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A Study of Novel Antiallergic Agents with Eosinophilic Infiltration Inhibiting Action

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Abstract: The antiallergic action of a series of novel mono-O-substituted trimethylhydroquinones was investigated. Among this series of the compounds, 4-[4-[4-(diphenylmethyl)-1-piperazinyl]butoxy]-2,3,6-trimethylphenol (compound **3**) showed a potent antihistaminic action (pA_2=7.11) and an antiasthmatic action (100 mg/kg *p. o.*) on sensitized guinea pigs. Moreover, this compound exhibited a strong eosinophilic infiltration inhibiting action on sensitized mice (100 mg/kg *p. o.*).

In the past, because asthma bronchiale was conceived of as a reversible contraction of airway, bronchus expansion agents were mainly used for therapeutic purpose. Since allergic inflammation is recently shown to play an important role in the morbid state formation, the fundamental treatment of the disease has been thought to be suppression of the inflammation.[2]

Allergic inflammation is caused by accumulation of inflammatory cells such as lymphocytes and eosinophils after degranulation of mast cells.[3] Chemical mediators and cytokines from mast cells and T cells are related to the induction and activation of eosinophils.[4] Leucotrienes are chemical mediators produced in mast cells and basophils, and have an activity of contracting smooth muscles of airway, thereby being deeply involved in aggravation of the allergic symptoms.[5] Leucotriene B_4 is active in accumulating inflammatory cells and is important in the formation of allergic inflammation.[6] When mast cells are activated, leucotrienes are biosynthesized on the arachidonic acid cascade with the aid of 5-lipoxygenase within the cells. Active oxygen produced from eosinophils and neutrophils also plays an important role in allergic inflammation.[7] We have so far synthesized compounds **1**-**7** that are expected to have an inhibitory action on 5-lipoxygenase as well as an antioxidative action and obtained the results that show the

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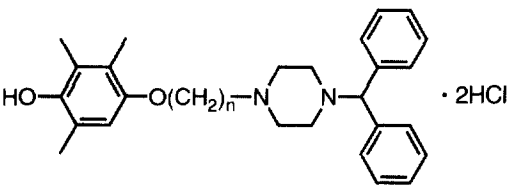
compounds synthesized are good in both activities.[8] Hence, we have further carried out a medicinal chemical study on the compounds **1**-**7**.

First, these compounds were tested with their antihistaminic action using guinea pig ilea[9] because they have a moiety of diphenylmethylpiperazine similar to that of oxatomide which is known as an antihistaminic agent.[10] As a result, compound **2** had the highest antihistaminic activity (pA_2=7.13) among the compounds tested as shown in Table 1, while compound **3** with a strong 5-lipoxygenase inhibiting action and antioxidative action showed an activity of pA_2=7.11.

Table 1. Effects of compounds **1**–**7** on guinea pig ileal contraction caused by histamine



Compound	RBL-1 cell 5-Lipoxygenase IC_{50} (nM)[8]	Antihistaminic action (pA_2)
1 (n=2)	820	6.93
2 (n=3)	426	7.13
3 (n=4)	358	7.11
4 (n=5)	351	6.82
5 (n=6)	526	6.81
6 (n=8)	1065	6.56
7 (n=10)	2215	6.39
Oxatomide	–	7.34

Compound **3** was then examined with its inhibitory effects on histamine release from rat peritoneal exudate cells containing mast cells and on cyclooxygenase from sheep seminal vesicle microsomes. Contrary to the expectation, this compound was ineffective in the concentration range of 10^{-5}-10^{-7}M (data not shown here).

Further, the effect of compound **3** was examined on the airway contraction of guinea pigs immunized with egg albumin. The experiments were performed after injecting mepyramine, an antihistaminic agent, into the animals intraperitoneally to exclude the influence of spasms due to histamine. Thus, after immunizing the animals with two ip injections of egg albumin, mepyramine was given, followed by an oral administration of the compound **3**. An hour after the oral administration, the spasm was induced in the animals by an inhalation of egg albumin and the breathing resistance was measured. The results are shown in Figure 1, where a more potent suppressive action is indicated for compound **3** than that for oxatomide used as the positive control. Since the major substances responsible for this airway contraction are likely to be leucotrienes, the action of the compound would be to inhibit the production of these substances.

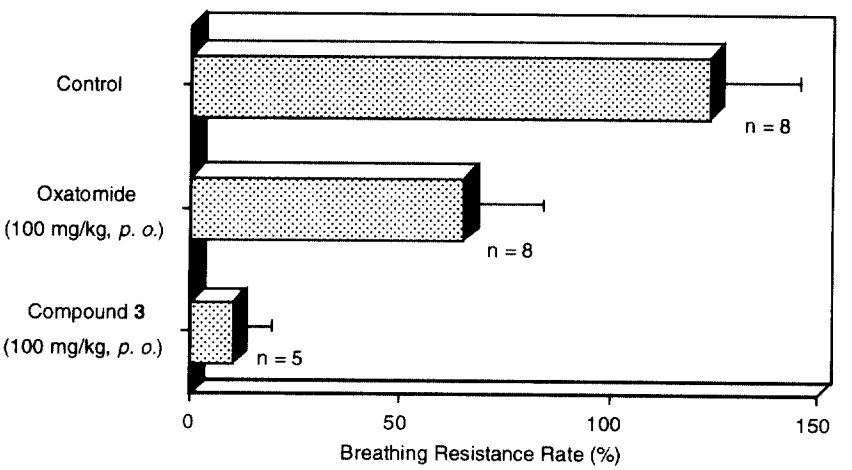


Figure 1. Effects of compound **3** and oxatomide on guinea pig airway

The effect of compound **3** on eosinophilic infiltration was finally investigated in mice immunized with egg albumin. After the animals were immunized with egg albumin in the same way as above, they were given the compound and allowed to suck egg albumin 1 h later. Then, the compound was again given to the animals 6-8 h after sucking. This treatment was conducted once everyday for five days and then the inflammatory patterns of lung tissues were evaluated for the animals. Figure 2 shows the results obtained, in which eosinophilic infiltration is hardly observed with compound **3** administered group. It is

known that cytokines and chemical mediators such as leucotrienes are induced by the action of active oxygen on the epithelia of airway.[11] Hence, compound **3** is suggested to have an inhibitory action on eosinophilic infiltration because of its antioxidative action.

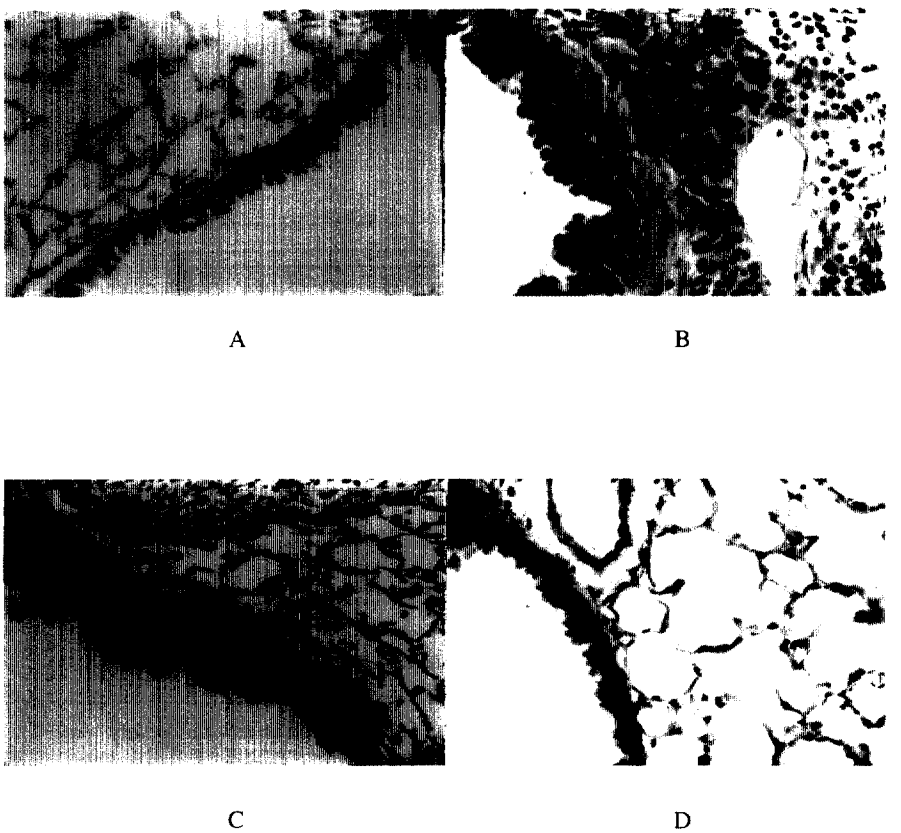


Figure 2. Effects of compound **3** and oxatomide on eosinophilic infiltration in mouse lung
A; Nonsensitized, B; Sensitized with egg albumin, C; Oxatomide 100 mg/kg/time administered, D; Compound **3** 100 mg/kg/time administered

In conclusion, the novel trimethylhydroquinone derivative, compound **3**, was found to possess antihistaminic, antiasthmatic, and eosinophilic infiltration inhibiting actions. The results obtained in this work suggest that the compounds synthesized would be potential leading compounds for developing new antiallergic drugs.

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