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Design, synthesis and biological activity evaluation of desloratadine analogues as H_1 receptor antagonists

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ABSTRACT

A series of N-substituted desloratadine analogues were designed and synthesized. They were tested for H_1 antihistamine activity by inhibiting histamine-induced contraction of isolated ileum muscles of guinea-pigs in vitro and inhibiting histamine-induced asthmatic reaction in guinea-pigs in vivo. All the evaluated compounds exhibited significant antihistamine activity compared with desloratadine. Five active compounds induced no sedative effects on mouse and four of them exhibited lower anticholinergic side effects than desloratadine. Among these analogues, compound **10**, (1*S*,4*S*)-4-chlorocyclohexyl desloratadine displayed the highest activity and best safety profile. And it was believed to be a potential candidate as the 3rd generation antihistamine.

1. Introduction

Histamine is one of the most important chemical mediators. And through its interactions with H_1 receptors existing in tissues, histamine is involved in many allergic disorders, such as allergic rhinitis, asthma and urticaria.[1–4] H_1 receptor antagonists, that is, antihistamines, are used as the first-line treatment for these allergic diseases.[5–7] The first-generation H_1 antihistamines are effective, but their applications are considerably limited due to the sedative and anticholinergic effects.[8,9] This led to the development of the second- and third-generation antihistamines.[10–14] And the third-generation are usually used to describe some new antihistamines that are selective isomers or active metabolites of older second-generation antihistamine.[15] These two generations were devoid of the side effects of the first generation and exhibit distinguished antihistamine activity. Among them, desloratdine (**a**) is one of the remarkable representatives. Desloratadine is the active metabolite of loratadine (**b**), while it is at least 10 times more potent than loratadine.[10,16] For its widely use in clinic, desloratadine demonstrates the advantages over other H_1 antihistamines in that it has high H_1 antihistamine activity, wide therapeutic range and low potential for drug interactions.[10,17,18] On the other hand, it was reported that low concentration of desloratadine showed similar affinity to histamine H_1 receptor and muscarinic (M) receptor, and it may inevitably cause dry mouth, dizziness, fatigue and other symptoms and may also induce sedation effect on patients with compromised blood–brain barrier.[19] Therefore, researchers are paying much attention to investigate novel histamine antagonists based on the structure of desloratadine.[12,20,21]

It was reported that the environment of the tertiary amine nitrogen atom in the antihistamine molecule is closely related with the antihistamine activity.[22,23] In our previous work, the structure–activity relationship study showed that the introduction of hydroxyalkyl group to the tertiary amine nitrogen atom in desloratadine could effectively enhance the H_1 antihistamine activity of the compounds and the oxygen atom in the molecules may play important part in the high activity.[24,25] *N*-(3-hydroxypropyl) desloratadine (**1**) was the most active compound in the tests. Then we considered if other heteroatom groups can play the similar effect on the antihistamine activity. In this paper, we summarized our work on a new series of desloratadine derivatives, in which *N*-(3-hydroxypropyl) desloratadine (**1**) as lead compound, heteroatom and semi-rigid cyclohexyl groups were introduced to the molecules, respectively. Eleven desloratadine derivatives **1**–**11** (Fig. 1) were designed, synthesized and evaluated for their antihistamine activities. The results showed that all of them exhibited significant antihistamine activity compared with desloratadine. Then five active compounds **1**–**4** and **10** were evaluated for the sedation effect and anticholinergic side effect. It turned out that most of them

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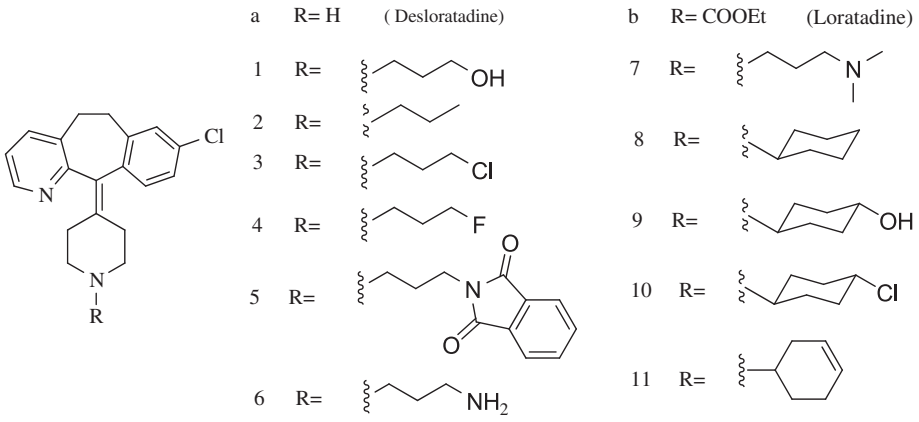
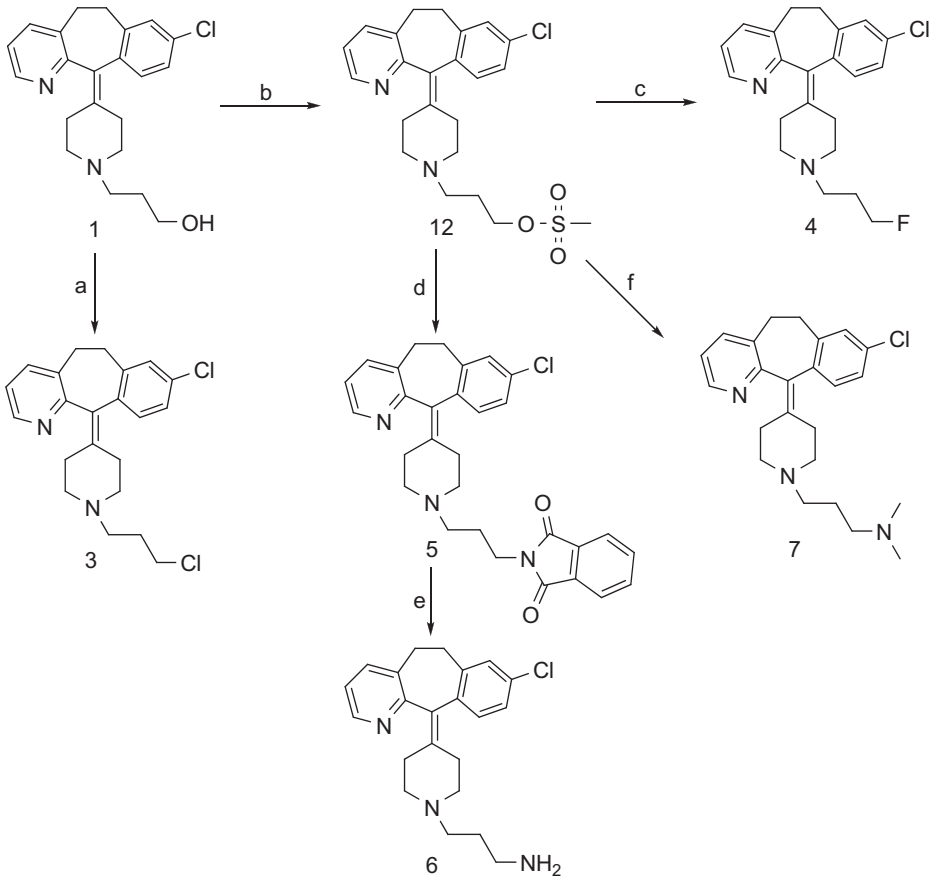


Figure 1. Structures of desloratadine, loratadine and 11 designed compounds.

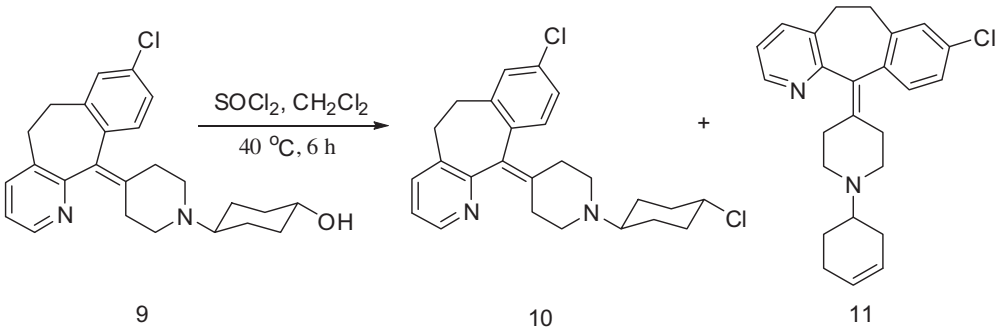
exhibited almost no sedative side effects and much lower anticholinergic effects than desloratadine.

2. Chemistry

In this paper, compounds **1**, **2**, **8** and **9** were synthesized according to the procedure described in our previous work.[24,25] With compounds **1** and **9** in hand, substitution of the hydroxyl group with suitable reagents yields the designed target compounds (Scheme 1 and Scheme 2). Compound **3** was synthesized by the chlorination of compound **1** with $SOCl_2$ in good yield.[26,27] Because alcohol **1** is quite stable, it should be converted to compound **12** by esterification of methyl sulfonylchloride in the presence of triethylamine and then it can be easily substituted by other groups.[28] By this method, the fluoride **4** was obtained by fluorination of compound **c** with tetrabutylammoniumfluoride in acetonitrile.[29–31] The Gabriel reaction of compound **12** led to compounds **5** and **6** sequentially.[32–34] Compound **7** was obtained by the treatment of compound **12** with dimethylamine in methanol. On the other hand, with the same synthetic method of compound **3**, the chlorination



Scheme 1. Synthesis of desloratadine derivatives **3**–**7**. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, 40 °C, 6 h; (b) MsCl, Et_3N, CH_2Cl_2, 50 °C, 0.5 h; (c) TBAF, CH_3CN, 3 h; (d) phthalimide potassium, DMF, 4 h; (e) $H_2NNH_2{\cdot}H_2O$, CH_3OH, 80 °C, 7 h; (f) $HN(CH_3)_2{\cdot}H_2O$, CH_3OH, 6 h.



Scheme 2. Synthesis of compounds **10** and **11**.

of compound **9** with the hydroxyl group on six member ring afforded the desired compound **10**, accompanied with certain amounts of elimination product **11** (Scheme 2).[26,27,35]

3. Results and discussion

Alcohol **1**, as the lead compound, was reported previously in our work, which exhibited more potent antihistamine activity than loratadine.[24,25] In order to explore the effect of hydroxyl group in the molecule, we designed and synthesized compounds **2**–**4** and **6** based on biological isostere principle. The amino derivatives **5** and **7** were also synthesized. Meanwhile, replacement of carbon chain in compound **1** by the cyclohexyl group resulted in compound **8**. For comparison, derivatives **9**, **10** and **11** were synthesized as well. In order to determine the structure-activity relationships, the eleven synthesized compounds and desloratadine were evaluated for the effects on isolated ileum smooth muscle tension in guinea pigs in vitro and asthma-relieving effects on the histamine-induced asthmatic reaction in guinea pigs in vivo. Besides, five of them and desloratadine were evaluated for the sedation and anticholinergic activity.

Firstly, the eleven synthesized compounds (**1**–**11**) were chosen to be assessed for their ability to inhibit histamine-induced contraction of guinea pigs ileum.[24,25] This test is a reliable measure of H_1-antagonist activity. Desloratadine was used as the standard in this test. Smooth muscle tensions at three different times were recorded and the antispasmodic percentages were figured out to preliminarily judge the antihistamine activity of these compounds in vitro. All the results were listed in Table 1. And in order to show the trends visually, the results were described in Figure 2.

As shown in Figure 2, after the synthesized compounds addition, the average muscle tensions reduced sharply in 5 min in these groups (P <0.05). And it can be seen that all the tested compounds can antagonize the spasm induced by histamine. Compared with the negative control group, it is easy to see the great advantages of compounds **1**, **2**, **3**, **4**, **10** and desloratadine group (P <0.05). Among these compounds, compound **10** exhibited the most potent antihistamine activity and much better than desloratadine (the antispasmodic percentage: 61.13% vs 49.12%).

Meanwhile, alcohol **1** was found to show great antihistamine activity and this was consistent with the results in our previous work. It is interesting to notice that another alcohol **9** with the hydroxyl group linked to the six-member ring showed the least antihistamine activity in the series. Besides, simple substitution pattern without heteroatom was also investigated. Compound **2** showed good activity while compound **8** was not so active. Additionally, other heteroatom groups were investigated. The results revealed that halogen containing compounds **3**, **4** and **10**, with distinct decrease of muscle tension, were proved to be promising H_1-antagonists. They were much more active than the other compounds in the test (except compound **1**). With the comparisons of compounds **1** and **9**, compounds **2** and **8**, compounds **3** and **10**, it can be seen that the linker group played complicated role in the interaction with histamine receptor. Moreover, the effects of different nitrogen containing groups were considered. Compounds **5**, **6** and **7** exhibited certain antagonistic activity, but they were not as active as their counterparts.

For the uncertainty relationship between the bioactivity in vitro and in vivo, these compounds were also investigated for the asthma-relieving effects on the histamine-induced asthmatic guinea-

Table 1
The effects of compounds on the inhibition of histamine-induced smooth muscle spasms[a] ($\bar{x} \pm s$, $n = 8$)

Test groups	Smooth muscle tension (g)			Antispasmodic percentage (%)
	Before drug	After histamine	After drug	
Negative control group	1.86 ± 0.08	3.39 ± 0.87	3.37 ± 1.05[c]	1.27 ± 5.65[c]
Desloratadine	1.85 ± 0.18	3.32 ± 0.51	1.67 ± 0.30[b,d]	49.12 ± 9.55[b]
Compound **1**	1.80 ± 0.11	3.77 ± 1.50	1.73 ± 0.39[b,d]	45.17 ± 28.58[b]
Compound **2**	1.84 ± 0.19	3.27 ± 0.89	1.80 ± 0.31[b,d]	42.51 ± 14.82[b]
Compound **3**	1.86 ± 0.09	3.33 ± 0.71	1.81 ± 0.40[b,d]	43.04 ± 18.14[b]
Compound **4**	1.83 ± 0.17	3.51 ± 0.49	1.74 ± 0.50[b,d]	48.73 ± 19.89[b]
Compound **5**	1.79 ± 0.16	3.69 ± 1.85	2.71 ± 1.45	26.56 ± 11.34[b]
Compound **6**	1.87 ± 0.21	3.25 ± 1.31	2.36 ± 0.89	25.96 ± 10.93[b]
Compound **7**	1.81 ± 0.14	3.95 ± 1.23	2.66 ± 0.65	30.36 ± 12.41[b]
Compound **8**	1.87 ± 0.11	3.75 ± 1.43	2.57 ± 0.90	29.39 ± 12.88[b]
Compound **9**	1.86 ± 0.11	3.35 ± 1.17	2.93 ± 1.13	13.03 ± 8.56[b]
Compound **10**	1.80 ± 0.09	3.66 ± 1.22	1.29 ± 0.15[b,c,d]	61.13 ± 13.52[b,c]
Compound **11**	1.88 ± 0.12	3.44 ± 0.94	2.38 ± 1.30[b,d]	28.31 ± 16.22[b]

[a] The concentration of desloratadine and the 11 compounds was 0.2 mg/mL.
[b] Compared to the negative control group: $P < 0.05$.
[c] Compared to the desloratadine group: $P < 0.05$.
[d] Compared to the effects before drug: $P < 0.05$.

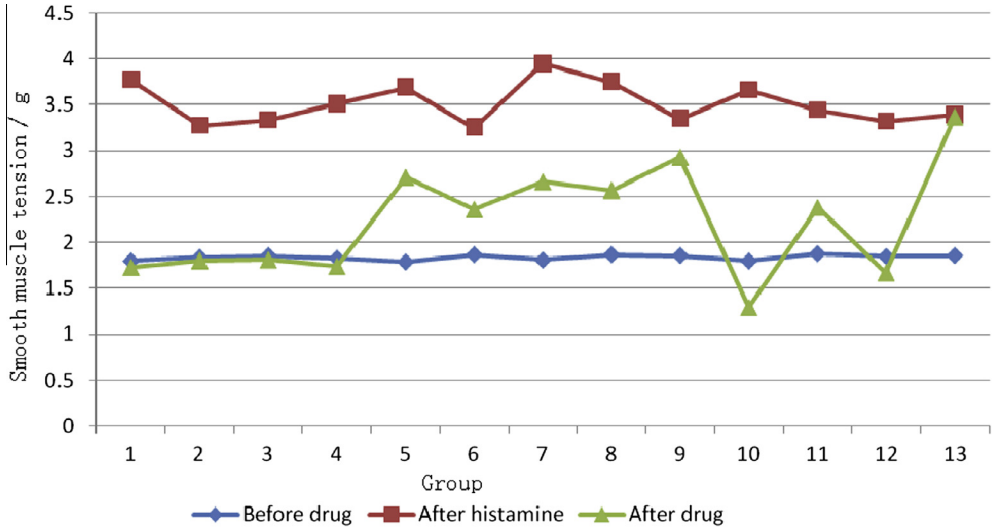


Figure 2. The effects of compounds on the inhibition of histamine-induced smooth muscle spasms. Groups 12 and 13 in this figure represent desloratadine and the negative control group, respectively.

pigs in vivo.[24,25] Desloratadine was also chosen as the standard. The guinea-pigs were pretreated with intragastric administration of desloratdine or the eleven synthesized compounds, and then they were sprayed with histamine hydrochloric solution to induce experimental asthma model of the guinea-pigs. The asthmogenic latent periods were determined in order to determine the antihistamine activity of the target compounds. The obtained results were summarized in Table 2.

As shown in Table 2, all tested compounds and desloratadine group can significantly prolong the asthmogenic latent periods of histamine-induced asthmatic guinea-pigs with the prolongation over 100 s. More importantly, most of the tested compounds exhibited similar or more potent activity than desloratadine, even though their dosages were only 1% of desloratadine group in the test (0.01 mg/kg vs 1.00 mg/kg). Besides, the results showed that compounds **3**, **4**, **10** and **11** exhibited excellent antihistamine activity, while alcohol **1** and amino derivative **6** were not so active compared with them. It can be seen that the antihistamine activity was improved by substituent groups with varying lipophilic characteristic. In the series of amino derivatives **5**, **6** and **7**, the most hydrophilic compound **6** showed the least antihistamine activity. Even so, compound **6** was still more active than desloratadine. Additionally, the introduction of halogen atom to the molecule contributed to enhancing the in vivo activity effectively. The antihistamine activities of compounds **3**, **4** and **10** were found to be much better than that of the other analogues. Noticeably, compound **10** was the most active one in this test. And this accorded with the results in vitro.

Table 2
The effects of synthesized compounds on the inhibition of histamine [a] ($\bar{x} \pm s$, $n = 10$)

Test groups	The incubation period before drug (s)	The incubation period after drug (s)
Negative control group	99.10 ± 46.69	127.10 ± 40.46[c]
Desloratadine group	117.50 ± 44.29	278.20 ± 56.93[b,d]
Compound **1**	102.30 ± 41.56	221.90 ± 89.30[b,d]
Compound **2**	119.30 ± 44.65	255.10 ± 44.40[b,d]
Compound **3**	108.30 ± 46.25	256.90 ± 74.34[b,d]
Compound **4**	89.90 ± 26.86	269.40 ± 49.29[b,d]
Compound **5**	97.00 ± 34.56	247.90 ± 113.43[b,d]
Compound **6**	97.70 ± 37.58	182.80 ± 74.48[b,d]
Compound **7**	93.90 ± 50.19	212.80 ± 67.11[b,d]
Compound **8**	108.20 ± 42.91	250.30 ± 83.75[b,d]
Compound **9**	92.80 ± 41.84	222.00 ± 100.15[b,d]
Compound **10**	98.00 ± 47.00	325.20 ± 41.16[b,d]
Compound **11**	98.20 ± 48.18	262.70 ± 79.56[b,c,d]

[a] The desloratadine group (1.00 mg/kg) and eleven compounds groups (0.01 mg/kg) were pretreated with intragastric administration in 2 mL/kg bw.
[b] Compared to the negative control group: $P < 0.05$.
[c] Compared to the desloratadine group: $P < 0.05$.
[d] Compared to the effects before drug: $P < 0.05$.

According to the antihistaminic activity results, it can be seen that there is some consistency between the in vitro results and in vivo results. In the in vitro test, compounds **1**–**4** and **10** can significantly antagonize the spasm induced by histamine, thus they exhibited better antihistamine activity than their counterparts. And in the in vivo test, it is obvious that compounds **1**–**4** and **10** can prolong the asthmogenic latent periods of histamine-induced asthmatic guinea-pigs and showed excellent activity. On the other hand, there are some discrepancy between the in vitro results and in vivo results. It is because that the organism environment is complex, sometimes inferior in vitro results can also lead to positive effects in organism. As seen the results in Table 1 and Table 2, apart from compounds **1**–**4** and **10**, compounds **5**, **8**, **9** and **11** also exhibited good in vivo antihistamine activity, though the in vitro results of them were not much outstanding. Although the mechanism was unknown, it can be seen that it is of great necessity to analysis both in vitro results and in vivo results.

The next area of exploration in this paper was the side effects of the selected active compounds **1–4** and **10**. These antihistaminic compounds were chosen to be tested for the sedative effects. Firstly, the effects of five compounds on the ordinary behaviors of mouse were determined. After the administration of saline, desloratadine, or the synthesized compounds, each animal in the test groups acted normal in the following seven days. All mice in the test showed no sleep abnormalities and did not have other abnormal performances, such as excitement, irritability, convulsion, salivation, muscle tremors. The mental state and body activity of the mice in the synthesized-compound groups were similar with those in the saline control group and desloratadine group. This indicated that the five tested compounds almost caused no side effect on the ordinary behavior and cannot induce sedation action of mouse when it was administrated alone. Previous studies showed that

Table 3
Five compounds on the hypnotic effects of pentobarbital sodium [a] ($\bar{x} \pm s$, $n = 10$)

Groups	Dosage (mg/kg)	Loss of righting reflex latency (min)	Recovery of righting reflex (min)
Pentobarbital sodium alone	100	1.94 ± 0.25	90 ± 12
Pentobarbital sodium and desloratadine	100 + 1	2.23 ± 0.44	93 ± 14
Pentobarbital sodium and low doses of compound **1**	100 + 50	1.54 ± 0.11$^{**▲▲}$	76 ± 2$^{**▲▲}$
Pentobarbital sodium and high doses of compound **1**	100 + 200	1.46 ± 0.19$^{**▲▲}$	100 ± 7*
Pentobarbital sodium and low doses of compound **2**	100 + 50	1.47 ± 0.25$^{**▲▲}$	76 ± 2$^{**▲▲}$
Pentobarbital sodium and high doses of compound **2**	100 + 200	1.61 ± 0.32$^{*▲▲}$	99 ± 8
Pentobarbital sodium and low doses of compound **3**	100 + 50	1.48 ± 0.26$^{**▲▲}$	97 ± 16
Pentobarbital sodium and high doses of compound **3**	100 + 200	1.58 ± 0.24$^{**▲▲}$	120 ± 13$^{**▲▲}$
Pentobarbital sodium and low doses of compound **4**	100 + 50	1.47 ± 0.27$^{**▲▲}$	98 ± 20
Pentobarbital sodium and high doses of compound **4**	100 + 200	1.45 ± 0.27$^{**▲▲}$	123 ± 13$^{**▲▲}$
Pentobarbital sodium and low doses of compound **10**	100 + 50	1.61 ± 0.18$^{**▲▲}$	82 ± 5$^{▲}$
Pentobarbital sodium and high doses of compound **10**	100 + 200	1.62 ± 0.19$^{**▲▲}$	103 ± 4$^{**▲}$

[a] Compared to the group use pentobarbital sodium alone: $^{*}P$ <0.05, $^{**}P$ <0.01; Compared to the group use pentobarbital sodium and desloratadine: $^{▲}P$ <0.05, $^{▲▲}P$ <0.01.

the sedative effect of H_1 antagonist is exhibited due to their blood brain barrier penetration for which lipophilicity of compounds plays an important role in the hydrophobic interactions at the receptor site. While in our test hydrophilic compounds **1** and **10** exhibited no significant difference compared with other lipophilic compounds. This may showed the great importance of desloratadine structure.

Then we tested the effects of the five active compounds (**1–4** and **10**) on the hypnotic effect caused by pentobarbital sodium, which can preliminarily judge the interaction between the synthesized compounds and pentobarbital sodium. After the administration of the tested compounds, the mice were injected with pentobarbital sodium. The loss of righting reflex latency and the recovering period were recorded. The results were described in Table 3. As seen in Table 3, desloratadine had basically no effect on the hypnotic effect caused by pentobarbital sodium because the loss of righting reflex latency and its recovering period in this group showed no significant differences compared with the pentobarbital sodium group. While compared with these two groups, the loss of righting reflex latency was shortened by the synthesized five compounds both in high dose and low dose groups (P <0.05). It meant that the synergistic effect was observed when these five compounds were separately administrated with pentobarbital sodium. On the other hand, compounds **1**, **2** and **10** in the low dose group gave rise to the significant short periods of the righting reflex recovery. Though the mechanism was unknown, it seemed that low dose of these three compounds can alleviate the hypnotic effects caused by pentobarbital sodium to some extent. And it should be noticed that even the low dose of the tested five compounds was much more than the dose of desloratadine, which meant that these compounds were not totally inferior to desloratadine on the hypnotic effects caused by pentobarbital sodium.

In addition, five active compounds **1**–**4** and **10** were evaluated for the inhibition of acetylcholine-induced smooth muscle tension in guinea pigs to judge the anticholinergic side effects of these compounds. Atropine was used as positive control group, desloratadine and the five compounds were tested and the test method was similar to the former one for antihistamine selectivity in vitro. The results were showed in Table 4. It can be seen that the addition of acetylcholine caused strong contraction of smooth muscles and sharp increase of the muscle tension. Atropine, a kind of anticholinergic drug, can relieve muscle spasm effectively. The results in Table 4 showed that even a few of atropine (0.1 μg/mL) can dramatically decrease the smooth muscle tension and its antispasmodic percentage was up to 74.90%. Besides, desloratadine and selected five compounds can significantly inhibit the acetylcholine-induced smooth muscle contraction and displayed varying antispasmodic percentages. It indicated that desloratadine and the

Table 4
The effects of compounds on the inhibition of acetylcholine-induced smooth muscle spasms[a] ($\bar{x}$± s, $n = 8$).

Groups	Final concentration (μg/mL)	Smooth muscle tension (g)			Antispasmodic percentage (%)
		Before drug	After acetycholine	After drug	
Negative control group		5.24 ± 0.31	5.24 ± 0.31	5.17 ± 0.36	1.31 ± 3.66
Acetylcholine	0.2	4.92 ± 0.88	14.53 ± 3.05	12.25 ± 4.00	17.64 ± 16.83
Atropine	0.1	4.78 ± 1.11	14.84 ± 5.78	3.47 ± 1.20**	74.90 ± 8.90$^{♦♦}$
Desloratadine	1.0	4.74 ± 0.78	19.46 ± 7.14	4.19 ± 2.38**	75.11 ± 15.99$^{♦♦}$
High doses of compound **1**	2.0	4.59 ± 0.75	18.81 ± 5.54	6.04 ± 3.24**	67.06 ± 18.34$^{♦♦}$
Middle doses of compound **1**	1.4	5.02 ± 0.98	19.66 ± 11.00	6.72 ± 1.56**	58.27 ± 16.95$^{♦♦●}$
Low doses of compound **1**	1.0	4.47 ± 1.29	14.72 ± 4.77	7.43 ± 1.99**	45.87 ± 19.31$^{♦♦●●▲▲}$
High doses of compound **2**	1.0	4.87 ± 0.73	16.13 ± 4.13	3.58 ± 1.35**	77.06 ± 9.40$^{♦♦}$
Middle doses of compound **2**	0.6	4.82 ± 0.89	17.01 ± 5.38	4.38 ± 2.53**	73.09 ± 15.85$^{♦♦}$
Low doses of compound **2**	0.2	5.54 ± 0.67	17.71 ± 3.77	7.51 ± 2.07**	56.14 ± 13.24$^{♦♦●●▲}$
High doses of compound **3**	1.4	5.09 ± 0.94	20.37 ± 9.85	5.68 ± 2.27**	69.51 ± 12.33$^{♦♦}$
Middle doses of compound **3**	1.0	4.56 ± 0.64	14.90 ± 5.11	6.94 ± 5.24**	56.45 ± 23.89$^{♦♦}$
Low doses of compound **3**	0.6	4.78 ± 1.14	18.67 ± 9.67	8.56 ± 3.18**	47.21 ± 26.13$^{♦●▲}$
High doses of compound **4**	1.0	4.54 ± 0.92	11.20 ± 2.32	4.13 ± 1.74**	61.41 ± 15.82$^{♦♦}$
Middle doses of compound **4**	0.6	4.57 ± 0.92	18.80 ± 7.09	6.58 ± 2.24**	62.47 ± 12.20$^{♦♦●▲}$
Low doses of compound **4**	0.2	4.68 ± 0.69	20.90 ± 6.17	9.11 ± 2.25**	54.35 ± 13.72$^{♦♦●●▲▲}$
High doses of compound **10**	2.0	4.79 ± 1.16	15.68 ± 6.58	4.40 ± 1.91**	70.61 ± 9.50$^{♦♦}$
Middle doses of compound **10**	1.4	5.63 ± 0.91	16.42 ± 1.72	5.59 ± 2.25**	61.39 ± 23.70$^{♦♦}$
Low doses of compound **10**	1.0	4.72 ± 1.11	12.78 ± 2.85	7.07 ± 2.89**	44.89 ± 19.63$^{♦♦●▲▲}$

[a] Compared to after acetycholine: $^{*}P$ <0.05, $^{**}P$ <0.01; compared to acetycholine group:$^{♦}P$ <0.05, $^{♦♦}P$ <0.01; compared to atropine group:$^{●}P$ <0.05, $^{●●}P$ <0.01; compared to desloratadine group: $^{▲}P$ <0.05, $^{▲▲}P$ <0.01.

five synthesized compounds antagonized cholinergic responses to varying degrees in these models. While it also can be seen that antispasmodic percentages of compounds **1**, **3**, **4** and **10** were much lower than that of desloratadine, and so were their anticholinergic side effects. Especially, both compounds **1** and **10** had showed much lower inhibitory effects on acetylcholine-induced smooth muscle contraction than their counterparts in the assay. Considering their good antihistaminic activity, they can be potential for the new antihistamines.

4. Conclusion

A series of desloratadine derivatives were designed and synthesized. All the compounds can effectively inhibit histamine-induced contraction of guinea pigs ileum and exhibit promising antihistaminic activity against histamine-induced asthmatic guinea-pigs. They showed similar activity even at 1% dosages of desloratadine group in vivo. The tested five compounds induced no sedative effects on mice. And when administrated together with pentobarbital sodium, they showed synergistic effects to some extent. Four of the five compounds exhibited lower anticholinergic side effects than desloratadine. Among these analogues, compound **10**, (1*S*,4*S*)-4-chlorocyclohexyl desloratadine, was the most active antagonist. It showed far more potent antihistaminic activity than desloratadine both in vitro and in vivo and much lower side effects than desloratadine. Therefore, it could serve as a drug candidate for further study.

5. Experimental sections

Almost chemicals were purchased from Guangfu Technology Development Co., Ltd, Tianjin (China). And all chemicals used in this study were of analytical grade or purified according to standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on INOVA 500 Hz spectrometer in $CDCl_3$ with TMS as an internal standard. The ^{19}F NMR spectrum was recorded on INOVA 400 Hz spectrometer in $CDCl_3$ with $CFCl_3$ as external standards. HR-MS was recorded on MicroOTOF-Q II.

The target compounds **1**, **2**, **8** and **9** were synthesized according to our previous papers.[24,25] Compound **1** was obtained from 3-amino-1-propanol. Similarly, compounds **2**, **8** and **9** were obtained from propylamine, cyclohexylamine and *t*-4-aminocyclohexanol, respectively.

Compound **2**: 45.7%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.40 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.14 (m, 3H), 7.08 (dd, J_1 = 4.5 Hz, J_2 = 7.5 Hz, 1H), 3.44–3.33 (m, 2H), 2.86–2.73 (m, 4H), 2.56–2.50 (m, 1H), 2.45 (t, J = 5.3 Hz, 1H), 2.43–2.37 (m, 2H), 2.33–2.26 (m, 2H), 2.13–2.05 (m, 2H), 1.54–1.46 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 157.90, 146.81, 139.72, 139.45, 138.07, 137.38, 133.58, 132.79, 132.60, 131.08, 129.14, 126.17, 122.23, 60.77, 55.17, 55.13, 32.05, 31.63, 31.24, 30.98,20.43, 12.26; HR-MS (ESI), calcd $C_{22}H_{25}ClN_2$: $[M+H]^+$ m/z: 353.1779, found: 353.1787.

Compound **8**: 32.0%; ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.40 (t, J = 2.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 4.0 Hz, 3H), 7.09–7.07 (m, 1H), 3.44–3.34 (m, 2H), 2.86–2.78 (m, 4H), 2.53–2.48 (m, 1H), 2.42–2.32 (m, 6H), 1.85 (s, 2H), 1.77 (s, 2H), 1.61 (d, J = 7.0 Hz, 1H), 1.26–1.20 (m, 4H), 1.10–1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 158.07, 146.85, 140.02, 139.72, 138.11, 137.34, 133.63, 132.76, 132.34, 131.21, 129.16, 126.17, 122.22, 63.85, 50.83, 50.72, 32.12, 31.78, 31.65, 31.53, 29.18, 29.06, 27.13, 26.59, 26.28. HR-MS (ESI), calcd $C_{25}H_{29}ClN_2$: $[M+H]^+$ m/z: 393.2092, found: 393.2096.

Compound **9**: 48.2%; ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.39 (s, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.17 (s, 1H),7.14–7.10 (m, 2H), 7.09–7.07 (m, 1H), 3.54 (m, 1H), 3.43–3.33 (m, 2H), 2.86–2.76 (m, 4H), 2.52–2.46 (m, 1H), 2.43–2.36 (m, 6H), 2.05–2.00 (m, 2H), 1.88–1.83 (m, 2H), 1.35–0.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 157.93, 146.83, 139.72, 139.63, 138.01, 137.44, 133.67, 132.83, 132.50, 131.16, 129.29, 126.21, 122.30, 70.72, 62.85, 51.09, 51.00, 34.98, 34.97, 32.09, 31.64, 31.38, 27.13, 26.66, 26.58. HR-MS (ESI), calcd $C_{25}H_{29}ClN_2O$: $[M+H]^+$ m/z: 409.2041, found: 409.2053.

5.1. Synthesis of compounds 3[26,27]

Thionyl chloride (38.4 mmol) was added to the solution of compound **1** (4.8 mmol) in 50 mL CH_2Cl_2 at 0–5 °C. Then the mixture was heated to reflux for 6 h. Dichloromethane and the excess thionyl chloride were removed under vacuum. The residue was dissolved by the solution of ethanol and water (ethanol/water = 2:1, V/V) 40 mL. And then the mixture was adjusted to pH = 10 with 10% wt. NaOH aqueous solution, followed by extraction with CH_2Cl_2. The organic phase was dried by anhydrous magnesium sulfate. After filtration and concentration, the residue was purified by silica gel column (petroleum ether/ethyl acetate/methanol = 3:1:0.2, V/V/V) to afford **3** in the yield of 63.8%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.40 (d, J = 5.0 Hz, 1H), 7.42 (d, J = 6.5 Hz, 1H), 7.12 (t, J = 9.8 Hz, 3H), 7.09 (t, J = 6.0 Hz, 1H), 3.58 (t, J = 6.8 Hz, 2H), 3.33–3.46 (m, 2H), 2.72–2.86 (m, 4H), 2.30–2.53 (m, 6H), 2.09–2.15 (m, 2H), 1.91–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 157.83, 146.84, 139.75, 139.09, 138.05, 137.47, 133.63, 132.87, 132.85, 131.06, 129.18, 126.22, 122.31, 55.54, 55.20, 55.14, 43.57, 32.05, 31.66, 31.96, 30.32. HR-MS (ESI), calcd $C_{22}H_{24}Cl_2N_2$: $[M+H-HCl]^+$ m/z: 351.1623, found: 351.1633.

5.2. Synthesis of compound 12[28]

Compound **1** (5.4 mmol) and 40 mL CH_2Cl_2 were added to a two-necked flask, followed by the addition of triethylamine (7.6 mmol). Then methylsulfonyl chloride (28.2 mmol) was added slowly to the stirring mixture with the temperature controlled at 0–5 °C. After that, the mixture was warmed to room temperature and kept stirring for 0.5 h. The mixture was washed by 10% wt. K_2CO_3 aqueous solution and brine successively. Then it was dried over anhydrous $MgSO_4$, followed by filtration and concentration. The residue was used for further reactions directly.

5.3. Synthesis of compound 4[29–31]

The mixture of compound **12** (4.7 mmol) and tetrabutylammoniumfluoride (7.1 mmol) was refluxed in 40 mL acetonitrile for 3 h. After acetonitrile was removed under vacuum, the residue was dissolved in 40 mL CH_2Cl_2 and washed by brine. The organic phase was dried by anhydrous magnisium sulfate, followed by filtration and concentration. The residue was purified by silica gel column (petroleum ether/ethyl acetate/methanol = 3:1:0.1, V/V/V) to give **4** in the total yield of 28.8%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.40 (t, J = 2.3 Hz, 1H), 7.42 (dd, J_1 = 1.5 Hz, J_2 = 6.0 Hz, 1H), 7.15 (s, 1H), 7.13 (d, J = 1.5 Hz, 2H), 7.07–7.11 (m, 1H), 4.55 (t, J = 6.3 Hz, 1H), 4.46 (t, J = 6.3 Hz, 1H), 3.35–3.45 (m, 2H), 2.73–2.87 (m, 4H), 2.49–2.55 (m, 2H), 2.33–2.47 (m, 4H), 2.11–2.13 (m, 2H), 1.84–1.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 157.83, 146.88, 139.76, 139.11, 138.05, 137.50, 133.64, 132.88, 132.87, 131.08, 129.19, 126.25, 122.33, 83.54, 82.23, 55.17, 55.13, 54.45, 54.40, 32.06, 31.67, 31.19, 30.94, 28.43, 28.27. ^{19}F NMR ($CDCl_3$), δ: -219.86. HR-MS (ESI), calcd $C_{22}H_{24}ClFN_2$: $[M+H]^+$ m/z: 371.1690, found: 371.1688.

5.4. Synthesis of compound 5[32–34]

The mixture of KOH (3.9 g) in 50 mL methanol was added to phthalimide (68.0 mmol) in 50 mL dry ethanol. After stirring for

3 h, the mixture was filtrated and the residue phthalimide potassium was dried to give the yield of 92.3%.

Phthalimide potassium (5.6 mmol) and tetrabutyl ammonium bromide (0.2 g) were added to compound **12** in 35 mL DMF. The mixture was stirred at 50 °C for 4 h. After cooled to room temperature, the reaction mixture was dropped to 300 mL water and adjusted to pH = 10 by 10% wt. NaOH aqueous solution, followed by extraction with ethyl acetate. The organic layer was combined and dried by anhydrous $MgSO_4$. After filtration and concentration, the residue was purified by silica gel column (petroleum ether/ethyl acetate/methanol = 3:1:0.3, V/V/V) to give **5** in the yield of 77.8%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.37 (dd, J_1 = 1.8 Hz, J_2 = 3.0 Hz, 1H), 7.82 (q, J = 3.0 Hz, 1H), 7.70 (q, J = 3.0 Hz, 1H), 7.41 (dd, J_1 = 1.7 Hz, J_2 = 6.5 Hz, 1H), 7.05–7.12 (m, 4H), 3.74 (t, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2H), 3.31–3.39 (m, 2H), 2.70–2.82 (m, 4H), 2.38 (t, J = 7.0 Hz, 2H), 2.33–2.36 (m, 1H), 2.22–2.27 (m, 3H), 1.99–2.06 (m, 2H), 1.84–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 168.66, 157.89, 146.83, 139.69, 139.34, 138.00, 137.40, 134.09, 133.61, 132.80, 132.61, 132.44, 131.08, 129.17, 126.19, 123.34, 122.28, 56.11, 55.14, 55.10, 36.87, 32.06, 31.61, 31.15, 30.91, 25.87. HR-MS (ESI), calcd $C_{30}H_{28}ClN_3O_2$: $[M+H]^+$ m/z: 498.1943, found: 498.1945.

5.5. Synthesis of compound 6[32–34]

80% Hydrazine hydrate solution (4.4 mmol) was added to the solution of compound **5** (2.2 mmol) in 30 mL ethanol. The reaction mixture was heated to reflux for 7 h. After filteration, the filtrate was concentrated and purified by silica gel column (ethyl acetate/methanol/ammonia water = 1:1:0.2, V/V/V) to afford **6** in the yield of 43.4%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.31 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.10–7.14 (m, 3H), 7.08 (dd, J_1 = 3.0 Hz, J_2 = 5.0 Hz, 1H), 5.30 (s, 2H), 3.33–3.43 (m, 2H), 2.79–2.86 (m, 2H), 2.76 (t, J = 6.5 Hz, 4H), 2.48–2.54 (m, 1H), 2.31–2.42 (m, 5H), 2.07–2.14 (m, 2H), 1.62–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 159.80, 146.79, 139.72, 139.13, 138.00, 137.46, 133.61, 132.81, 132.75, 131.04, 129.15, 126.18, 122.30, 56.59, 55.18, 55.13, 40.91, 31.60, 31.16, 30.93, 30.04, 19.36. HR-MS (ESI), calcd $C_{22}H_{26}ClN_3$: $[M+H]^+$ m/z: 368.1888, found: 368.1891.

5.6. Synthesis of compound 7

30% Dimethylamine aqueous solution (3.1 mmol) was added to the solution of compound **12** (4.7 mmol) in 40 mL methanol. The mixture was heated to reflux for 6 h. After methanol was removed under vacuum, the residue was dissolved by 40 mL CH_2Cl_2 and washed by saturated salt water. Then the organic phase was combined and dried by anhydrous $MgSO_4$, followed by filtration and concentration. The residue was purified by silica gel column (petroleum ether/ethyl acetate/methanol = 3:1:0.1, V/V/V) to afford **7** in the total yield of 67.0%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.39 (d, J = 5.0 Hz, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.17 (s, 1H), 7.08–7.14 (m, 3H), 3.32–3.47 (m, 2H), 2.94–2.99 (m, 4H), 2.80–2.87 (m, 2H), 2.78 (s, 3H), 2.70–2.73 (m, 6H), 2.60–2.68 (m, 1H), 2.45–2.64 (m, 4H), 2.08–2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 156.82, 146.82, 139.85, 137.89, 137.58, 135.96, 134.53, 133.69, 133.24, 130.57, 129.24, 126.38, 122.64, 56.43, 54.80, 54.49, 43.78, 39.57, 31.83, 31.68, 29.81, 29.56, 21.80. HR-MS (ESI), calcd $C_{24}H_{30}ClN_3$: $[M+H]^+$ m/z: 396.2201, found: 396.2202.

5.7. Compound 10 and 11 were obtained by the same synthetic method of compound 3

Compound **10**: yield 40.7%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.39 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.12 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 3H), 7.08–7.06 (m, 1H), 4.38 (s, 1H), 3.44–3.33 (m, 2H), 2.85–2.76 (m, 4H), 2.53–2.48 (m, 1H), 2.45–2.31 (m, 6H), 2.07–2.04 (m, 2H), 1.87–1.72 (m, 4H), 1.66–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 157.92, 146.85, 139.74, 139.56, 138.04, 137.43, 133.65, 132.84, 132.63, 131.14, 129.18, 126.21, 122.29, 62.68, 59.35, 50.75, 50.65, 33.74, 33.72, 32.09, 31.66, 31.58, 31.32, 22.92, 22.61. HR-MS (ESI), calcd $C_{25}H_{28}C_{l2}N_2$: $[M+H]^+$ m/z: 427.1702, found: 427.1710.

Compound **11**: yield 53.1%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 8.39 (d, J = 3.5 Hz, 1H), 7.42 (d, J = 6.5 Hz, 1H), 7.15–7.10 (m, 3H), 7.08–7.06 (m, 1H), 5.64–5.59 (m, 2H), 3.44–3.33 (m, 2H), 2.86–2.76 (m, 4H), 2.64–2.60 (m, 1H), 2.55–2.49 (m, 1H), 2.45–2.32 (m, 5H), 2.16–2.01 (m, 4H), 1.92–1.90 (m, 1H), 1.48–1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 158.01, 146.88, 139.80, 139.73, 138.07, 137.40, 133.65, 132.82, 132.52, 131.20, 129.19, 127.09, 126.22, 126.05, 122.27, 60.21, 51.03, 50.58, 32.12, 31.68, 31.43, 27.61, 27.14, 26.36, 26.10. HR-MS (ESI), calcd $C_{25}H_{27}ClN_2$: $[M+H]^+$ m/z: 391.1936, found: 391.1944.

6. Biological methods

6.1. Antihistamine active assay

The effects on isolated ileum smooth muscle tension in guinea pigs in vitro and asthma-relieving effects on the histamine induced asthmatic reaction in guinea-pigs in vivo were examined according to our previous work.[24,25]

(1) Effects on isolated ileum smooth muscle tension in guinea pigs in vitro.

After the guinea-pigs were knocked out, the abdomens were opened and 15 cm of the ileum sections were cut out. The pieces were placed in a Petri dish containing Tyrode's solution at 37 °C and continuously bubbled with oxygen. For the contraction experiments, the intestines were sliced (1 cm length) and put into Tyrode's solution that was continuously bubbled with oxygen at 37 °C. One end of the intestine was fixed to a ventilation hook and the other end was fixed to a tension transducer which was connected to a computer interface. The smooth muscle tension data was recorded by a BL system.

The experiments were conducted containing the negative control group, desloratadine group and synthesized eleven compounds groups (Table 1).The smooth muscle tension values were recorded after the ileum peristalsis curve tended to stabilized. Then histamine (0.05 mL) was added and the average tension values in each group were recorded. When the maximum contraction was achieved, the eleven synthesized compounds or the blank DMSO (the negative control group) were added. After 3 min, the average tension values were recorded. The parallel operation was repeated for 8 times. The antispasmodic percentage was evaluated using the following formula.

Formula:

$$\text{Antispasmodic percentage} = \frac{\text{Tension after histamine} - \text{Tension after drug}}{\text{Tension after histamine}} \times 100$$

(2) Asthma-relieving effects on the histamine induced asthmatic reaction in guinea pigs in vivo.

The guinea pigs were placed in a plexiglass jar. After the histamine hydrochloride solution (0.8 mg/mL) was sprayed by the ultrasonic nebulizer on the guinea pigs, the convulsions and falls time was recorded as the asthmogenic latent periods of the guinea pigs. Guinea pigs whose latent periods exceeded 180 s were eliminated from the trial. The selected 130 guinea pigs were randomly divided into 13 groups, 10 each group: the negative control group, the desloratadine group (1 mg/kg) and the eleven compounds groups (0.01 mg/kg). Sixty min after intragastric administration

at 2 mL/kg bw, the guinea pigs were put into the glass bell jar and sprayed with the histamine hydrochloride as pretreated. The asthma latent period was then recorded. If there was no asthma phenomenon for over 6 min, the latency was recorded as 6 min.

6.2. Sedative effects assay

(1) The effects of five compounds on mouse ordinary behavior.

The selected 130 guinea pigs were randomly divided into 13 groups, 10 in each group: the negative control group (saline 10 mL/kg), the desloratadine group (1 mg/kg), the pentobarbital sodium group (10 mg/kg), the selected five active compounds **1**, **2**, **3**, **4** and **10** low dose groups (0.05 mg/kg) and their high dose groups (0.2 mg/kg). The dosing capacity of each group was equally 10 mL/kg. After administration, the ordinary behavior concluding mental state and body activities were observed and other abnormal activities were checked.

(2) The effects of five compounds on the mouse hypnotic effect caused by pentobarbital sodium.

The selected 130 guinea pigs were randomly divided into 13 groups, 10 in each group: the negative control group (saline), the pentobarbital sodium group, the pentobarbital sodium and desloratadine group (1 mg/kg), the pentobarbital sodium and low dose of five compounds groups (0.05 mg/kg), the pentobarbital sodium and high dose of five compounds groups (0.2 mg/kg). After administration for 30 min, 1% pentobarbital sodium was injected intraperitoneally (100 mg/kg, dosing capacity: 10 mL/kg). The righting reflex latency period and the recovery period were recorded.

6.3. Anticholinergic activity assay

After the guinea-pigs were knocked out, the abdomens were opened and 15 cm of the ileum sections were cut out. The pieces were placed in a Petri dish containing Tyrode's solution at 37 °C and continuously bubbled with oxygen. For the contraction experiments, the intestines were sliced (1 cm length) and put into Tyrode's solution that was continuously bubbled with oxygen at 37 °C. One end of the intestine was fixed to a ventilation hook and the other end was fixed to a tension transducer which was connected to a computer interface. The smooth muscle tension data was recorded by a MPA2000 system.

The experiments were conducted containing the negative control group, acetylcholine group, atropine group, desloratadine group, and selected five compounds groups in three concentrations (the final concentration of each group was given in Table 4).The smooth muscle tension values were recorded after the ileum peristalsis curve tended to stabilized. Then acetycholine (0.2 μg/mL) was added and the average tension values in each group were recorded. When the maximum contraction was achieved, the five synthesized compounds or the blank water (the negative control group) were added. After 3 min, the average tension values were recorded. The parallel operation was repeated for 8 times. The antispasmodic percentage was evaluated using the following formula.

Formula:

$$\text{Antispasmodic percentage} = \frac{\text{Tension after acetylcholine} - \text{Tension after drug}}{\text{Tension after acetylcholine}} \times 100$$

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.05.004.

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