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Synthesis and antihistamine evaluations of novel loratadine analogues

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ABSTRACT

A series of loratadine analogues containing hydroxyl group and chiral center were synthesized. The effect of the synthesized compounds on the histamine-induced contractions of guinea-pig ileum muscles was studied. In addition, the in vivo asthma-relieving effect of the analogues in the histamine induced asthmatic reaction in guinea-pigs was determined. Most of the compounds exhibited definite H_1 antihistamine activity. The *S*-enantiomers, compounds **2**, **4** and **8**, are more potent than the *R*-enantiomers, compounds **1**, **3** and **7**. Compound **6** was the most active one among the eight synthesized compounds.

Allergy disorders, such as asthma, urticaria and allergic rhinitis, are common human diseases. Although pathogenic factors are complicated, investigations have indicated that these diseases are mainly caused by histamine.[1,2] Histamine can activate H_1 receptors which are present in nerve endings, smooth muscles, and glandular cells. Activation is followed by vasodilation and increased capillary permeability which leads to plasma exudation, local tissue swelling, and bronchial and gastrointestinal smooth muscle contractions.[3,4] Antihistamine compounds competitively bind to H_1 receptors to prevent them from attacking and being activated by histamine, which inhibits the biological effects of histamine.[5] Antihistamines are a class of commonly prescribed drugs, and numerous reviews are available[6–12] Loratadine, cetirizine and astemizole are second-generation antihistamines which have replaced first-generation antihistamines such as diphenhydramine and ketotifen because of they have fewer CNS (central nervous system) and anticholinergic side effects.[13–17] Loratadine has a potent therapeutic effect by reason of its semi-rigid conformation.[18,19] The chair conformation of the piperidine ring seems to be important in allowing the basic nitrogen to interact with the H_1 receptor.[20] Lewis et al. reported a series of loratadine-based compounds that exhibited both H_1 histamine receptor antagonist activity and 5-lipoxygenase (5-LO) inhibitory activity.[21] Liu et al. successfully synthesized a series of loratadine derivatives using c-alkylidene butenolide and found that several of them displayed potent activity for inhibiting histamine-induced effects.[22]

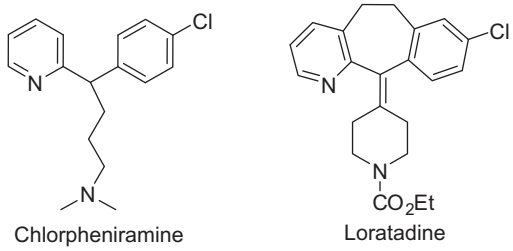

Figure 1.

In this paper, hydroxyl group and chiral center were introduced into the molecules in order to enhance its affinity for the H_1 receptor. The effect of different stereoisomers on the antihistamine effects was also investigated. Eight loratadine analogues 1–8 were synthesized and their antihistamine activities were evaluated against chlorpheniramine. Chlorpheniramine (Fig. 1) has better antihistamine activities than loratadine[23,24], although it is a kind of first-generation type H_1 antihistamine with CNS side-effects. Compounds synthesized based on the structure of loratadine can avoid such side-effects and are expected to exhibit good antihistamine activities.

A series of chiral hydroxyl group containing N-substituted-4-piperidones were obtained from chiral or achiral amino alcohols and methyl acrylate via a Michael addition, a Dieckmann cyclization and decarboxylation in about 35% yield. The various carbonyls obtained from the above piperidones were coupled with a tricyclic ketone using a low valent titanium catalyst to afford a series of target compounds in about 25% yield[25–29] (Scheme 1).

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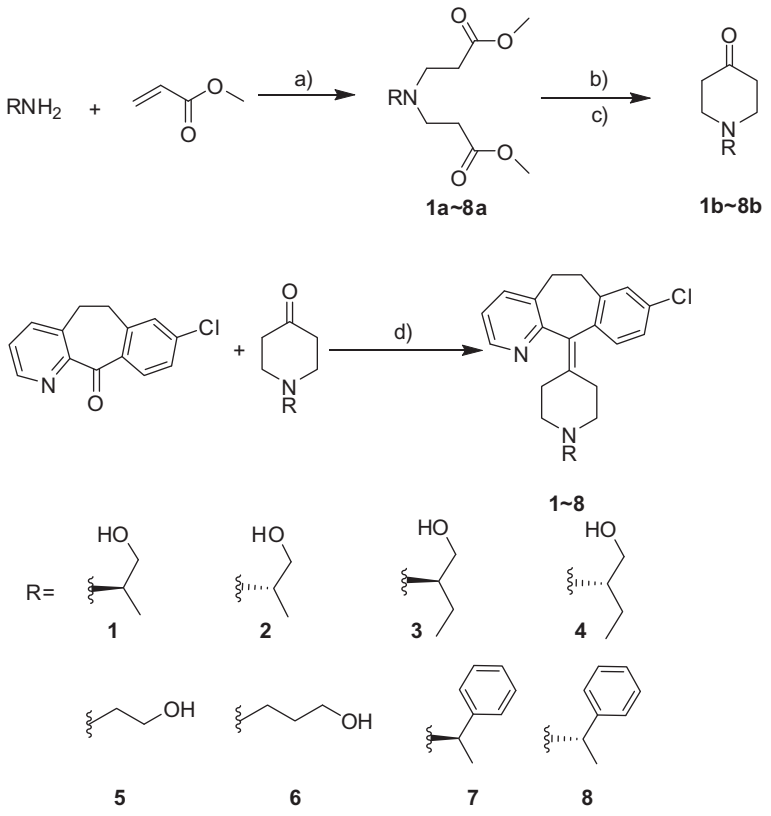

Scheme 1. Loratidine Analogues Synthesis. Reagents and conditions: (a) MeOH, 40 °C, 12 h; (b) MeONa/MeOH 30%aq, toluene, 110 °C, 5 h; (c) conc. HCl, 100 °C, 5 h; (d) $TiCl_4$/Zn, THF dry, 70 °C, 17 h; See Supplementary data for experimental details.

Table 1
The effects of eight synthesized compounds on the inhibition of histamine

Groups	Large dose groups [a]		Small dose groups [b]	
	The incubation period before drug (s)	The incubation period after drug (s)	The incubation period before drug (s)	The incubation period after drug (s)
Negative control group	98.70 ± 46.88	99.30 ± 30.06	97.00 ± 43.29	95.50 ± 18.98
Chlorphenira-mine group	98.10 ± 17.05	214.70 ± 29.20**	94.20 ± 16.80	105.70 ± 17.27
1	101.50 ± 34.31	215.60 ± 7.40**	99.20 ± 31.48	111.10 ± 26.42
2	95.10 ± 16.02	209.70 ± 9.56**	93.50 ± 16.37	112.80 ± 40.76
3	95.50 ± 19.85	229.20 ± 24.39**	94.10 ± 16.30	125.30 ± 40.33*
4	92.00 ± 22.35	216.00 ± 12.49**	92.90 ± 19.28	123.10 ± 23.20**
5	95.90 ± 17.16	248.50 ± 22.27**	93.10 ± 15.93	133.30 ± 27.79**
6	94.50 ± 16.96	360.00 ± 0.00**	91.90 ± 15.79	360.00 ± 0.00**
7	93.80 ± 27.48	309.60 ± 31.01**	93.10 ± 23.27	210.60 ± 51.82**
8	103.40 ± 33.79	273.20 ± 37.62**	100.50 ± 32.49	170.20 ± 57.45**

Compared to the negative control group: $^{*}P < 0.05$, $^{**}P < 0.01$.

[a] The large dose chlopheniramine group (0.5 mg/kg) and the eight large dose compounds groups (0.5 mg/kg) were pretreated with intragastric administration in 4 mL/kg bw.

[b] The small dose chlopheniramine group (0.2 mg/kg) and eight little dose compounds groups (0.2 mg/kg) were pretreated with intragastric administration in 4 mL/kg bw. See Supplementary data for assay details.

Compounds **1–8** were tested for their asthma-relieving effects by using the asthmatic reaction caused by histamine in guinea-pigs. (Table 1) Chlorpheniramine was used as the positive control. The guinea pigs were pretreated with intragastric administration of the chlorpheniramine and eight synthesized compounds and then sprayed with a histamine phosphate solution to induce the guinea pigs model of experimental asthma. The asthmogenic latent periods were determined in order to determine the anti-histamine activity of tested compounds. The untreated groups served as the negative control groups (blank control groups).

As shown in Table 1, it is apparent that the asthmogenic latency periods of the guinea pigs were prolonged by the eight compounds and chlopheniramine in both dose groups. The advantage is also significant compared to the negative control group ($P < 0.01$). In the large dosage groups, compounds **1–6,** which all contain a hydroxyl group, all prolonged the asthmogenic latent periods in the guinea pigs, compound **6** had the strongest effect with a period of over 360s. This indicates that the introduction of a hydroxyl group into the molecule can significantly enhance the antihistamine potency. Moreover, different positions of the hydroxyl group

Table 2
The effects of the eight compounds on the inhibition of histamine induced smooth muscle spasms in guinea pigs

Groups	Antispasmodic percentage (%)	Groups	Antispasmodic percentage (%)
Negative control group	0.31 ± 6.83	**4**	53.52 ± 7.54**
Chlorpheniramine group	41.31 ± 3.65**	**5**	50.63 ± 13.99**
1	32.37 ± 5.67**	**6**	53.73 ± 9.86**
2	49.73 ± 7.77**	**7**	31.45 ± 8.56**
3	29.37 ± 1.50**	**8**	32.06 ± 5.59**

Compared to the control group: *$P < 0.05$, **$P < 0.01$. The concentration of Chlorpheniramine and the 8 compounds was 2×10^{-3} mg/mL. See Supplementary data for assay details.

in the molecule led to different results. The effects of a 3-carbon linker are more obvious than a 2-carbon linker. For example, compound **6** led to a longer asthmogenic latent period than **5**. The linear hydroxyl side chain containing compound **5** is more potent than compounds **1, 2, 3** and **4** which have a hydroxyl side chain with an alkyl substituent group. The *R* and *S* enantiomers of compounds **1** and **3** and compounds **2** and **4** contributed no evident diversity. However, the *R* enantiomer of compound **7** with a benzene ring instead of a hydroxyl group was more active than its *S* enantiomer**.** The same trends were in the small dosage group. Compound **6** with a straight hydroxyl containing was the most active among the eight synthesized compounds with a latent period of over 360s.

The next area of focus was to investigate the effects of the eight compounds on the inhibition of in vitro histamine induced muscle spasms using isolated ileum smooth muscle from guinea pigs. Chlorpheniramine was again used as the positive control. The contraction intensity of guinea pig ileum was treated as index in order to preliminarily judge the anti-histamine activity of target compounds in vitro. The effects of eight compounds on the inhibition of guinea pigs smooth muscle spasms induced by histamine are shown in Table 2.

As shown in Table 2, all eight synthesized compounds and the chlorpheniramine control significantly inhibited the contractions induced by histamine with in reductions of both the contraction amplitude and a decrease in muscle tension. Among these, compounds **5** and **6** and the *S*-isomer of **2** and **4** had more significant inhibition than chlorpheniramine. The effects of the *S*-isomer of **2** and **4** were greater than the *R*-isomer. However, for compounds **7** and **8** that do not have a hydroxyl group, there was no significant difference between the isomers.

In conclusion, a series of hydroxyl group containing chiral loratadine analogues were synthesized. Most of them exhibited good H_1 antihistamine activity. The *S*-isomers of the chiral compounds are more potent than the *R*-isomers. Among the tested compounds, compound **6** would be the best compound for the development of new drugs as anti-allergy medications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.06.012.

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