenyl or *p*-isopropylphenyl group (**12-13**). Naphthyl analogues (**10, 11, 15, 16**) showed different antihistamine activity depending on the chain length. This result suggests an existence of a small lipophilic pocket in the histamine receptor.

The best bradykinin antagonists (**5, 8**) in this series had dimethyl or methylphenyl substituents. Introduction of longer flexible group (**9, 14**) resulted in activation of bradykinin instead of inhibition. Compounds with terminal aromatic groups (**10-16**) had lower bradykinin antagonistic effect compared to those with terminal carboxyl groups. This result indicates carboxylate anion could be anticipated in binding to receptor.

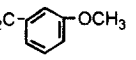
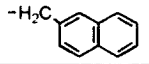
The distance between the piperazine N and carboxyl group in synthesized compounds were calculated to be 9.5-11 Å by computer modeling using Sybyl program. This is in a fairly good agreement with the distance between the two arginine positive charges separated in bradykinin, which was reported to be 10 Å.[10]

In summary, a new series of piperazine derivatives synthesized in this study showed antagonistic effects against histamine and bradykinin. Further structural optimization could lead to a better antagonist with dual activity.

Table 1. Structures and *in vitro* antihistamine, antibradykinin activity

No.	$-(CH_2)nO-$ R_1	R_2	%inhibition of histamine[a]	%inhibition of bradykinin[b]
Cetirizine	$-CH_2CH_2O-$	$-CH_2COOH$	50.7	27.0
1	$-CH_2CH_2O-$	$-CHCOOH$ CH_2CH_3	10.2	12.6
2	$-CH_2CH_2O-$		28.4	36.6
3	$-CH_2CH_2O-$	$-CHCOOH$ 	43.7	9.1
4	$-CH_2CHCH_2O-$ CH_3	$-CH_2COOH$	14.3	25.0
5	CH_3 $-CH_2CCH_2O-$ CH_3	$-CH_2COOH$	42.9	33.4
6	$-CH_2CH_2CHO-$ 	$-CH_2COOH$	52.7	25.4
7	$-CH_2CHO-$ 	$-CH_2COOH$	57.0	26.6
8	CH_3 $-CH_2CO-$ 	$-CH_2COOH$	12.5	45.6
9	$-CH_2CH_2O-$ CH_2CH_2 	$-CH_2COOH$	11	-3.7 [c]
10	$-CH_2CH_2O-$	$-CH_2$ 	20	17
11	$-CH_2CH_2O-$	$-H_2C$ 	10	-9.5
12	$-CH_2CH_2O-$	$-H_2C$  CH_3 CH_3	77.5	5
13	$-CH_2CH_2O-$	$-H_2C$  OCH_3	78.5	8.7

(Table 1. Continued.)

No.	$-(CH_2)nO-$ R_1	R_2	%inhibition of histamine[a]	%inhibition of bradykinin[b]
14	$-CH_2CH_2O-$		33	-10
15	$-CH_2CHCH_2O-$		63	11.9
16	$-CH_2CHCH_2O-$		26.4	17.7

(a) % Inhibition of histamine at 0.1 μM concentration of the synthesized compounds.
(b) % Inhibition of bradykinin at 0.1 μM concentration of the synthesized compounds.
(c) "–" means activation.

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