Med Chem Res (2012) 21:124–132
DOI 10.1007/s00044-010-9512-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and anti-allergic activities of novel (R)(-)-1-[(4-chlorophenyl)phenyl methyl]piperazine derivatives

Lisheng Wang · Tianwen Wang · Bin Yang · Zhigang Chen · Hua Yang

Received: 3 June 2010 / Accepted: 12 November 2010 / Published online: 1 December 2010

Abstract A series of novel (R)(-)-1-[(4-chlorophenyl) phenylmethyl]piperazine derivatives were designed, synthesized, and tested for in vivo anti-allergic activities. Most of these derivatives exhibited significant effects on both allergic asthma and allergic itching. Three of the 19 piperazine derivatives (namely, **3d**, **3i**, and **3r**) have stronger potency against allergic asthma than levocetirizine, the positive control drug. Meanwhile, in the test of allergic itching, five of the 19 compounds (namely, **3b**, **3g**, **3k**, **3o**, and **3s**) have more potent activities than levocetirizine.

Keywords Diphenylmethylpiperazine · Levocetirizine · Anti-allergy · Allergic asthma · Allergic itching

Introduction

Allergies are the most common serious disorders of the immune system (Akdis, 2009; Sicherer and Leung, 2009). Allergic reactions occur in response to environmental substances known as allergens, which vary largely. The number of patients suffering from allergies is gradually increasing with morbidity rate likewise growing (Li and Brown, 2009; Smith *et al.*, 2009; Mullins *et al.*, 2009). Histamine interacts with H_1 receptors and causes allergies with exposure to excessive amounts of an allergen. Currently, piperazine H_1 receptor antagonists (Slater *et al.*, 1999; Ishiwata *et al.*, 2004), having higher affinity to H_1 receptors than histamine (Banu and Watanabe, 1999; De Bruin *et al.*, 2002), are often clinically used in the treatment of allergies. Most piperazine drugs share the same pharmacophore diphenylmethylpiperazine. Among these drugs, levocetirizine has more potent activities and fewer side effects than classic antihistamines, such as diphenhydramine (Hancock, 2006) and promethazine (Wang *et al.*, 2001; Devalia *et al.*, 2001; Day *et al.*, 2004; Gandon and Allain, 2002). Therefore, we chose levocetirizine as the leading compound in the treatment of allergies and designed a series of derivatives to screen potential anti-allergy drugs.

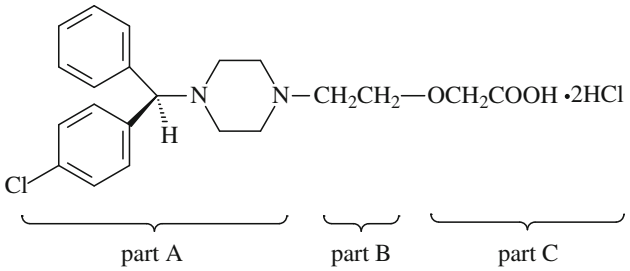
The target compounds (**3a**–**3q**) were designed and synthesized. Part C of levocetirizine (Scheme 1) was replaced with sulfonamides, Part A was unchanged, and Part B was kept either two or three carbons long (Scheme 2). Allergies are associated with subsequent inflammation. Some derivatives of sulfonamides reported showed good anti-inflammatory activities (Husain, 2009; Lloret *et al.*, 2009); hence, sulfonamides may produce synergistic action with the pharmacophore of levocetirizine. The new combined compounds are anticipated to be more potent than levocetirizine and were therefore systemically studied. Glycine and alanine, as kinetophores, were attached to the pharmacophore in an attempt to generate suitable bioavailability (**3r** and **3s** in Scheme 2). To the best of our knowledge, these compounds have not been reported in literatures.

Results and discussion

Chemistry

The (R)(-)-1-[(4-chlorophenyl)benzyl]piperazine derivatives (**3a**–**3s**) (Table 1) were prepared according to the synthetic routes shown in Scheme 2. The derivatives were obtained by the reaction of compound **1** with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane, and

L. Wang (✉) · T. Wang · B. Yang · Z. Chen · H. Yang
School of Chemistry and Chemical Engineering,
Guangxi University, 530004 Nanning, China
e-mail: lswang@gxu.edu.cn



Scheme 1 Structure of levocetirizine

subsequently with appropriate sulfonamides or amino acids to produce **3a–3s** in yields ranging from 40 to 71%. Intermediate **2b** was prepared by the reaction of excessive 1-bromo-3-chloropropane with **1**. 1-Bromo-3-chloropropane has a high boiling point, making its removal by distillation difficult. After the reaction was completed, the dilute solution of hydrogen chloride was added into the reaction mixture to convert **5** into its hydrochloride salt, which dissolves in water. The acidic aqueous layer of the salt of **2b** was separated from the organic layer, and unreacted 1-bromo-3-chloropropane was left in the organic layer. The dilute solution of sodium hydroxide was then used to adjust the pH value to 8 to give **2b**. The R groups of **3r** and **3s** are glycine and alanine, respectively. The methyl esters of glycine and alanine are not soluble in most organic solvents. After many solvents were tested, the synthesis of **3r** and **3s** from the methyl esters of glycine and alanine was carried out in acetonitrile of a homogeneous phase to generate a high yield. The synthesized compounds were characterized through infrared (IR), proton nuclear magnetic resonance (^{1}HNMR), mass spectrometry (MS), and elemental analyses.

Based on the R configuration of levocetirizine, all designed compounds have configurations identical to levocetirizine.

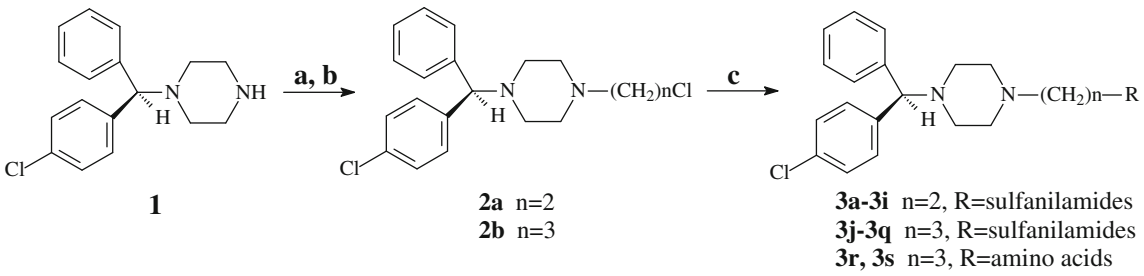
Anti-asthmatic activity

The anti-asthmatic activities of the target compounds (**3a–3s**) were determined using asthmatic cavies (*Cavia procellus*) as model animals; their asthma was caused by histamine phosphate (Kayasuga *et al.*, 2002; Mavrova *et al.* 2006). Compounds **3b**, **3d**, **3f–3j**, **3l**, **3m**, **3o**, and **3q–3s** showed significantly more potent anti-asthmatic activities than that of the control group (Table 2). Compounds **3d**, **3i**, and **3r** exhibited significantly more potent anti-asthmatic activities than levocetirizine. Compounds **3h**, **3j**, **3m**, **3q**, and **3s** showed activities similar to levocetirizine.

The structure–activity relationships of compounds **3a–3s** were analyzed. Target compounds **3d** and **3m** (with intermediates **2a** and **2b**, respectively) connected to the N position of the phenylamino group (Scheme 2), were more active than **3c** and **3l** (with respective intermediates **2a** and **2b**) connected to the N position of the sulfonylamino group. Their activities might be closely related to R group configurations in the foregoing compounds. When there was a methoxypyridazine ring in the R group, the anti-asthmatic activities of compounds **3h**, **3i**, and **3q** were clearly more effective than that of levocetirizine. Results indicate that the methoxypyridazine ring of compounds **3h**, **3i**, and **3q** play an important role in the anti-asthmatic activities. **3q** was significantly more active than **3k**, in which the electron-withdrawing chlorine atom on the pyridazine ring was replaced with an electron-donating methoxy group. Both compounds **3r** and **3s**, having an amino acid group as Part C, showed very strong activities, particularly **3s**. As kinetophores, these amino acid groups can enhance efficacies in the treatment of allergies by increasing pharmacological bioavailability. Compounds **3e**, **3g**, **3n**, and **3p**, having pyrimidine or dimethylpyrimidine rings, showed weak activities, which may cause a weak interaction with the H_1 receptor.

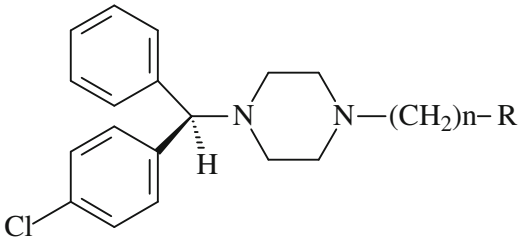
Anti-pruritic activity

The anti-pruritic activities of compounds **3a–3s** were also determined using cavies as model animals; their skin itching was caused by histamine phosphate. Results indicate that compounds **3b–3d**, **3f–3h**, and **3j–3s** had stronger anti-pruritic activities compared with the control group



Scheme 2 Synthetic route of the target compounds. (Reagents and conditions: **a** $Br(CH_2)_2Cl$, TEA, toluene, 55°C; **b** $Br(CH_2)_3Cl$, TEA, toluene, 55°C; **c** **3a–3q**: HR, K_2CO_3, acetone, ref.; **3r**, **3s**: HR, TEA, CH_3CN, ref)

Table 1 Structures of compounds **3a–3s**



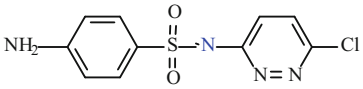
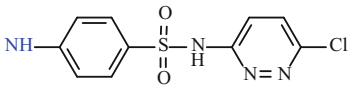
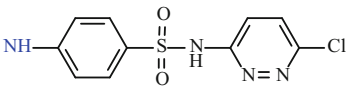
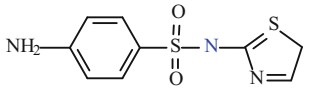
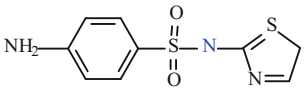
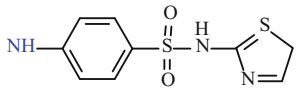
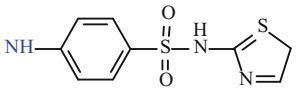
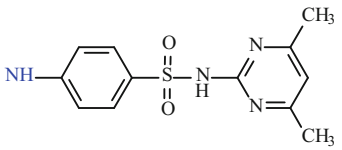
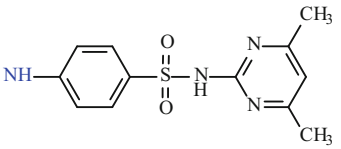
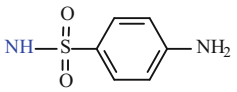
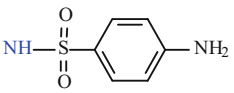
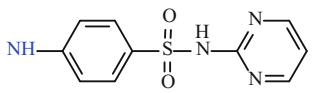
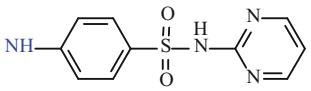
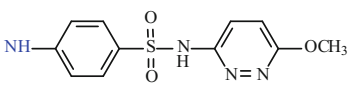
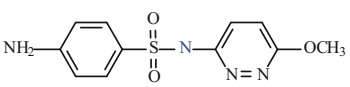
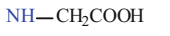
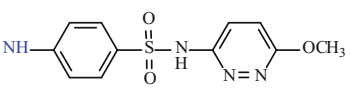
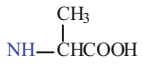
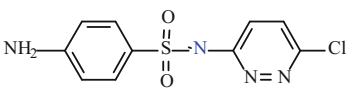
Compd.	n	R	Compd.	n	R
3a	**2**		**3k**	**3**	
3b	**2**		**3l**	**3**	
3c	**2**		**3m**	**3**	
3d	**2**		**3n**	**3**	
3e	**2**		**3o**	**3**	
3f	**2**		**3p**	**3**	
3g	**2**		**3q**	**3**	
3h	**2**		**3r**	**3**	
3i	**2**		**3s**	**3**	
3j	**3**				

Table 2 Comparison of anti-asthmatic activities of compounds **3a**–**3s** at a dose of 50 mg/kg with that of levocetirizine of the same dose

Compounds	Latency before administration (/s)	Latency after administration (/s)
Control	113.0 ± 123.4	115.4 ± 126.2
Levocetirizine	99.2 ± 17.2	274.0 ± 99.4[c]
3a	103.50 ± 32.4	151.2 ± 110.0
3b	95.0 ± 27.4	255.5 ± 109.2[a]
3c	95.5 ± 53.5	184.8 ± 100.4
3d	98.6 ± 30.9	360.0 ± 0.0[cd]
3e	100.7 ± 13.9	167.4 ± 103.4
3f	100.5 ± 17.2	266.2 ± 125.7[a]
3g	97.3 ± 17.6	246.4 ± 117.5[a]
3h	103.4 ± 48.9	288.0 ± 112.5[c]
3i	95.0 ± 17.8	360.0 ± 0.0[cd]
3j	102.5 ± 34.6	301.8 ± 120.1[c]
3k	110.4 ± 37.5	184.1 ± 149.7
3l	94.4 ± 17.0	240.3 ± 112.8[a]
3m	93.3 ± 17.6	324.8 ± 71.9[c]
3n	115.3 ± 53.5	136.8 ± 115.8
3o	103.9 ± 32.7	269.4 ± 118.5[a]
3p	97.9 ± 17.8	229.2 ± 119.3
3q	92.2 ± 27.7	295.6 ± 103.8[c]
3r	97.8 ± 16.0	360.0 ± 0.0[cd]
3s	105.8 ± 48.0	307.6 ± 107.9[c]

Comparison with control group: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$
Comparison with levocetirizine group: [d] $P < 0.05$

Table 3 Anti-pruritic activity data of target compounds **3a**–**3s** at a dose of 50 mg/kg

Chemicals	Concentration of histamine (mg/g)	Percent increase relative to (%)	
		Control	Levocetirizine
Control	0.09 ± 0.03	–	–
Levocetirizine	0.42 ± 0.35[b]	383.54	–
3a	0.09 ± 0.07	6.40	−78.00
3b	0.85 ± 0.78[c]	883.81	103.46[d]
3c	0.46 ± 0.47[b]	429.01	9.40
3d	0.34 ± 0.29[a]	292.61	−18.80
3e	0.17 ± 0.13	92.07	−60.28
3f	0.43 ± 0.42[b]	395.87	2.55
3g	1.33 ± 0.31[c]	1436.72	217.80[f]
3h	0.68 ± 0.56[b]	686.34	62.62
3i	0.33 ± 0.38	279.65	−21.49
3j	0.46 ± 0.57[b]	432.37	10.10
3k	0.76 ± 0.50[c]	783.62	82.74[d]
3l	0.43 ± 0.45[b]	395.34	2.44
3m	0.34 ± 0.32[a]	296.34	−18.04
3n	0.42 ± 0.45[b]	382.83	−0.15
3o	0.87 ± 0.58[c]	901.67	107.15[d]
3p	0.59 ± 0.48[b]	576.61	39.93
3q	0.60 ± 0.52[b]	593.50	43.42
3r	0.51 ± 0.30[b]	493.36	22.71
3s	0.89 ± 0.37[c]	933.80	113.80[e]

Comparison with control group: [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$
Comparison with levocetirizine group: [d] $P < 0.05$, [e] $P < 0.01$, [f] $P < 0.001$

(Table 3). Compounds **3b**, **3g**, **3k**, **3o**, and **3s** were more active than levocetirizine, and compounds **3c**, **3f**, **3h**, **3j**, **3l**, **3n**, **3p**, **3q**, and **3r** showed anti-pruritic activities similar to levocetirizine.

The activities of **3b** and **3k** were significantly superior to those of **3a** and **3j**. Intermediates **2a** and **2b** were linked to the amino N position of the sulfonamide, generating **3b** and **3k**, respectively, whereas intermediates **2a** and **2b** were linked to the sulfonylamino N position of the sulfonamide, yielding **3a** and **3j**, respectively. The different linking methods generate different configurations of Part C moiety, which plays an important role in enhancing anti-pruritic activities. The type of Part C moiety also plays a significant role in anti-pruritic and anti-asthmatic activities (Scheme 2; Tables 2, 3). For example, both compounds **3r** and **3s**, with amino acid groups, showed very strong anti-pruritic (Table 3), as well as anti-asthmatic activities (Table 2).

Conclusion

A series of levocetirizine analogs were successfully synthesized and characterized through IR, ^{1}H NMR, MS, and elemental analyses. Results of in vivo biological tests show that compounds **3d**, **3i**, and **3r** had significantly more potent anti-allergic asthma activities than levocetirizine, whereas compounds **3b**, **3g**, **3k**, **3o**, and **3s** exhibited stronger anti-pruritic activities than levocetirizine. Compounds **3r** and **3s**, having amino acid groups as Part C moiety, showed very strong anti-pruritic and anti-asthmatic activities, which warrants the synthesis of more amino acid analogs and the further study of their biological activities. These suggest that the given target compounds with more potent activities than levocetirizine are worthy of further evaluation by more biological tests.

Experimental protocols

Chemistry

IR spectra were recorded on a JASCO IR Report 100 (KBr), and ^{1}H NMR spectra were recorded on a Brucker

Avance (500 MHz) instrument. Chemical shifts were reported in parts per million (ppm) using tetramethyl silane as internal standard. All protons were confirmed by the addition of $DCCl_3$, except in compounds **3f**, **3h**, and **3s**, in which protons were confirmed by the addition of CD_3OD. Elemental analyses (C, H, and N) were conducted with a Perkin–Elmer model 240C analyzer, and all analyses results were consistent with theoretical values (within ±0.3%), unless otherwise indicated. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel GF254-coated glass plates, visualized by UV light. Mass spectra were obtained with an Agilent 1100 series ion trap mass spectrometer. For all compounds, the mass spectrometer was operated under electron spray ionization mode. Melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. All chemical reagents used in the experiment were of analytical grade and were obtained from Sinopharm Chemical Reagent Co., Ltd.

Synthesis of intermediate 1

The preparation of **1** is in accordance with literature (Wang *et al.*, 2007).

*Synthesis of **2a** and **2b***

A 250 ml round-bottomed flask connected to a reflux condenser was charged with **1** (16 g, 0.056 mol), 1-bromo-3-chloropropane (11 ml, 0.112 mol) (instead of 1-bromo-2-chloroethane used for **2a**), and toluene (120 ml). The mixture was stirred and heated at 55°C until TLC indicated the absence of any starting material. The mixture was cooled to ambient temperature and then filtered. Diluted hydrochloric acid (250 ml) was added to the filtrate while shaking, and the yellow solid was precipitated. The mixture was filtered to remove the yellow solid. The solid was then washed with toluene (60 ml). Subsequently, the yellow solid was transferred to a 1000 ml beaker containing 250 ml of distilled water. The mixture was adjusted to pH 12–13 by sodium hydroxide and extracted with chloroform (3 × 50 ml). The combined organic phases were concentrated using a rotary evaporator (45°C, 40 mmHg), producing 14.2 g (70%) of product **2b** in the form of yellow oil.

*General procedure for the preparation of **3a–3i** and **3j–3q** (Fan et al., 2007; Boos et al., 2006; Girisha et al., 2009)*

Piperazine derivatives **3a–3i** were prepared by the reaction of appropriate substituted sulfonamides (0.01 mol) and intermediate **2a** (instead of **2b** used for **3j–3q**) with potassium carbonate (0.03 mol) as a catalyst in acetone (50 ml), followed by an overnight reflux period. The mixture was cooled to ambient temperature and was filtered to remove potassium carbonate. After removing the solvent, the residue was purified on a silica gel column eluted with ethyl acetate and petroleum ether (1:1, v/v), yielding products **3a–3i** and **3j–3q**.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[N-(6-chloropyrida zine-3-yl)-N-(4-amino benzenesulfonylamino)]amino]ethylpiperazine (**3a**)*

Yield: 45%. m.p.: 109–112°C. $[\alpha]_D^{30}$: −6.46 (c = 1, EtOH). IR (KBr) cm^{-1}: 3462, 3384, 3219 (N–H), 3057, 3025 (Ar–H), 2944, 2877, 2804 (–CH_2–) 1625, 1597, 1481, 1449 (aromatic ring); ^{1}H-NMR ($CDCl_3$) δ: 2.20–2.42 (m, 6H), 2.59 (t, J = 6.4, 2H), 4.05 (t, J = 6.7, 2H), 4.14 (s, 1H), 4.22 (t, 2H), 6.61 (d, J = 8.7, 2H), 7.41 (d, J = 8.7, 2H), 7.46 (d, J = 9.2, 1H), 7.86 (d, J = 9.2, 1H), 7.20–7.84 (m, 9H), 7.28(s, $CDCl_3$). MS *m/z*: 597.4 (M^+). Anal. Calcd for $C_{29}H_{30}Cl_2N_6O_2S$: C, 58.29; H, 5.30; N, 14.07; Found: C, 58.60; H, 5.21; N, 14.12.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[4-[N-(6-chloropyridazine-3-yl amino] sulfonyl] phenylamino]ethylpiperazine (**3b**)*

Yield: 51%. m.p.: 120–122° C. $[\alpha]_D^{30}$: −7.13 (c = 1, EtOH). IR (KBr) cm^{-1}: 3452, 3364, 3229 (N–H), 3058, 3025 (Ar–H), 2955, 2879, 2809 (–CH_2–), 1616, 1594, 1529, 1492 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.20–2.75 (m, 8H), 3.95 (s, 2H), 4.15 (s, 1H), 4.34 (t, J = 6.7, 2H), 6.55 (d, J = 8.6, 2H), 7.68 (d, J = 8.6, 2H), 8.24 (d, J = 9.5, 1H), 7.22–7.39 (m, 10H), 7.28 (s, $CDCl_3$). MS *m/z*: 597.2 (M^+). Anal. Calcd for $C_{29}H_{30}Cl_2N_6O_2S$: C, 58.29; H, 5.30; N, 14.07; Found: C, 58.37; H, 5.32; N, 13.89.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[N-(thiazole-2-yl)-N-(4-aminophenylsulfonyl)] amino]ethylpiperazine (**3c**)*

Yield: 42%. m.p.: 96–98°C. $[\alpha]_D^{30}$: −4.33 (c = 1, EtOH). IR (KBr) cm^{-1}: 3448, 3383, 3219 (N–H), 3057, 3025 (Ar–H), 2959, 2877, 2809 (–CH_2–), 1631, 1594, 1488, 1448 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.37–2.55(m, 6H), 2.70 (t, J = 7.0, 2H), 4.03(t, J = 7.5, 2H), 4.21 (d, 3H), 6.60 (d, J = 8.7, 2H), 7.60 (d, J = 8.7, 2H), 6.97 (d, J = 3.6, 1H), 7.19–7.38 (m, 10H), 7.28 (s, $CDCl_3$). MS *m/z*: 582.1 (M^+). Anal. Calcd for $C_{28}H_{30}ClN_5O_2S_2$: C, 57.75; H, 5.50; N, 12.03; Found: C, 57.58; H, 5.35; N, 11.86.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[4-[N-(thiazole-2-yl)amino]sulfonyl]phenyl amino]ethylpiperazine (**3d**)*

Yield: 64%. m.p.: 110–112°C. $[\alpha]_D^{30}$: −5.76 (c = 1, EtOH). IR (KBr) cm^{-1}: 3451, 3369, 3237 (N–H), 3058, 3025 (Ar–H), 2956, 2879, 2809 (–CH_2–), 1625, 1594, 1501, 1435 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.32–2.44(m, 8H), 2.62 (t, J = 6.0, 2H), 4.01 (m, 4H), 4.15(s, 1H), 6.38 (d, J = 4.7, 1H), 6.91 (d, J = 4.7, 1H), 6.60 (d, J = 8.7, 2H), 7.72 (d, J = 8.7, 2H), 7.20–7.37 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 582.1 (M^+). *Anal.* Calcd for $C_{28}H_{30}ClN_5O_2S_2$: C, 57.75; H, 5.50; N, 12.03; Found: C, 57.25; H, 5.41; N, 12.12.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[4-[N-(4,6-dimethylpyrimidine-2-yl)amino] sulfonyl]phenylamino]ethylpiperazine (**3e**)*

Yield: 61%. m.p.: 115–117°C. $[\alpha]_D^{30}$: −6.23 (c = 1, EtOH). IR (KBr) cm^{-1}: 3443, 3382 (N–H), 3059, 3024 (Ar–H), 2953, 2883, 2809 (-CH_2-, -CH_3), 1625, 1594, 1555, 1493 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 6H), 2.38–2.75 (m, 6H), 2.81 (t, J = 7.2, 2H), 4.10 (s, 2H), 4.24 (s, 1H), 4.35 (t, J = 7.2, 2H), 6.55 (s, 1H), 6.62 (d, J = 8.6, 2H), 7.96 (d, J = 8.6, 2H), 7.20–7.94 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 591.2 (M^+). Anal. Calcd for $C_{31}H_{35}N_6O_2S$: C, 62.97; H, 5.92; N, 14.22; Found: C, 62.74; H, 5.85; N, 14.50.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[(4-amino)sulfonyl]phenylamino]ethyl piperazine (**3f**)*

Yield: 71%. m.p.: 72–75°C. $[\alpha]_D^{30}$: −5.02 (c = 1, EtOH). IR (KBr) cm^{-1}: 3461, 3382, 3243 (N–H), 3059, 3024 (Ar–H), 2938, 2875, 2815 (–CH_2–), 1627, 1596, 1503, and 1452 (atomatic ring). ^{1}H-NMR (CD_3OD) δ: 2.43 (m, 8H), 2.92 (t, J = 7.0, 2H), 3.32 (t, J = 1.4, 2H), 4.24 (s, 1H), 6.67 (d, J = 8.2, 2H), 7.52 (d, J = 8.2, 2H), 7.20–7.39 (m, 9H), 4.88 (s, CD_3OD). MS *m/z*: 485.2 (M^+). Anal. Calcd for $C_{25}H_{29}ClN_4O_2S$: C, 61.92; H, 5.99; N, 11.56; Found: C, 61.91; H, 6.12; N, 11.36.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[4-[N-(pyrimidine-2-yl)amino]sulfonyl]phenyl amino]ethylpiperazine (**3g**)*

Yield: 60%. m.p.: 110–112°C. $[\alpha]_D^{30}$: −8.13 (c = 1, EtOH). IR (KBr) cm^{-1}: 3465, 3378, 3222 (N–H), 3059, 3038 (Ar–H), 2958, 2875, 2809 (–CH_2–), 1625, 1601, 1487, 1438 (atomatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.20–2.65 (m, J = 7.2, 6H), 2.82 (m, 2H), 4.13 (s, 2H), 4.24 (s, 1H), 4.35 (t, 2H), 6.61 (d, J = 8.7, 2H), 7.94 (d, J = 8.7, 2H), 6.83 (t, J = 4.8, 1H), 8.42 (d, J = 4.8, 2H), 7.20–7.43 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 563.2 (M^+). Anal. Calcd for $C_{29}H_{31}ClN_6O_2S$: C, 61.87; H, 5.51; N, 14.93; Found: C, 61.70; H, 5.42; N, 15.12.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[N-(6-methoxypyridazine-3-yl)-N-(4-amino benzenesulfonyl)]amino]ethylpiperazine (**3h**)*

Yield: 40%. m.p.: 95–97°C. $[\alpha]_D^{30}$: −6.20 (c = 1, EtOH). IR (KBr) cm^{-1}: 3437 (N–H), 3062, 3024 (Ar–H), 2927, 2812 (–CH_2–, –CH_3), 1632, 1598, 1459, 1452 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.20–2.42 (m, 6H), 2.53 (t, J = 6.4, 2H), 2.93 (t, J = 6.6, 2H), 4.11 (s, 3H), 4.13 (s, 2H), 4.14 (s, 1H), 6.61 (t, J = 8.7, 2H), 6.99 (d, J = 8.7, 1H), 7.70 (d, J = 8.7, 2H), 7.72 (d, J = 8.2, 1H), 7.23–7.39 (m, 9H), 7.27 (s, $CDCl_3$). MS *m/z*: 593.3 (M^+). Anal. Calcd for $C_{30}H_{33}ClN_6O_3S$: C, 60.76; H, 5.57; N, 14.18; Found: C, 60.94; H, 5.56; N, 14.01.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[2-[4-[N-(6-methoxypyridazine-3-yl)amino] sulfonyl]phenylamino]ethylpiperazine (**3i**)*

Yield: 42%. m.p.: 102–104°C. $[\alpha]_D^{30}$: −5.63 (c = 1, EtOH). IR (KBr) cm^{-1}: 3447, 3368, 3240 (N–H), 3055, 3031(Ar–H), 2941, 2870, 2809 (–CH_2–, –CH_3), 1636, 1594, 1501, 1452 (aromatic ring) ^{1}H-NMR ($CDCl_3$) δ: 2.30–2.48 (m, 6H), 2.75 (t, J = 6.2, 2H), 3.83 (s, 3H), 3.90 (s, 2H), 4.16 (s, 1H), 4.31 (t, J = 6.2, 2H), 6.54 (d, J = 8.3, 2H), 6.97 (d, J = 10.0, 2H), 7.70 (d, J = 8.3, 2H), 8.20 (d, J = 10.0, 1H), 7.21–7.60 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 593.2 (M^+). Anal. Calcd for $C_{30}H_{33}ClN_6O_3S$: C, 60.76; H, 5.57; N, 14.18; Found: C, 60.85; H, 5.48; N, 14.25.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[N-(6-chloropyrida zine-3-yl)-N-(4-amino benzenesulfonyl)]amino]propylpiperazine (**3j**)*

Yield: 43%. m.p.: 91–92°C. $[\alpha]_D^{30}$: −6.88 (c = 1, EtOH). IR (KBr) cm^{-1}: 3440 (N–H), 3051, 3023 (Ar–H), 2948, 2882, 2813 (–CH_2–), 1630, 1597, 1503, 1484 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (m, 2H), 2.23 (m, 8H), 3.97 (d, J = 9.4, 2H), 4.19 (s, 1H), 4.22 (t, J = 9.4, 2H), 6.61 (d, J = 8.7, 2H),7.47 (d, J = 9.4, 1H), 7.89 (d, J = 9.4, 1H), 7.20–7.38 (m, 11H), 7.27 (s, $CDCl_3$). MS *m/z*: 611.3 (M^+). Anal. Calcd for $C_{30}H_{32}Cl_2N_6O_2S$: Calculated: C, 58.91; H, 5.24; N, 13.75; Found: C, 58.97; H, 5.63; N, 13.86.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[4-[N-(6-chloropyridazine-3-yl)amino]sulfonyl] phenylamino]propylpiperazine (**3k**)*

Yield: 42%. m.p.: 106–107°C. $[\alpha]_D^{30}$: −7.17 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3441, 3368, 3233 (N–H), 3061, 3024 (Ar–H), 2952, 2882, 2806 (–CH_2–), 1619, 1597, 1528, 1488 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (m, 2H), 2.30–2.40 (m, 8H), 3.86 (s, 2H), 4.18 (s, 1H), 4.30 (ddd, $J = 7.7$, $J = 3.9$, 2H), 6.53 (d, $J = 8.6$, 2H),7.68 (d, $J = 8.6$, 2H), 7.20 (d, $J = 9.8$, 1H), 8.25 (d, $J = 9.8$, 1H), 7.23–7.38 (m, 9H), 7.27 (s, $CDCl_3$). MS *m/z*: 611.3 (M^+). Anal. Calcd for $C_{30}H_{32}Cl_2N_6O_2S$: C, 58.91; H, 5.24; N, 13.75; Found: C, 58.85; H, 5.23; N, 14.02.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[N-(thiazole-2-yl)-N-(4-aminobenzene sulfonyl)]amino]propylpiperazine (**3l**)*

Yield: 40%. m.p.: 97–99°C. $[\alpha]_D^{30}$: −8.80 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3447, 3385, 3213 (N–H), 3069, 3022 (Ar–H), 2956, 2875, 2805 (–CH_2–), 1625, 1594, 1497, 1458 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.88 (m, 2H), 2.44 (m, 8H), 3.93 (t, $J = 7.0$, 2H), 4.20 (s, 3H), 6.61 (d, $J = 7.1$, 2H), 6.98 (d, $J = 3.4$, 1H), 7.20–7.39 (m, 10H), 7.56 (d, $J = 8.1$, 2H), 7.27 (s, $CDCl_3$). MS *m/z*: 597.2 (M^+). Anal. Calcd for $C_{29}H_{32}ClN_5O_2S_2$: C, 58.41; H, 5.71; N, 11.75; Found: C, 58.56; H, 5.62; N, 11.69.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[4-[N-(thiazole-2-yl)amino]sulfonyl] phenylamino]propylpiperazine (**3m**)*

Yield: 63%. m.p.: 107–109°C. $[\alpha]_D^{30}$: −3.63 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3455, 3369, 3237 (N–H), 3059, 3024 (Ar–H), 2953, 2879, 2809 (–CH_2–), 1629, 1598, 1505, 1431 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.84 (m, 2H), 2.26 (t, $J = 7.4$, 2H), 2.33 (m, 6H), 3.98 (m, 4H), 4.19 (s, 1H), 6.38 (d, $J = 4.7$, 1H), 6.56 (d, $J = 8.5$, 2H), 6.83 (d, $J = 4.7$, 1H), 7.71 (d, $J = 8.5$, 2H), 7.19–7.38 (m, 9H), 7.27 (s, $CDCl_3$). MS *m/z*: 597.2 (M^+). Anal. Calcd for $C_{29}H_{32}ClN_5O_2S_2$: C, 58.41; H, 5.71; N, 11.75; Found: C, 58.47; H, 5.82; N, 11.81.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[4-[N-(4,6-dimethylpyrimidine-2-yl)amino] sulfonyl]phenylamino]propylpiperazine (**3n**)*

Yield: 65%. m.p.: 213–215°C. $[\alpha]_D^{30}$: −4.50 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3465, 3364, 3250 (N–H), 3062, 3024 (Ar–H), 2958, 2875, 2816 (–CH_2–, –CH_3), 1636, 1598, 1560, 1445 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (m, 2H), 2.29 (s, 6H), 2.30–2.62 (m, 8H), 4.11 (s, 2H), 4.22 (s, 1H), 4.25 (s, 2H), 6.53 (s, 1H), 6.61 (d, $J = 8.7$, 2H), 7.88 (d, $J = 8.7$, 2H), 7.19–7.39 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 605.1 (M^+). Anal. Calcd for $C_{32}H_{37}ClN_6O_2S$: C, 63.49; H, 6.12; N, 13.89; Found: C, 63.47; H, 6.35; N, 13.75.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[(4-amino)sulfonyl]phenylamino]propyl piperazine (**3o**)*

Yield: 59%. m.p.: 73–75°C. $[\alpha]_D^{30}$: −6.41 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3465, 3371, 3243 (N–H), 3062, 3027(Ar–H), 2955, 2878, 2812(–CH_2–), 1625, 1598, 1487, 1448 (aromatic ring). ^{1}H-NMR (CD_3OD) δ: 1.61 (m, 2H), 2.43 (m, 8H), 2.92 (t, $J = 7.0$, 2H), 3.32 (t, $J = 1.4$, 2H), 4.24 (s, 1H), 6.67 (d, $J = 8.2$, 2H), 7.52 (d, $J = 8.2$, 2H), 7.20–7.39 (m, 9H), 4.88 (s, CD_3OD). MS *m/z*: 499.2 (M^+). Anal. Calcd for $C_{26}H_{31}ClN_4O_2S$: C, 65.59; H, 6.22; N, 11.23; Found: C, 62.32; H, 6.31; N, 11.33.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[4-[N-(pyrimidine-2-yl)amino] sulfonyl] phenylamino]propylpiperazine (**3p**)*

Yield: 50%. m.p.: 109–111°C. $[\alpha]_D^{30}$: −6.23 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3468, 3375, 3243 (N–H), 3062, 3027 (Ar–H), 2955, 2882, 2816 (–CH_2–), 1625, 1598, 1483, 1448 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, $J = 7.0$, 2H), 2.05 (t, $J = 7.0$, 2H), 2.45–2.51 (m, 6H), 3.75 (q, $J = 7.0$, 1H), 4.14 (s, 1H), 4.25 (t, $J = 7.0$, $J = 9.4$, 3H), 6.62 (t, $J = 7.5$, 2H), 6.82 (d, 1H), 7.86 (t, $J = 7.5$, 1H), 8.41 (d, $J = 4.6$, 2H), 7.19–7.39 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 577.2 (M^+). Anal. Calcd for $C_{30}H_{33}ClN_6O_3S$: C, 62.45; H, 5.72; N, 14.57; Found: C, 62.60; H, 5.79; N, 14.78.

*(R)(-)-1-[(4-chlorophenyl)phenyl]methyl-4-[3-[4-[N-(6-methoxypyridazine-3-yl)amno] sulfonyl]phenylamino]propylpiperazine (**3q**)*

Yield: 53%. m.p.: 101–103°C. $[\alpha]_D^{30}$: −5.12 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3450, 3361, 3222 (N–H), 3055, 3024 (Ar–H), 2939, 2875, 2810 (–CH_2–, –CH_3), 1631, 1596, 1501, 1452 (aromatic ring). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (m, 2H), 2.43 (m, 8H), 3.83 (s, 3H), 3.85 (s, 2H), 4.19 (s, 1H), 4.25 (t, $J = 6.2$, 2H), 6.55 (d, $J = 8.6$, 2H), 7.70 (d, $J = 8.6$, 2H), 6.97 (d, $J = 9.4$, 1H), 8.21 (d, $J = 9.4$, 1H), 7.20–7.39 (m, 9H), 7.28 (s, $CDCl_3$). MS *m/z*: 607.2 (M^+). Anal. Calcd for $C_{31}H_{35}ClN_6O_3S$: C, 61.34; H, 5.77; N, 13.85; Found: C, 61.12; H, 5.86; N, 13.69.

*General procedure for the preparation of **3r** and **3s***

Glycine methyl ester (0.89 g, 0.01 mol) (instead of L-alanine methyl ester used for **3s**) was added to a stirring solution of TEA (4 ml, 0.028 mol) and **2b** (3.63 g,

0.01 mol) in acetonitrile (30 ml). When TLC analysis showed no remaining starting material, the mixture was filtered to remove the triethylamine hydrochloride. The filtrate was concentrated using a rotary evaporator (40°C, 40 mmHg). The residue was dissolved in chloroform (30 ml) and then washed with water (3 × 20 ml). After chloroform was removed, methanol (20 ml) and 2N sodium hydroxide (10 ml) were added to the residue, stirred at room temperature for 6 h, and evaporated to remove methanol under reduced pressure. The pH value was adjusted to 5 with dilute hydrogen chloride, extracted with chloroform (3 × 20 ml). The organic layer was washed with brine (3 × 20 ml), dried overnight with magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified on a silica gel column eluted with ethanol and chloroform (1:2, v/v), producing product **3r** (**3s**).

*(R)(-)-2-[3-[4-(4-chlorophenyl)phenylmethyl]piperazine-1-yl]propylamino acetic acid (**3r**)*

Yield: 54%. m.p.: 111–113°C. $[\alpha]_D^{30}$: −5.58 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3430 (N–H), 3180–2521 (COO–H), 3059, 3024 (Ph–H), 2962, 2817 (–CH_2–), 1624, 1486, 1449 (benzene ring). ^{1}H-NMR (CD_3OD) δ: 1.79–1.88 (m, 2H), 2.52–2.70 (m, 10H), 3.08 (d, $J = 8.4$, 2H), 3.14 (d, $J = 5.8$, 1H), 3.48 (d, $J = 7.2$, 1H), 4.32 (s, 1H), 7.18–7.46 (m, 9H), 7.29 (t, $J = 4.8$, 4H), 7.40–7.45 (m, 4H), 4.88 (s, CD_3OD). MS *m/z*: 402.2 (M^+). Anal. Calcd for $C_{22}H_{28}ClN_3O_2$: C, 65.75; H, 6.97; N, 10.46; Found: C, 65.45; H, 6.88; N, 10.52.

*(R)(-)-2-[3-[4-(4-chlorophenyl)phenylmethyl]piperazine-1-yl]propylamino propanoic acid (**3s**)*

Yield: 52%. m.p.: 125–126°C. $[\alpha]_D^{30}$: −6.00 ($c = 1$, EtOH). IR (KBr) cm^{-1}: 3420 (N–H), 3199–2500 (COO–H), 3059, 3027 (Ph–H), 2953, 2875, 2809 (–CH_2–, –CH_3), 1622, 1489, 1454 (benzene ring). ^{1}H-NMR (CD_3OD) δ: 1.46 (d, $J = 7.2$, 3H), 1.79–1.88 (m, 2H), 2.52–2.70 (m, 10H), 3.08 (d, $J = 8.4$, 2H), 3.13 (d, $J = 5.8$, 1H), 3.49 (d, $J = 7.2$, 1H), 4.32 (s, 1H), 7.19–7.46 (m, 9H), 4.88 (s, CD_3OD). MS *m/z*: 416.2 (M^+). Anal. Calcd for $C_{23}H_{30}ClN_3O_2$: C, 66.43; H, 7.22; N, 10.11; Found: C, 66.67; H, 7.35; N, 10.24.

Anti-allergic activity

All synthesized compounds were tested for anti-allergic activities using cavies, purchased from Center of Animal Research in Guangxi Medical University. The cavies had a weight range of 200 ± 20 g. The tested compounds were dispersed in distilled water at a concentration of 10 mg/ml.

Anti-asthmatic activity

Cavies were divided into 23 groups ($n = 10$/group). The administration group was fed with 5 ml/kg (10 mg/ml, i.e., 50 mg/kg) of the target compounds, while the positive control group was orally administered with levocetirizine (50 mg/kg). Meanwhile, the blank control group was given distilled water of equal volumes. One hour after administration, all the cavies were treated with histamine phosphate (0.2%) in the state of ultrasonic pulverization for 20 s. The latent period of asthma was recorded, and final data were statistically analyzed (Table 2).

Anti-pruritic activity

The experimental animals were divided into 23 groups ($n = 10$/group). The administration group was fed with 5 ml/kg (10 mg/mL, i.e., 50 mg/kg) of the target compounds, while the positive control group was orally administered with levocetirizine (50 mg/kg). Meanwhile, the blank control group was given distilled water of equal volumes. One hour after administration, histamine phosphate (0.05 ml, 0.01%) was dropped on the scraped right hind feet of the cavies; the amount of histamine phosphate was increased by 0.01, 0.02, 0.03, 0.04, and 0.05% every 3 min until the cavies began licking their right hind foot. The total amount of histamine phosphate was recorded, and final data were statistically analyzed (Table 3).

Acknowledgments The work was supported by the Scientific Research Startup Foundation of Chinese Ministry of Education for Returnee (*jiaowaisiliu*-2007-1108) and the Scientific Research Startup Foundation of Guangxi University (X071038).

References

Akdis M (2009) Immune tolerance in allergy. Curr Opin Immunol 21:1–8

Banu Y, Watanabe T (1999) Augmentation of antigen receptor–mediated responses by histamine H1 receptor signaling. J Exp Med 189:673–682

Boos TL, Greiner E, Jason Calhoun W et al (2006) Structure–activity relationships of substituted *N*-benzyl piperidines in the GBR series: synthesis of 4-(2-(bis(4-fluorophenyl)methoxy)ethyl)-1-(2-trifluoromethylbenzyl) piperidine, an allosteric modulator of the serotonin transporter. Bioorg Med Chem 14:3967–3973

Day JH, Ellis AK, Rafeiro E (2004) Levocetirizine: a new selective H1 receptor antagonist for use in allergic disorders. Drugs Today 40:415–423

De Bruin ML, van Puijenbroek EP, Egberts ACG et al (2002) Non-sedating antihistamine drugs and cardiac arrhythmias-biased risk estimates from spontaneous reporting systems? Br J Clin Phamcol 53:370–374

Devalia JL, De Vos C, Hanotte F et al (2001) A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. Allergy 56:50–57

Fan H, Xu G, Chen Y et al (2007) Synthesis and antibacterial activity of oxazolidinones containing triazolyl group. Eur J Med Chem 42:1137–1143

Gandon JM, Allain H (2002) Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. Br J Clin Pharmacol 54:51–58

Girisha HR, Narendra Sharath Chandra JN, Boppana S et al (2009) Active site directed docking studies: synthesis and pharmacological evaluation of cis-2,6-dimethyl piperidine sulfonamides as inhibitors of acetylcholinesterase. Eur J Med Chem 44:4057–4062

Hancock AA (2006) The challenge of drug discovery of a GPCR target: analysis of preclinical pharmacology of histamine H3 antagonists/inverse agonists. Biochem Pharmacol 71:1103–1113

Husain A (2009) Amide derivatives of sulfonamides and isoniazid: synthesis and biological evaluation. Acta Pol Pharm 66:513–521

Ishiwata K, Kawamura K, Wang W-F et al (2004) Evaluation of in vivo selective binding of [^{11}C] doxepin to histamine H_1 receptors in five animal species. Nucl Med Biol 31:493–502

Kayasuga R, Sugimoto Y, Watanabe T et al (2002) Histamine H1 receptors are involved in mouse nasal allergic responses: a demonstration with H1 receptor-deficient mice. Int Immunopharmacol 2:745–750

Li X-M, Brown L (2009) Efficacy and mechanisms of action of traditional Chinese medicines for treating asthma and allergy. J Allergy Clin Immunol 123:297–306

Lloret GR, Neto ÁC, Rittner R et al (2009) Synthesis and rational design of anti-inflammatory compounds: *N*-phenyl-cyclohexenyl sulfonamide derivatives. J Phys Org Chem 22:1188–1192

Mavrova ATs, Anichina KK, Vuchev DI et al (2006) Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-1H-benzimidazol-2-ylthioacetylpiperazine derivatives. Eur J Med Chem 41:1412–1420

Mullins RJ, Dear KBG, Tang MLK (2009) Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007. J Allergy Clin Immunol 123:689–693

Sicherer SH, Leung DYM (2009) Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2008. J Allergy Clin Immunol 123:319–327

Slater JW, Zechnich AD, Haxby DG (1999) Second-generation antihistamines: a comparative review. Drugs 57(1):31–47

Smith HE, Hogger C, Lallemant C et al (2009) Is structured allergy history sufficient when assessing patients with asthma and rhinitis in general practice? J Allergy Clin Immunol 123:646–650

Wang DY, Hanotte F, De Vos C et al (2001) Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. Allergy 56:339–343

Wang L-S, Wand T-W, Zhu H-Y (2007) Synthesis of levocetirizine. J Guangxi Univ (Nat Sci Ed) 32:384–386