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Stereoselective synthesis of desloratadine derivatives as antagonist of histamine

Gai-Zhi Liu [a,b], Hai-Wei Xu [a,b,c], Guang-Wei Chen [a], Peng Wang [a], Ya-Na Wang [a], Hong-Min Liu [a,b,*], De-Quan Yu [a,d]

[a] School of Pharmaceutical Science, Zhengzhou University, Ke Xue Da Dao 100, Zhengzhou 450001, PR China
[b] New Drug Research & Development Center, Zhengzhou University, Zhengzhou 450001, PR China
[c] Furen Science and Technology Pharmaceutical Weiwu Road, Zhengzhou City 450003, PR China
[d] Institute of Materia Medica Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing City 100050, PR China

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ABSTRACT

A series of desloratadine derivatives were stereoselectively synthesized and evaluated for H_1 antihistamine activity. For the evaluation of H_1 antihistamine activity, the in vitro histamine-induced contraction of the guinea-pig ileum assay (HC) was used. The synthesized desloratadine derivatives **7**, **8** and **9** are structurally related to rupatadine and were generated by replacement of the 5-methyl-3-pyridine group of rupatadine with γ-alkylidene butenolide. Their H_1 antihistamine activities have shown a high dependence on the exact nature of the substituent in the lactone ring. Optimum structures **7**, **8a** and **8g** display potent activity inhibiting histamine-induced effects.

1. Introduction

Allergic rhinitis (AR) is a global health concern of increasing prevalence that can impact the quality of life and work of affected individuals. Antihistamines are recommended as the first-line treatment for AR.[1–3] They can be classified into three groups. First-generation antihistamines such as promethazine and ketotifen have a considerably limited use because of their sedative and anticholinergic effects. Second-generation antihistamines such as cetirizine, loratadine (1) and mizolastine have significantly fewer undesirable CNS (central nervous system) and anticholinergic effects than first-generation. New Generation antihistamines include fexofenadine, levocetirizine, desloratadine (2) and rupatadine (3) (Fig. 1). While many of these agents were largely devoid of CNS side effects, their tendency for drug–drug interactions (e.g., terfenadine and astemizole) resulted in an increased incidence of cardiotoxicity. Furthermore, the second-generation H_1 antagonists exhibited weak anti-inflammatory properties and had no effect on nasal congestion. These observations emphasized the need for newer anti-allergic agents with a broader spectrum of activity and an improved safety profile.[4]

Among the H_1 antagonists in clin. development, the third-generation H_1 antagonist (New Generation antihistamines) desloratadine (**2**)[5,6] is one of the most widely studied. Loratadine (**1**) undergoes extensive first-pass metabolism[7] to yield the active metabolite desloratadine (**2**) (Fig. 2). It has a rapid onset of action, and desloratadine (**2**) has demonstrated clin. efficacy in AR, chronic idiopathic urticaria (CIU), and seasonal asthma.[8] It has several advantages over other H_1 antagonists in that it has proven decongestant activity, a sparing effect on the use of bronchodilators (β2-agonists) and a low potential for drug interactions. The broad anti-inflammatory properties of desloratadine (**2**), which distinguish this agent from other H_1 antagonists in clin. development, suggest that they may have a more profound impact on the underlying disease in patients suffering from different forms of allergy.

Elena Carceller and co-workers[9,10] have reported the synthesis and platelet-activating factor (PAF) antagonist and H_1 antihistamine activity evaluation of two series of benzocycloheptapyridines, that is to say, the desloratadine (**2**) derivatives, replacement of the ethoxycarbonyl group of loratadine (**1**): nicotinoyl derivatives **Ia** and 3-pyridylalkyl derivatives **Ib** (Fig. 1). Exploration of the effect of different pyridine substituents in the two mentioned series led to the

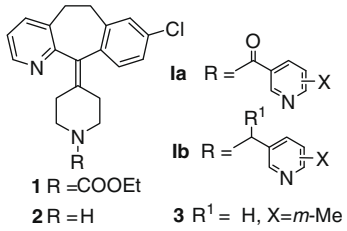

Figure 1.

* Corresponding author. Tel./fax: 86 371 67781739.
E-mail address: liuhm@zzu.edu.cn (H.-M. Liu).

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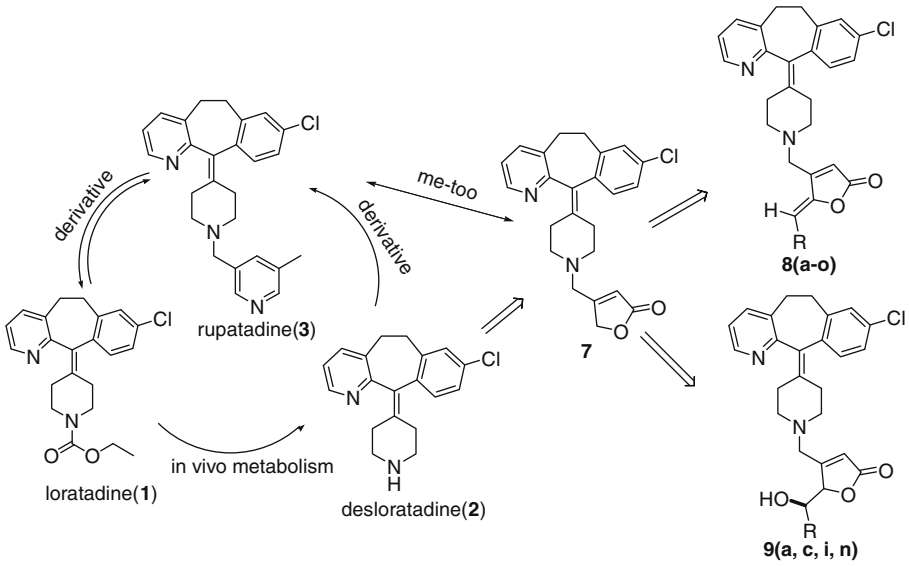


Figure 2.

discovery of rupatadine[11–17] (**3**), a new generation H_1 antihistamine, which is a potent dual antagonist of antihistamine and PAF. Developed by Uriach, it is indicated for the management of AR and CIU in Europe, though China has not yet imported it. Literature has prolifically[18–30] reported its synthesis, but its analogues except for **Ia** and **Ib** are not reported.

Based on our previous work on the synthesis and bioactivity of γ-alkylidene butenolides,[31–34] and for the importance of the five-membered lactones ring in the bioactive natural products, the present paper deals with the design (Fig. 2), synthesis and H_1 antihistamine activity evaluation of rupatadine (**3**) analogue **7** and series of novel desloratadine (**2**) derivatives **8** and **9** (Scheme 1 and Table 1), replacement of the 5-methyl-3-pyridine of the rupatadine (**3**) by α,β-unsaturated-γ-alkylidene butenolide, which was never reported. Exploration of the effect of different substituents in the lactone ring of mentioned **7** led to the discovery of **8a** and **8g** together with the compound **7**, three potential lead compounds for anti-allergy drugs.

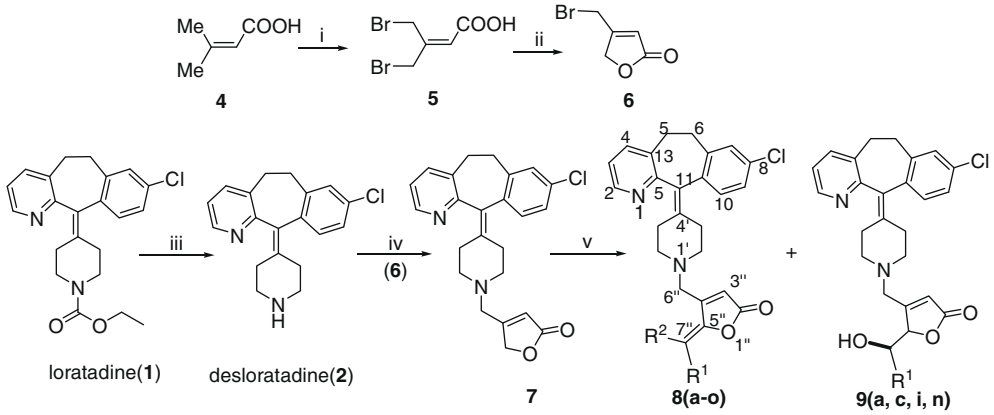
2. Results and discussion

2.1. Chemistry

Firstly, a key intermediate **6**[35,36] was synthesized (Scheme 1) by an intramolecular substitution reaction from the trivial starting material **4** in 70% yield. Compound **5** was obtained by the bromine substitution reaction of compound **4** with NBS in good yield.

The target compounds **8** and **9** were prepared in three steps from loratadine (**1**). Loratadine (**1**) hydrolyzed with alkali potassium hydroxide in 80% ethanol to give desloratadine (**2**) in 85% yield, which was refined by recrystallization in ethyl acetate. Then desloratadine (**2**) reacted with **6** by nucleophilic substitution reaction in mild condition to give the key intermediate **7** in a moderate yield (65%). The base-sensitive nature of the alkylidene butenolide **6** was circumvented by using weak organic bases such as TEA or diaminoethane as catalysts. The solvent carbon tetrachloride proved to be effective in promoting the reaction. The structure of **7** was elucidated by the analysis of IR, NMR, and HR-MS spectra. Compound **7** retained the basic skeleton of desloratadine (**2**) by replacing the 3-methyl-pyridine of rupatadine (**3**) with γ-butenolide. The presence of signals at δ_H 6.00 (δ_C 117.0), δ_H 4.87 (δ_C 72.9) and δ_C 173.7 (C=O) in the ^1H and ^{13}C NMR spectra confirmed the existence of butane lactone group in compound **7**.

With rupatadine (**3**) analogue **7** in hand, based on our previous work on the synthesis and bioactivity of γ-alkylidene butenolides,[31–34] the crucial direct vinylogous aldol condensation process could be attempted. γ-Alkylidene derivatives **8** and **9** (Scheme 1 and Table 1) were synthesized by intermediate **7** reacting with various aldehydes and ketones. During the condensation reaction, compound **7** formed carbanion at γ-position of lactones under



Scheme 1. Reagents and conditions: (i) 2.2 equiv NBS, $Ph(CO)_2O_2$, CCl_4, reflux, 95%; (ii) 5% aq NaOH, rt 12 h, 70%; (iii) KOH, 80% CH_3CH_2OH, reflux, 88%; (iv) CCl_4, TEA, rt 65%; (v) aldehyde or ketone, CH_3OH, Na_2CO_3, rt, 30–90%.

Table 1
Compounds synthesized

Compds	R^1	R^2	Compds	R^1	R^2	Compds	R^1	R^2
8/**9a**	*o*-MeOPh	H	**8f**	*p*-$SO_2(CH_3)$Ph	H	**8k**	*p*-BrPh	H
8b	*p*-OHPh	H	**8g**	*p*-$N(CH_3)_2$Ph	H	**8l**	*p*-MeOPh	H
9c	Ph	H	**8h**	*m*-MeO-*p*-OHPh	H	**8m**	*p*-FPh	H
8d	3,4,5-triMeOPh	H	**9i**	*o*-ClPh	H	**8**/**9n**	$CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$	H
8e	*p*-ClPh	H	**8j**	Furoyl	H	**8o**	CH_3	CH_3

alkaline environment, then this carbanion reacted with aldehyde or ketone carbonyl by the nucleophilic addition reaction to give intermediates **9**, which were detected in almost all the reactions. While most reactions occurred dehydration reaction to give more stable products **8** quickly. We could also make **9** translated into **8** fully by extending the reaction time in most cases. Some $C_{7''}$ hydroxyl retained products **9**(**a**, **c**, **i**, **n**) were isolated too.

In order to prepare more alkylidene derivatives, its conditions were optimized with respect to the limited stability of **7** as well as to the relatively sensitive functionality present in the target γ-alkylidene butenolides. We investigated the effect of base and solvent on the reaction of **7** with vanillic aldehyde. At room temperature or 50 °C below, Na_2CO_3 proved to be more effective in promoting the reaction. The catalysts TEA or diaminoethane could also promote the reaction at room temperature. The solvents such as methanol and ethanol proved to be effective in promoting the reaction. Under the above optimized conditions, most of the desired products could be obtained in moderate to good yields and stereoselectivity.

The NMR spectra data showed that **8**(**a**–**n**) should be single isomers. However, their stereochemistry could not be confirmed based on the present data. According to the vinylogous aldol reaction, **10a**–**10d** should be the possible intermediates to yield the compounds **8**(**a**–**o**) by an elimination reaction. In order to prove the geometry of the double bond ($\Delta^{5'',7''}$) in compounds **8**(**a**–**o**), the three-dimensional conformation of intermediates **10a**–**10d** were shown in Figure 3. According to the principle of trans-coplanar for elimination reaction, the conformation of intermediates **10a**–**10d** shown in Figure 3 were necessary condition for the elimination reaction. It could be found that an obvious steric hindrance exists between the phenyl group and desloratadine (**2**) skeleton in intermediates **10b** and **10d**. On the contrary, the conformation of intermediates **10a** and **10c** is favorable to the elimination reaction. So the conformation of **10a** and **10c** should be the advantage conformation. Based on the conformation of **10a** and **10c**, the geometry of the double bond ($\Delta^{5'',7''}$) was deduced to be *Z* configuration. Above analysis could also give the reason that ketone is hard to react with **7** under the same conditions. The corresponding product **8o** was obtained by the reaction of **7** and acetone under reflux with organic base ethylenediamine as catalyst in relatively low yield (35%).

In the NOE spectrum of **8h** (Fig. 4), the correlation between signals of H-7″ (δ_H 6.35) and H-6″ (δ_H 3.49) showed the geometry of double bond ($\Delta^{5'',7''}$) in **8h** was *Z* isomer. The perspective drawing

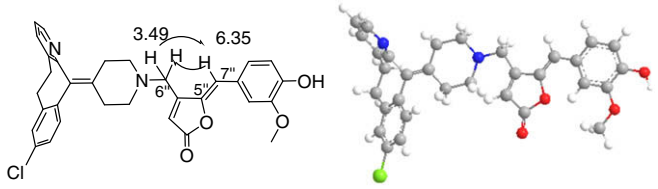


Figure 4. The NOE experiments of **8h** and a computer generated perspective drawing of the final mode of **8h**.

of the final mode (Fig. 4) of **8h** also proves *Z* isomer should be the dominant conformation. Similarly, the signals of $\delta_{H\text{-}7''}$ of most compounds **8** are single peaks. These compounds were confirmed to be single isomers, in which the geometry of the double bond ($\Delta^{5'',7''}$) were *Z* configuration. While signals of $\delta_{H\text{-}7''}$ of compounds **8d**, **8e** and **8f** showed double peaks and their $\delta_{C\text{-}7''}$ signals appeared in pairs, these compounds were obtained as mixtures of *Z*/*E* (1:1) isomers.

2.2. Antihistamine activities

The H_1 antihistamine activity of the above synthesized compounds was evaluated by the in vitro histamine-induced contraction of the guinea-pig ileum assay (HC). We set three concentrations for the evaluation of antihistamine activity according to the literature.[6,37] Loratadine (**1**) and desloratadine (**2**) were the standards. The results are gathered in Table 2 and Figure 5. The H_1 antihistamine activity evaluation results indicate that replacing the 3-methyl-pyridine of rupatadine (**3**) by the five-membered lactones ring system is an efficient modification. Their γ-alkylidene butenolides derivatives also show moderate to good antihistamine activity. But different arylidene derivatives give inconsistent bioactivity results. Structure–activity relationships have been obtained from the analyses of the inhibition values of compounds **1**, **2**, **7**, **8** and **9**. The first observation is that modification of desloratadine (**2**) with γ-alkylidene butenolides is an efficient approach to improve their H_1 antihistamine activity. In vitro activity screening of the above derivatives showed that **7**, **8a** and **8g** demonstrated excellent antihistamine activity, and are better than the two standards. Compounds **7** showed much better activities than the standard loratadine (**1**) with inhibitory values at the three different concentrations 3×10^{-6} mol/L, 10×10^{-6} mol/L and 30×10^{-6}mol/L were 33.44%, 79.00% and 94.75%, respectively,

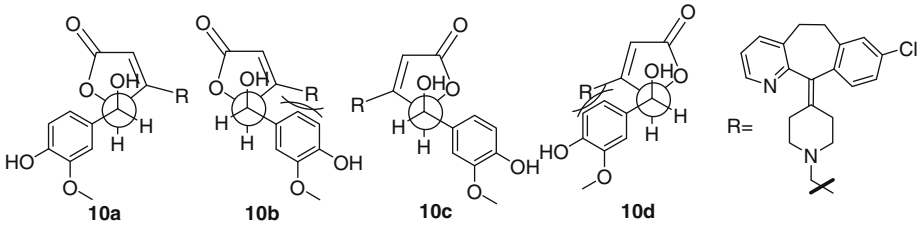


Figure 3. The three-dimensional conformation of intermediates **10a**–**10d**.

Table 2
Inhibitory of the histamine-induced contraction of the guinea-pig ileum

Compds	Concn (10^{-6})	N	In. (%)	Compds	Concn (10^{-6})	N	In. (%)
1	0	6	0	**9c**	10	6	60.44 ± 1.04*
	3	6	15.67 ± 4.55*		30	6	76.81 ± 2.72*
	10	6	33.36 ± 2.96*	**8d**	0	6	0
	30	6	64.70 ± 5.88*		3	6	4.23 ± 1.72
2	0	6	0		10	6	32.89 ± 5.71*
	3	6	47.42 ± 3.52*		30	6	52.80 ± 5.23*
	10	6	77.71 ± 1.51*	**8e**	0	6	0
	30	6	80.44 ± 3.18*		3	6	37.05 ± 1.76*
7	0	6	0		10	6	51.30 ± 6.66*
	3	6	33.44 ± 6.36*		30	6	66.66 ± 3.26*
	10	6	79.00 ± 4.25*	**8f**	0	6	0
	30	6	94.75 ± 1.94*		3	6	12.37 ± 2.57
8a	0	6	0		10	6	50.40 ± 5.39*
	3	6	29.43 ± 2.30*		30	6	71.93 ± 3.84*
	10	6	59.24 ± 5.02*	**8g**	0	6	0
	30	6	87.85 ± 1.88*		3	6	61.58 ± 2.88*
9a	0	6	0		10	6	77.61 ± 0.93*
	3	6	40.76 ± 3.79*		30	6	82.34 ± 1.39*
	10	6	61.47 ± 3.08*	**8h**	0	6	0
	30	6	74.07 ± 2.22*		3	6	4.67 ± 2.69
8b	0	6	0		10	6	42.55 ± 6.72*
	3	6	3.54 ± 1.02		30	6	62.65 ± 4.57*
	10	6	41.02 ± 2.39*	**8m**	0	6	0
	30	6	65.61 ± 5.35*		3	6	6.99 ± 2.36
9c	0	6	0		10	6	18.97 ± 5.10*
	3	6	42.72 ± 5.90*		30	6	30.64 ± 4.21*

Compared with the blank control group *p <0.05 (application of SPSS10.0 version of statistical software for statistical analysis).

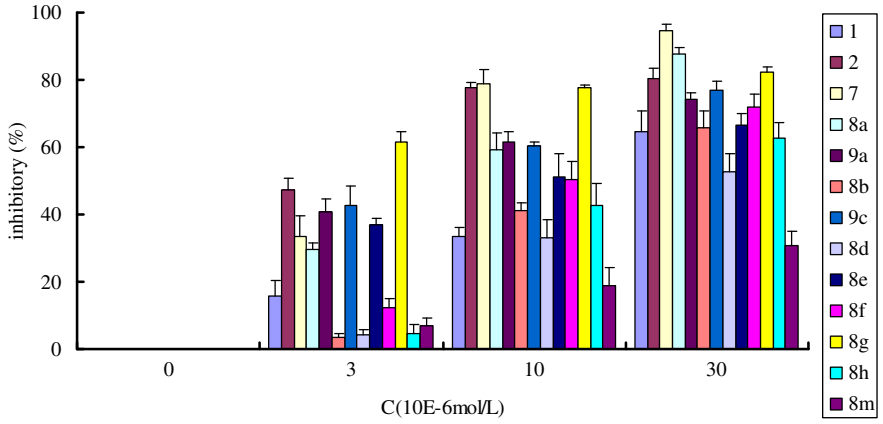


Figure 5. The relationship between concentration and inhibitory.

the corresponding inhibitory values of loratadine (**1**) were 15.67%, 33.36% and 64.70%, respectively. The H_1 antihistamine activity of compound **7** even better than the standard desloratadine (**2**) at two higher concentrations. The inhibitory values of desloratadine (**2**) were 77.71% and 80.44% at 10×10^{-6} mol/L and 30×10^{-6} mol/L, respectively. It is also found that inhibitory activities show significant dependence on the substituents in phenyl. For example, an aromatic ring with electron-donating substituents such as **8a** and **8g** are favorable to the H_1 antihistamine activity. The comparison of **8a** and **8g** to the two standards **1** and **2** are similar to compound **7**. The inhibitory values were 29.43%, 59.24% and 87.85%, respectively at the three different concentrations for compounds **8a**, and 29.43%, 59.24% and 87.85% for compound **8g**. Compounds **8e** and **8m** bearing halogen atoms in phenyl are detrimental to the H_1 antihistamine activity. An aromatic ring with hydroxyl substituent such as **8b** and **8h** may not beneficial enough to the H_1 antihistamine activity. In addition, $C_{7''}$ hydroxyl retained products **9a** and **9c** also showed good H_1 antihistamine activity (Table 2 and Fig. 5).

3. Conclusion

In summary, a novel family of antagonist of histamine was synthesized. Their structures were identified by the analysis of IR, NMR, HR-MS spectra. Most of the products exhibit moderate to good H_1 antihistamine activity. **7**, **8a** and **8g** would be lead compounds for the development of new drugs as anti-allergy medications.

4. Experimental section

4.1. General methods

Melting points were determined on a Beijing Keyi XT5 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR200) Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100 MHz with TMS as internal standard. Mass spectra were taken by Waters Q-Tof micro mass spectrometer.

4.2. General procedure for antihistamine activity assay

This test was performed according to the method of literatures.[6,37] Male Dunkin–Hartley guinea pigs (bw 300–350 g), fasted overnight, were used. Animals were stunned, the abdomen was opened, and 2 cm long ileum sections were cut off. The sections were placed in a petri dish containing Tyrode's solution at 37 °C and continuously bubbled with oxygen. The ileum fragments were washed with Tyrode's solution and then transferred to an organ bath. Ileum contraction was measured using an isometric transducer. The initial load was 1 g. After a stabilization period of 20 min in which the organ was immersed in Tyrode's solution at 37 °C continuously bubbled with oxygen, noncumulative stimuli with submaximal doses of histamine (5×M) were given. The contraction in absence or presence (3–5 min incubation) of the test compounds was recorded. The activities of the antagonists are expressed as inhibitory values at three different concentrations of synthesized compounds. The completed date was September 3, 2009.

4.3. Synthesis

4.3.1. Desloratadine (2)

A solution of loratadine (**1**) (38.2 g, 0.1 mol) and 15 equiv KOH (84 g, 1.5 mol) in 80% CH_3CH_2OH (334 ml) was heated under reflux for 10 h and the reaction was monitored by TLC to completion. Ethyl alcohol was evaporated under reduced pressure, and then extracted with ethyl acetate (3 × 100 ml), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 40 ml) and brine (2 × 100 ml) and dried over anhydrous Na_2SO_4, the solution was evaporated under reduced pressure to give a crude desloratadine (2), which was refined by recrystallization in ethyl acetate to give 27 g white crystal. Yield: 88%. $C_{19}H_{19}ClN_2$. mp = 154–154.5 °C. IR (KBr, cm^{-1}): 3305, 3055, 3014, 1635, 1586, 1480, 878, 847, 815, 777, 725, 702. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.40 (dd, 1H, J = 4.8 Hz, J = 1.6 Hz), 7.43 (dd, 1H, J = 7.6 Hz, J = 1.6 Hz), 7.15 (d, 1H, J = 8.0 Hz), 7.14 (1H, d, J = 8.0 Hz), 7.13 (s, 1H), 7.08 (dd, 1H, J = 7.6 Hz, J = 4.8 Hz), 3.34–3.47 (m, 2H), 3.01–3.08 (m, 2H), 2.76–2.88 (m, 2H), 2.64–2.72 (m, 2H), 2.26–2.44 (m, 4H), 1.58 (br s, 1H).

4.3.2. Bis (bromomethyl)acrylie acid (5)[35,36]

A solution of **4** (30 g, 0.3 mol) and NBS (118 g, 0.66 mol) in $CC1_4$ (600 ml) was heated under reflux for 3 h during which benzoyl peroxide (0.9 g) was added in small portions at 20 min intervals. After heating for an additional l h, the reaction mixture was allowed to cool to rt. The precipitated succinimide was removed by filtration, and the filtrate evaporated under reduced pressure to give a crude **5** which was chromatographed on silica gel (elution with petroleum ether/ethyl acetate, 4:1) to afford 74 g (95%) of **5** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.20 (s, 2H), 4.67 (s, 2H), 6.08 (s, 1H), 10.30 (s, 1H).

4.3.3. 4-(Bromomethyl) furan-2(5*H*)-one (6)[35,36]

To the acid **5** (40 g, 0.16 mol) at rt was added dropwise 5% NaOH (130 ml) over l h, and the milky solution was stirred at rt for 12 h. The reaction mixture was extracted with CH_3C1 (3 × 100 ml), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 40 ml) and brine (2 × 100 ml) and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with petroleum ether/ethyl acetate, 4:1) afforded 19 g (70%) of **6** as yellow oil: ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.28 (s, 2H), 4.96 (m, 2H), 6.15 (s, 1H).

4.3.4. 1-[(Furan-2(5*H*)-one)-4-methyl]-desloratadine (7)

To a carbon tetrachloride solution of desloratadine (**2**) 31 g (0.1 mol) and TEA (0.06 mol) was added 1.2 equiv compound **6** (0.12 mol). The mixture was stirred at room temperature for 6 h and the reaction was monitored by TLC to completion. The reaction mixture was washed with water and ethyl acetate, dried and purified by column chromatography (elution with chloroform/ethyl acetate/acetone = 3:1:1) afforded 26 g (65%) of **7** as a pink oil: Yield: 65%. IR(KBr, cm^{-1}): 1776, 1748, 1637, 1589, 1476, 1438, 1142, 1031, 886, 830. ^1H NMR (400 MHz, DMSO, TMS): δ 8.37 (d, J = 3.7 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 1.2 Hz, 1H), 7.18–7.11 (m, 3H), 6.00 (s, 1H, $=C_{(3'')}H$), 4.87 (s, 2H), 3.41 (s, 2H), 3.39–3.30 (m, 2H), 2.86–2.82 (m, 2H), 2.72–2.70 (m, 2H), 2.47–2.42 (m, 2H), 2.33–2.24 (m, 4H); ^{13}C NMR (100.6 MHz, DMSO, TMS): δ 173.74, 169.33, 157.93, 146.83, 140.81, 138.77, 138.36, 138.09, 134.24, 133.23, 132.91, 131.48, 129.53, 126.31, 122.94, 117.00, 72.87, 55.85, 55.45, 55.38, 32.02, 31.56, 31.29, 31.16; HR-MS (ESI), calcd $C_{24}H_{23}ClN_2O_2$: $[M+H]^+$ m/z: 407.1526; found: 407.1519.

4.3.5. General procedure of 8 and 9

Compound **7** (0.01 mol) and anhydrous sodium carbonate (0.01 mol) were dissolved in methanol solution, and then the corresponding aromatic aldehyde (0.012 mol) was added. The mixture was stirred at room temperature for 3–12 h and the reaction was monitored by TLC to completion. The reaction solution was evaporated under reduced pressure to steam out of most of the methanol, the reaction mixture was washed with water and ethyl acetate, dried and purified by column chromatography.

4.3.5.1. 1-[((*Z*)-5-(2-Methoxybenzylidene) furan-2(5*H*)-one)-4-methyl]-desloratadine (8a). Yield: 40%. Yellow solid, mp = 117–119 °C. IR (KBr, cm^{-1}): 1766, 1598, 1488, 1464, 1438, 1247, 1112, 1024, 826, 756. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.41 (d, J = 4.2 Hz, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.31–7.28 (m, 1H), 7.17–7.09 (m, 4H), 7.01 (m, 1H), 6.92 (s, 1H, $=C_{(7'')}H$), 6.91–6.88 (m, 1H), 6.14 (s, 1H, $=C_{(3'')}H$), 3.90 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2), 3.43–3.38 (m, 2H), 2.84–2.79 (m, 4H), 2.59–2.46 (m, 2H), 2.45–2.36 (m, 2H), 2.30–2.26 (m, 2H); HR-MS (ESI), calcd $C_{32}H_{29}ClN_2O_3$; $[M+H]^+$ m/z: 525.1945; found: 525.1923; $[M+Na]^+$ m/z: 547.1764; found: 547.1741.

4.3.5.2. 1-[(5-(Hydroxyl (2-methoxyphenyl) methyl) furan-2(5*H*)-one)-4-methyl]-desloratadine (9a). Yield: 60%. Yellow solid, mp = 137–138.9 °C. IR (KBr, cm^{-1}): 2905, 1752, 1590, 1490, 1477, 1466, 1438, 1241, 1024, 830, 757. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.41 (m, 1H), 7.49–7.44 (q, J = 7.5 Hz, J = 14.4 Hz, 2H), 7.29 (m, 1H), 7.16–7.09 (m, 4H), 7.01 (m, 1H), 6.92 (d, J = 4.2 Hz, 1H), 6.02 (s, 1H, $=C_{(3'')}H$), 5.27 (d, J = 7.2 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 5.02 (d, J = 7.2 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 3.85 (s, 3H, OCH_3), 3.40–3.29 (m, 4H), 2.84–2.79 (m, 2H), 2.71–2.68 (m, 2H), 2.41–2.30 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 171.89, 166.44, 160.00, 146.67, 139.49, 137.49, 136.83, 133.76, 133.39, 132.91, 130.54, 129.21, 129.01, 127.81, 127.33, 126.14, 122.32, 121.46, 120.70, 110.82, 110.79, 86.77, 86.74, 68.98, 68.91, 60.41, 55.86, 55.55, 54.96, 54.80, 54.75, 54.68, 31.67, 31.41, 30.44, 30.13; HR-MS (ESI), calcd $C_{32}H_{31}ClN_2O_4$: $[M+H]^+$ m/z: 543.2043; found: 543.2011.

4.3.5.3. 1-[((*Z*)-5-(4-Hydroxybenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8b). Yield: 90%. Yellow solid, mp = 198–200 °C. IR (KBr, cm^{-1}): 1747, 1605, 1573, 1513, 1439, 1371, 1290, 1222, 1166, 928, 827. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (d, J = 4.6 Hz, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.17–7.05 (m, 4H), 6.89 (d, J = 8.6 Hz, 2H), 6.42 (s, 1H, $=C_{(7'')}H$), 6.03 (s, 1H, $=C_{(3'')}H$), 3.48 (s, 2H), 3.41–3.37 (m, 2H), 2.84–2.76 (m, 4H), 2.41–2.38 (m, 2H), 2.32–2.23 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 169.95, 158.78, 157.21, 156.83, 145.90, 145.85, 139.24, 138.32, 137.94, 137.21, 133.94, 132.81, 132.23, 130.78, 129.03, 126.06, 124.45, 122.55, 116.34, 114.55,

112.40, 54.76, 54.69, 53.87, 40.65, 31.66, 31.22, 30.70, 29.62; HR-MS (ESI), calcd $C_{31}H_{27}ClN_2O_3$: $[M+H]^+$ *m*/*z*: 511.1788; found: 511.1745.

4.3.5.4. 1-[(5-(Hydroxyl (phenyl) methyl) furan-2(5*H*)-one)-4-methyl]-desloratadine (9c). Yield: 30%. Yellow solid, mp = 116–118 °C. IR (KBr, cm^{-1}): 1757, 1643, 1589, 1478, 1439, 1174, 1025, 829, 754, 701. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (d, *J* = 4.6 Hz, 1H), 7.46–7.29 (m, 6H), 7.17–7.09 (m, 4H), 5.83 (s, 1H, $=C_{(3'')}H$), 5.35 (d, *J* = 2.8 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 5.19 (d, *J* = 2.8 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 3.30 (s, 2H, CH_2), 3.39–3.32 (m, 2H), 2.84–2.74 (m, 4H), 2.73–2.43 (m, 2H), 2.42–2.35 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 171.76, 156.82, 146.57, 139.49, 139.46, 138.69, 137.57, 137.43, 137.41, 136.48, 133.88, 133.39, 132.94, 130.48, 128.99, 128.33, 128.03, 126.91, 125.87, 122.34, 119.76, 85.88, 85.84, 71.80, 71.75, 55.68, 55.24, 55.05, 54.98, 31.61, 31.40, 30.44, 30.19, 29.65; HR-MS (ESI), calcd $C_{31}H_{29}ClN_2O_3$: $[M+H]^+$ *m*/*z*: 513.1945; found: 513.1901.

4.3.5.5. 1-[(5-(3,4,5-Trimethoxybenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8d) (*Z*/*E* = 1:1). Yield: 50%. Yellow oil. IR(KBr, cm^{-1}): 2923, 2361, 2342, 1755, 1638, 1589, 1439, 830, 701; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (dd, 1H, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.44 (d, 1H, *J* = 7.6 Hz), 7.17–7.04 (m, 4H), 6.68 (s, 2H), 6.10 (d, *J* = 2.7 Hz, 1H, $=C_{(7'')}H$), 5.78 (s, 1H, $=C_{(3'')}H$), 3.93 (s, 6H, OCH_3), 3.91 (s, 3H, OCH_3), 3.41–3.30 (m, 6H), 2.84–2.07 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 169.10, 157.13, 153.29, 153.20, 147.35, 146.42, 139.49, 139.43, 137.79, 137.64, 133.53, 133.13, 132.87, 130.66, 128.99, 128.67, 128.38, 126.10, 122.31, 115.84, 111.45, 108.21, 61.01, 60.96, 56.35, 56.10, 54.98, 53.84, 31.72, 31.43, 30.81, 30.65; HR-MS (ESI), calcd $C_{34}H_{33}ClN_2O_5$: $[M+H]^+$ *m*/*z*: 585.2156; found: 585.2151.

4.3.5.6. 1-[(5-(4-Chlorobenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8e) (*Z*/*E* = 1:1). Yield: 60%. Yellow solid, mp = 129.3–131.2 °C. IR (KBr, cm^{-1}): 1760, 1588, 1490, 1438, 1409, 1091, 1014, 830. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.43–7.29 (m, 4H), 7.17–7.08 (m, 4H), 6.11 (d, *J* = 2.5 Hz, 1H, $=C_{(7'')}H$), 5.79 (s, 1H, $=C_{(3'')}H$), 3.38–3.29 (m, 4H), 2.85–2.77 (m, 5H), 2.48–2.34 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.27, 156.80, 148.53, 147.78, 146.69, 140.85, 139.53, 137.65, 137.49, 136.08, 135.46, 134.30, 133.37, 133.09, 132.55, 132.28, 131.89, 131.07, 130.42, 129.19, 129.02, 128.65, 127.01, 126.22, 122.39, 109.51, 67.31, 54.96, 51.39, 31.64, 31.49, 30.32, 30.04; HR-MS (ESI), calcd $C_{31}H_{26}Cl_2N_2O_2$: $[M+H]^+$ *m*/*z*: 529.1450; found: 529.1436.

4.3.5.7. 1-[((*Z*)-5-(4-(Methylsulfonyl)benzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8f) (*Z*/*E* = 1:1). Yield: 65%. Yellow oil. IR (KBr, cm^{-1}): 1759, 1646, 1590, 1505, 1460, 1422, 1329, 1239, 1127 and 1004. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.69 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.19–7.08 (m, 4H), 6.26 (d, *J* = 1.60 Hz, 1H, $=C_{(7'')}H$), 5.91 (s, 1H, $=C_{(3'')}H$), 3.08 (s, 3H, CH_3), 3.41–3.38 (m, 4H), 2.84–2.76 (m, 4H), 2.41–2.38 (m, 2H), 2.32–2.23 (m, 4H); HR-MS (ESI), calcd $C_{32}H_{29}ClN_2O_4S$: $[M+H]^+$ *m*/*z*: 573.1615; found: 573.1611.

4.3.5.8. 1-[((*Z*)-5-(4-(Dimethylamino)benzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8g). Yield: 40%. Brown solid, mp = 124.3–126 °C. IR (KBr, cm^{-1}): 2921, 2360, 2341, 1747, 1651, 1603, 1525, 1478, 1438, 1374, 1294, 1154, 919, 906, 874, 830, 750. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.40 (dd, 1H, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.71 (d, *J* = 8.8 Hz, 2H, Ph), 7.15–7.07 (m, 5H, Ar), 6.68 (d, *J* = 8.8 Hz, 2H, Ph), 6.35 (s, 1H, $=C_{(7'')}H$), 6.00 (s, 1H, $=C_{(3'')}H$), 3.49 (s, 2H), 3.02 (s, 6H, $N(CH_3)_2$), 3.41–3.38 (m, 4H), 2.80–2.74 (m, 4H), 2.32–2.06 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 171.64, 163.71, 157.23, 146.58, 146.53, 139.66, 139.60, 137.66, 137.48, 133.71, 133.51, 133.49, 132.85, 132.83, 132.60, 130.56, 129.01, 126.06, 122.24, 119.98, 111.95, 100.09, 60.37, 55.04, 51.64, 45.53, 40.21, 31.72, 31.24, 30.81, 30.57; HR-MS (ESI), calcd $C_{33}H_{32}ClN_3O_2$: $[M+H]^+$ *m*/*z*: 538.2621; found: 538.2601.

4.3.5.9. 1-[((*Z*)-5-(4-Hydroxy-2-methoxybenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8h). Yield: 80%. Yellow solid, mp = 168–170 °C. IR (KBr, cm^{-1}): 3418, 2925, 1749, 1635, 1516, 1286, 1209, 1167, 1030; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.40 (dd, 1H, *J* = 4.7 Hz, *J* = 1.2 Hz), 7.46 (m, 2H), 7.19–7.09 (m, 5H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.35 (s, 1H, $=C_{(7'')}H$), 6.35 (s, 1H, $=C_{(3'')}H$), 3.90 (s, 3H, OCH_3), 3.49 (s, 2H), 3.41–3.38 (m, 2H), 2.87–2.77 (m, 4H), 2.58–2.46 (m, 2H), 2.36–2.24 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 169.49, 157.09, 156.70, 147.49, 147.03, 146.26, 146.06, 139.34, 137.91, 137.51, 137.44, 133.48, 132.73, 132.66, 130.67, 128.88, 125.94, 125.52, 125.16, 122.21, 114.92, 114.74, 112.57, 111.90, 55.85, 54.89, 54.83, 53.78, 31.62, 31.26, 30.71, 30.56; HR-MS (ESI), calcd $C_{32}H_{29}ClN_2O_4$: $[M+H]^+$ *m*/*z*: 541.1894; found: 541.1869.

4.3.5.10. 1-[(5-((2-Chlorophenyl) (hydroxy) methyl) furan-2(5*H*)-one)-4-methyl]-desloratadine (9i). Yield: 35%. Pink oil. IR(KBr, cm^{-1}) *v*: 2922, 2361, 2343, 1758, 1646, 1589, 1476, 1439, 1054, 1030, 830, 754; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.34 (dd, 1H, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.68 (m, 1H), 7.45 (d, *J* = 3.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30–7.01 (m, 6H), 6.01 (s, 1H, $=C_{(3'')}H$), 5.55 (dd, *J* = 6.4 Hz, *J* = 2.0 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 5.30 (d, *J* = 2.0 Hz, 1H, $C_{5''}H$–$C_{7''}H$), 3.35 (s, 2H, CH_2), 3.34–3.32 (m, 2H), 2.81–2.52 (m, 4H), 2.51–2.32 (m, 2H), 2.06–2.31 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 172.71, 166.20, 157.19, 146.44, 139.45, 137.59, 137.49, 137.47, 137.42, 137.17, 137.08, 133.58, 133.55, 133.19, 132.87, 131.33, 131.31, 130.70, 129.14, 129.09, 129.05, 127.19, 126.09, 122.36, 119.93, 119.90, 85.01, 85.00, 68.06, 68.04, 60.41, 55.33, 55.30, 55.09, 55.04, 55.00, 31.73, 31.33, 30.83, 30.77, 30.62, 30.57; HR-MS (ESI), calcd $C_{31}H_{28}Cl_2N_2O_3$: $[M+H]^+$ *m*/*z*: 547.1555; found: 547.1568.

4.3.5.11. 1-[((*Z*)-5-(Furan-2-ylmethylene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8j). Yield: 75%. Brown oil. IR(KBr, cm^{-1}) *v*: 1755, 1645, 1474, 1438, 1244, 1085, 1017, 984, 829, 742; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.41 (dd, 1H, *J* = 4.7 Hz, *J* = 1.3 Hz), 7.51 (d, *J* = 1.5 Hz, 1H), 7.45 (dd, 1H, *J* = 7.6 Hz, *J* = 1.1 Hz), 7.16–7.04 (m, overlap, 5H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.53 (s, 1H, $=C_{(7'')}H$), 6.09 (s, 1H, $=C_{(3'')}H$), 3.64 (s, 2H, CH_2), 3.47–3.38 (m, 2H), 2.83–2.75 (m, 4H), 2.56–2.46 (m, 2H), 2.40–2.13 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.81, 157.26, 155.91, 148.95, 146.60, 145.95, 144.04, 139.49, 137.77, 137.69, 137.40, 133.37, 133.22, 132.78, 130.68, 128.93, 126.05, 122.17, 116.04, 115.38, 113.05, 100.30, 55.02, 54.98, 53.89, 31.73, 31.44, 30.84, 30.64; HR-MS (ESI), calcd $C_{29}H_{25}ClN_2O_3$: $[M+H]^+$ *m*/*z*: 485.1632; found: 485.1623.

4.3.5.12. 1-[((*Z*)-5-(4-Bromobenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8k). Yield: 80%. Yellow solid, mp = 129.2–130 °C. IR (KBr, cm^{-1}) *v*: 1764, 1681, 1586, 1486, 1398, 1224, 1173, 1070, 1010, 829, 759; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.36 (m, 1H), 7.63 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.3 Hz), 7.15–7.06 (m, 4H), 6.13 (s, 1H, $=C_{(7'')}H$), 5.76 (s, 1H, $=C_{(3'')}H$), 3.37–3.30 (m, 4H), 2.93–2.76 (m, 4H), 2.45–2.30 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.13, 156.61, 147.68, 146.41, 141.23, 139.39, 137.56, 135.97, 133.30, 132.87, 132.27, 131.95, 131.42, 131.40, 130.31, 128.91, 128.88, 127.21, 126.03, 122.29, 121.31, 109.59, 67.09, 54.72, 51.19, 31.50, 31.29, 30.15, 29.86; HR-MS (ESI), calcd $C_{31}H_{26}BrClN_2O_2$: $[M+H]^+$ *m*/*z*: 573.0944; found: 573.0916.

4.3.5.13. 1-[((*Z*)-5-(4-Methoxybenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8l). Yield: 67%. Yellow solid, mp = 117.5–119 °C. IR (KBr, cm^{-1}) *v*: 1754, 1604, 1591, 1482, 1439, 1302, 1255, 1176, 1029, 930, 831; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39(dd, 1H, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.76 (d, 2H, *J* = 8.8 Hz), 7.44 (d, 1H, *J* = 7.6 Hz), 7.15–7.07 (m, 4H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.39 (s, 1H, $=C_{(7'')}H$), 6.08 (s, 1H, $=C_{(3'')}H$), 3.83 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2), 3.40–3.34 (m, 2H), 2.86–2.77 (m, 4H), 2.56–2.44 (m, 2H), 2.41–2.33 (m, 2H), 2.27–2.23 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 169.46, 160.26, 157.12, 156.76, 146.39, 146.32, 139.39, 137.76, 137.55, 137.37, 133.33, 132.97, 132.64, 132.43, 130.58, 128.85, 125.93, 125.54, 122.12, 114.88, 114.21, 111.29, 55.21, 54.90, 54.86, 53.79, 31.62, 31.29, 30.76, 30.58; HR-MS (ESI), calcd $C_{32}H_{29}ClN_2O_3$: $[M+H]^+$ *m*/*z*: 525.1945; found: 525.1926.

4.3.5.14. 1-[((*Z*)-5-(4-Fluorobenzylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8m). Yield: 77%. Brown solid, mp = 120.9–122 °C. IR (KBr, cm^{-1}) *v*: 1758, 1599, 1508, 1478, 1439, 1228, 1159, 1014, 988, 858, 832; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.37 (dd, 1H, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.79 (m, 2H), 7.41 (m, 3H), 7.15–7.01 (m, 4H), 6.18 (s, 1H, $=C_{(7'')}H$), 5.79 (s, 1H, $=C_{(3'')}H$), 3.36–3.31 (m, 4H), 2.83–2.75 (m, 4H), 2.48–2.29 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.50, 163.35, 161.80, 156.80, 156.77, 148.60, 147.14, 146.55, 139.53, 137.69, 136.21, 133.47, 132.78, 130.44, 129.05, 127.33, 127.25, 126.15, 122.43, 115.95, 115.22, 109.71, 67.31, 54.81, 51.35, 31.63, 31.40, 30.05, 29.77; HR-MS (ESI), calcd $C_{31}H_{26}ClFN_2O_2$: $[M+H]^+$ *m*/*z*: 513.1745; found: 513.1728.

4.3.5.15. 1-[(5-(3,7-Dimethylocta-2,6-dienylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8n). Yield: 45%. Brown oil. IR (KBr, cm^{-1}) *v*: 3417, 2925, 2855, 1757, 1633, 1590, 1440, 1376, 1174, 1026, 990, 831; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.41(dd, 1H, *J* = 4.6 Hz, *J* = 1.3 Hz), 7.46 (dd, 1H, *J* = 7.7 Hz, *J* = 0.9 Hz), 7.16–7.09 (m, 4H), 6.50 (m, 2H, =C*H*), 6.03 (m, 1H, =C*H*), 5.09 (m, 1H, =C*H*), 3.46 (s, 2H, CH_2), 2.19 (s, 6H, $=C(CH_3)_2H$), 3.39–3.34 (m, 2H), 2.83–2.76 (m, 4H), 2.75–2.20 (m, 4H), 1.89 (s, 3H, CH_3), 1.69 (m, 2H), 1.61 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 169.16, 157.25, 155.32, 148.33, 147.03, 146.53, 139.52, 137.94, 137.69, 137.56, 133.50, 133.13, 132.86, 132.33, 130.73, 129.01, 126.12, 123.35, 122.29, 118.43, 115.75, 109.40, 54.96, 53.97, 40.54, 31.95, 31.78, 30.97, 29.72, 26.52, 25.72, 22.71, 17.75, 17.50; HR-MS (ESI), calcd $C_{34}H_{37}ClN_2O_2$: $[M+H]^+$ *m*/*z*: 541.2598; found: 541.2622.

4.3.5.16. 1-[(5-(1-Hydroxy-3,7-dimethylocta-2,6-dienyl)furan-2(5*H*)-one)-4-methyl]-desloratadine (9n). Yield: 50%. Pink oil. IR (KBr, cm^{-1}) *v*: 3418, 1755, 1633, 1589, 1439, 1376, 1174, 1118, 827; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.40 (d, *J* = 4.52 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.15–7.08 (m, 4H), 6.00 (s, 1H, $=C_{(3'')}H$), 5.07 (m, 1H, =C*H*), 5.02 (m, 1H, =C*H*), 4.87 (m, 1H, $C_{5''}H$–$C_{7''}H$), 4.74 (m, 1H, $C_{5''}H$–$C_{7''}H$), 2.19 (s, 6H, $=C(CH_3)_2H$), 3.37–3.33 (m, 4H), 2.84–2.80 (m, 4H), 2.38–2.33 (m, 6H), 2.16–2.12 (m, 4H), 1.68 (s, 3H, CH_3); HR-MS (ESI), calcd $C_{34}H_{39}ClN_2O_3$: $[M+H]^+$ *m*/*z*: 559.2733; found: 559.2727.

4.3.5.17. 1-[(5-(Propan-2-ylidene)furan-2(5*H*)-one)-4-methyl]-desloratadine (8o). Yield: 35%. Pink oil. IR (KBr, cm^{-1}) *v*: 1745, 1654, 1590, 1476, 1438, 1369, 1193, 1131, 1034, 829; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.41 (dd, 1H, *J* = 4.8 Hz, *J* = 1.5 Hz), 7.45 (dd, 1H, *J* = 7.7 Hz, *J* = 1.6 Hz), 7.16–7.08 (m, 4H), 6.08 (s, 1H, $=C_{(3'')}H$), 3.41 (s, 2H, CH_2), 3.41–3.38 (m, 2H), 2.83–2.75 (m, 4H), 2.54–2.22 (m, 6H), 2.04 (s, 3H, $=C(CH_3)_2$), 2.03 (s, 3H, $=C(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ 168.96, 157.31, 155.35, 146.62, 145.03, 139.49, 138.01, 137.73, 137.39, 133.36, 133.13, 132.77, 130.69, 128.94, 126.07, 124.44, 122.17, 118.21, 56.35, 55.04, 55.01, 31.75, 31.46, 30.88, 30.66, 20.98, 19.07; HR-MS (ESI), calcd $C_{27}H_{27}ClN_2O_2$: $[M+H]^+$ *m*/*z*: 447.1839; found: 447.1819.

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