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Novel hybrids of natural isochroman-4-one bearing N-substituted isopropanolamine as potential antihypertensive candidates

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ABSTRACT

A series of novel hybrids of natural isochroman-4-one bearing isopropanolamine moiety were designed, synthesized and evaluated for their antihypertensive activity. It was found that compound **IIId**, prepared by hybridizing *N*-isopropyl substituted isopropanolamine functionality to a phenolic oxygen of isochroman-4-one, exhibited potent β_1-adrenoceptor blocking effect comparable to the well-known antihypertensive drug propranolol. Additionally, **IIId** significantly reduced the systolic and diastolic blood pressure in SHRs by over 40%, which was obviously stronger than the lead compounds 7,8-dihydroxy-3-methyl-isochroman-4-one (XJP) and its analogue XJP-B. Overall, **IIId** may be a promising antihypertensive candidate for further investigation.

1. Introduction

Hypertension, the most common cardiovascular disease, is a major risk factor in cardiovascular mortality. Intense efforts have been made during the last three decades in the development of new antihypertensive agents with different mechanism of action.[1] Searching for the active natural products from plants is always an important strategy for development of new antihypertensive drugs.[2] The banana peel has been widely used as a folk medicine for the treatment of hypertension, fungous infection and constipation in China. Previously, we have firstly reported a novel and structurally unique isochroman-4-one, (±)-7,8-dihydroxy-3-methyl-isochroman-4-one [(±)-XJP], isolated from the banana (*Musa sapientum* L.) peel, which displayed potent antihypertensive activity in both acute and therapeutic antihypertensive tests in renal hypertensive rats (RHRs).[3,4] In the further structure modification, we synthesized (±)-XJP-B, an analogue of (±)-XJP (Fig. 1), which was more active than (±)-XJP in SHRs. Later on, we prepared *R*-(−)-XJP and *S*-(+)-XJP by chiral separation of (±)-XJP and found that these two enantiomers possess similar pharmacodynamic effects, whereas the *R*-(−)-XJP is somewhat more potent than *S*-(+)-XJP in a few cases.[5] Searching for new isochroman-4-one derivatives and analogues with potential antihypertensive properties has remained our interest for the last several years and has been documented by several publications.[6] However, the antihypertensive effects of both (±)-XJP and (±)-XJP-B are still not potent enough for therapeutic use.

The β-receptor blockers, one of the oldest available classes of cardiovascular drugs, has established efficacy in achieving blood pressure (BP) control.[7] The therapeutic effects of β-receptor blockers are normally explained by their capacity to block the β-adrenoceptors, hindering the access of the endogenous agonists noradrenaline and adrenaline.[8] Since propranolol was commercially available in 1976, more than a dozen additional β-receptor blockers have been clinically utilized worldwide.[9,10]

Most of the clinically useful β-adrenoceptor antagonists contain a phenoxypropanolamine moiety, typically with isopropyl or *tert*butyl as an N-substituent, linked to an aromatic or heterocyclic ring system. Although the basic aryloxypropanolamine nucleus should remain intact for significant β-adrenoceptor antagonist activity, a wide variety of aromatic ring or nitrogen substituents can be tolerated.[11,12] When an isopropanolamine moiety, the classic side chain of β-blockers, is attached to the phenolic hydroxyl of (±)-XJP and (±)-XJP-B, the structure of the derivatives obtained quite resembles that of classic β-blockers (for instance,

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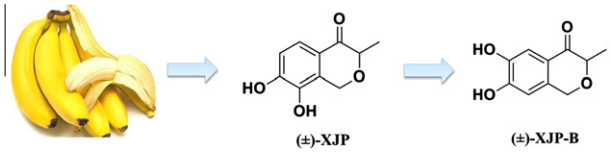


Figure 1. The structures of (±)-XJP and (±)-XJP-B.

propranolol and indolol) (Fig. 2). Therefore, we attempted to connect various N-substituted isopropanolamine functionalities to a phenolic oxygen of (±)-XJP or (±)-XJP-B, and synthesized a series of novel hybrids of isochroman-4-one derivatives. Herein, we report the synthesis and biological evaluation of these hybrids of isochroman-4-one derivatives.

2. Results and discussions

2.1. Chemistry

(±)-XJP, (±)-XJP-B and their intermediates **8**–**10** were synthesized by the similar route reported by our group.[3,4] And intermediate compounds **5**, **6**, and **8**–**10** were prepared as shown in Schemes 1 and 2. Substituted benzaldehyde **1** was reduced by sodium borohydride to the corresponding benzyl alcohol **2**. Subsequent alkylation of **2** with ethyl 2-bromopropionate in the presence of NaH followed by saponification of the ethyl ester provided acid **4**, which was treated with *n*-butyllithium in THF at −85 °C to provide ring-closing compounds **5** and **6**. After deprotection of methyl ethers **5** and **6** by using aluminum chloride, the phenolic compounds **8**–**10** were obtained.

The synthetic route of the target compounds **Ia–g**, **IIa–g** and **IIIa–g** was depicted in Scheme 3.[13–16] Compounds **8–10** were treated with epichlorohydrin in the presence of potassium carbonate to give corresponding epoxides **11**–**13**. Subsequent ring opening of the epoxides with various amines afforded the target compounds **Ia–g**, **IIa–g** and **IIIa–g**, respectively.

2.2. β_1-Adrenoceptor antagonism assay

β_1-Adrenergic blocking activity of the tested compounds was assessed using the rat isolated left atria. As shown in Table 1, the compounds bearing *N*-isopropyl-isopropanolamine or *N*-propyl-isopropanolamine moiety (**Id**, **IIc**, **IId**, **IIIc** and **IIId**) exhibited strong inhibitory activity. The potency of **Id** [(54.7 ± 4.9)%], **IId** [(42.5 ± 3.9)%] and **IIId** [(44.7 ± 5.0)%] was comparable or even superior to the reference drug propranolol [(49.7 ± 3.7)%] at dose of 10^{-7} M. The results demonstrated that selecting the natural isochroman-4-one structure as the aromatic ring can successfully remain the significant β-adrenoceptor blocking activity in the designed derivatives. Extending or shortening the carbon chain of *N*-alkyl may decrease the inhibitory effect, especially exemplified by those possessing *N*-ethyl (**IIb** and **IIIb**), *N*-butyl (**Ie** and **IIe**) or *N*-*tert*-butyl (**If**, **IIf** and **IIf**).

2.3. In vivo evaluation of antihypertensive activity

The active compounds **Id**, **IId** and **IIId** were selected for further evaluation of antihypertensive activity in SHRs (Table 2 and Fig. 3). After oral administration of the control drug propranolol (20 mg/kg), **Id**, **IId**, **IIId**, XJP and XJP-B (80 mg/kg, respectively), the blood pressure and heart rate of SHRs were determined. It was observed that **IIId** showed the strongest antihypertensive activity, and significantly reduced the systolic and diastolic blood pressure in SHRs throughout the observation period. The maximum reduction rate of blood pressure by **IIId** was over 40%, which was comparable to that of propranolol (36%). Moreover, **IIId** reduced the blood pressure much more significantly than the parent compounds XJP and XJP-B. Curiously enough, the other two compounds **Id** and **IId** which were more potent in vitro, reduced the blood pressure not more than 30%. The heart rate changes caused by **Id**, **IId** and **IIId** were much less than that by propranolol, suggesting that the three compounds may possess better cardioprotective effects than propranolol.

2.4. Structure–activity relationships (SARs) analysis

In SARs analysis, it was found: (1) selecting the natural isochroman-4-one structure as the aromatic ring can successfully remain the significant β-adrenoceptor antagonist activity; (2) for β_1-adrenergic blocking activity in vitro, N-substituent of isopropylamine played an important role; (3) compounds bearing isopropylamine or propylamine moiety in their structures exhibited the most potent inhibition; (4) extending or shortening the carbon chain of N-substituents may influence the inhibitory effect; (5) N-substituents at different positions of isochroman-4-one did not cause significantly affect on the β_1-adrenergic blocking activity; (6) when it comes to the evaluation in vivo, the place of substitution played a key role. The most suitable substitution was at the 7-position, and 7-substituted *iso*-propylamine derivatives played much higher antihypertensive activity than 6-substituted and 8-substituted ones.

3. Conclusions

By connecting various N-substituted isopropanolamine functionalies to a phenolic oxygen of the natural product (±)-XJP or its analogue (±)-XJP-B, a series of novel hybrids targeting β-adreno-

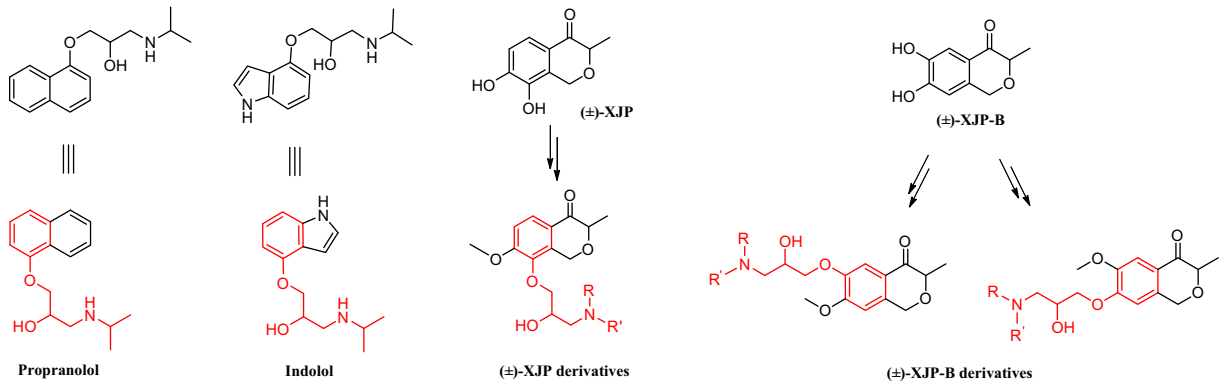
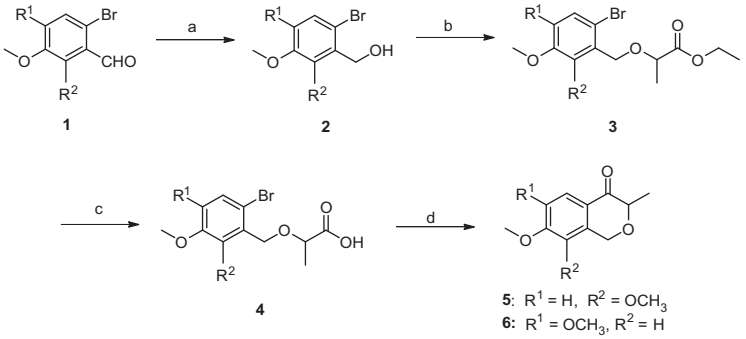
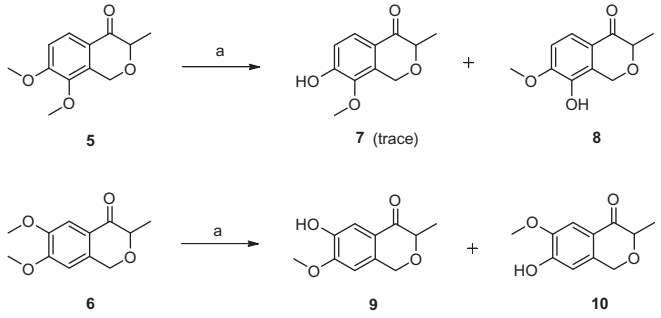


Figure 2. Strategy for the design of β-receptor blockers derived from natural isochroman-4-one.



Scheme 1. Synthetic routes of compound **5** and **6**. Reagents and conditions: (a) anhydrous MeOH, $NaBH_4$, 0 °C, 85–95%; (b) anhydrous DMF, NaH, 0 °C, 75–80%; (c) MeOH, 10% NaOH, rt, then 10% HCl, 85–90%; (d) *n*-BuLi, anhydrous THF, −85 °C to rt, 50–60%.



Scheme 2. Synthetic routes of key intermediates **8**–**10**. Reagents and conditions: (a) $AlCl_3$, NaI, $CHCl_3$, reflux, 50–55%.

ceptor were obtained. Compounds **Id**, **IId** and **IIId** bearing the *N*-isopropyl substituted isopropanolamine moiety exhibited the most powerful β_1-adrenoceptor blocking effects in vitro, which was comparable or superior to the reference drug propranolol. The further antihypertensive evaluation in SHRs showed that **IIId** significantly reduced the systolic and diastolic blood pressure in SHRs by over 40%, which was comparable to propranolol at the higher dose and obviously stronger than the lead compounds XJP and XJP-B at the same doses. Meanwhile, the heart rate changes caused by **IIId** were much less than that by propranolol, suggesting that this compound may possess better cardioprotective effects than propranolol. Biological evaluation proves that the hybrids by introducing *N*-isopropyl substituted isopropanolamine to the natural product isochroman-4-one possess more potent antihypertensive activity. Collectively, the isochroman-4-one ring structure can successfully remain intact for significant β-adrenoceptor antagonist activity. These findings may provide new insights into the development of novel therapeutic agents for the treatment of hypertension.

4. Experimental

4.1. Chemistry

Most chemicals and solvents were of analytical grade and, when necessary, were purified and dried by standard methods. Melting points were taken on an XT-4 micro melting point apparatus and uncorrected. IR spectra were recorded in KBr on a Nicolet Impact 410 grating infrared spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra were recorded with 300 MHz spectrometers in the indicated solvents (TMS as internal standard): the values of the chemical shifts are expressed in δ values (ppm) and the coupling constants (J) in Hz. High-resolution mass spectra were recorded using Agilent QTOF 6520. Purity of all tested compounds was $\geqslant$95%, as estimated by HPLC analysis. The major peak of the compounds analyzed by HPLC accounted for $\geqslant$95% of the combined total peak area when monitored by a UV detector at 254 nm. Flash chromatography was done on Merck silica gel 60 (230–400 mesh).

4.1.1. General procedure for the preparation of compounds 11–13

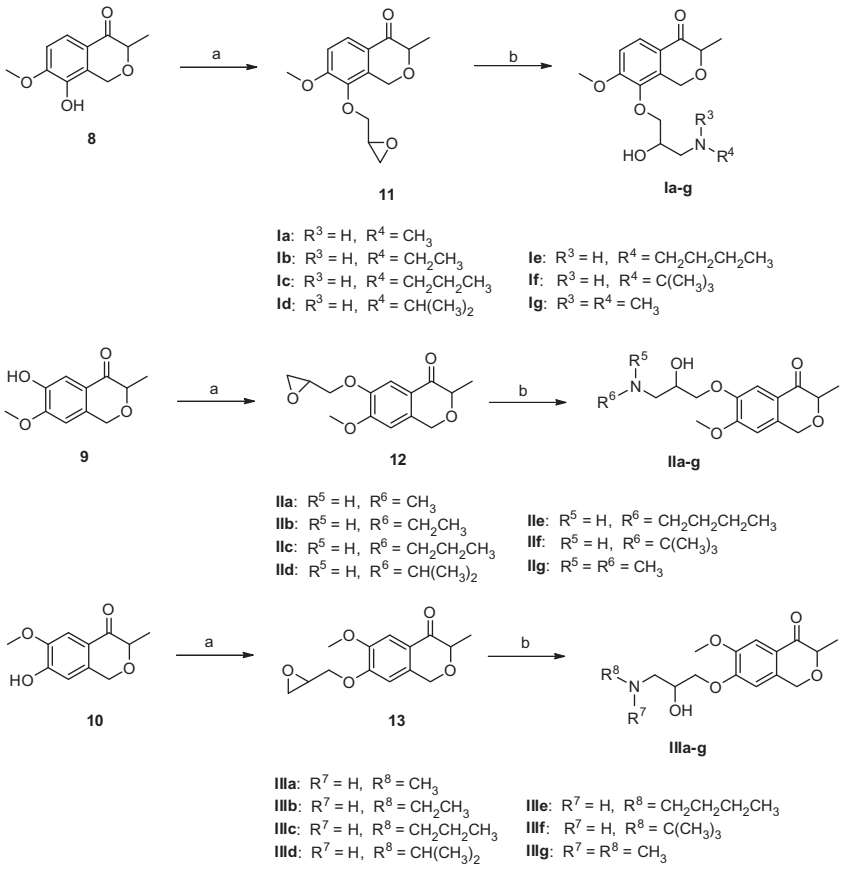
Intermediat **8–10** were synthesized by our reported routes.[3,4]

K_2CO_3 (0.276 g, 2 mmol) was added to a solution of compound **8** (0.208 g, 1 mmol) in anhydrous acetone (10–12 mL) and the mixture was refluxed for 30 min. Then epichlorohydrin (0.32 mL, 4 mmol) was added and the mixture was refluxed for 3 h. After filtrated and concentrated under reduced pressure, followed by purified by flash column chromatography with *n*-hexane/ethyl acetate (5:1, v/v) as eluent, compound **11** was afforded as white solid in yield of 80%. Compounds **12** and **13** were prepared by the above method.

4.1.1.1. 7-Methoxy-3-methyl-8-(oxiran-2-ylmethoxy) isochroman-4-one (11). White power, yield 80%, mp 102–104 °C; IR (KBr), cm^{-1}: 2982, 2931, 2833, 1687, 1593, 1491, 1400, 1337, 1284, 1218, 1123, 1074, 865; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.49 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.66–2.69 (m, 1H, $-CH_2-$), 2.87–2.89 (m, 1H, $-CH_2-$), 3.28–3.31 (m, 1H, –CH–), 3.87–3.98 (m, 1H, $-CH_2-$), 3.96 (s, 3H, $-OCH_3$), 4.19 (q, 1H, J = 6.7 Hz, –CH–), 4.26–4.36 (m, 1H, $-CH_2-$), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.20 (q, 1H, J = 7.5 Hz, $-CH_2-$), 6.93 (d, 1H, J = 8.7 Hz, Ar-H), 7.83 (d, 1H, J = 8.7 Hz, Ar-H); MS (ESI) m/z: 265.1 $[M+H]^+$.

4.1.1.2. 7-Methoxy-3-methyl-6-(oxiran-2-ylmethoxy) isochroman-4-one (12). White power, yield 75%, mp 104–106 °C; IR (KBr), cm^{-1}: 3024, 2844, 1671, 1637, 1602, 1512, 1400, 1358, 1276, 1201, 1110, 870; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.76–2.78 (m, 1H, $-CH_2-$), 2.90–2.93 (m, 1H, $-CH_2-$), 3.38–3.44 (m, 1H, –CH–), 3.93 (s, 3H, $-OCH_3$), 4.00–4.06 (m, 1H, $-CH_2-$), 4.24 (q, 1H, J = 6.7 Hz, –CH–), 4.30–4.35 (m, 1H, $-CH_2-$), 4.85 (s, 1H, $-CH_2-$), 6.62 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H); MS (ESI) m/z: 265.1 $[M+H]^+$.

4.1.1.3. 6-Methoxy-3-methyl-7-(oxiran-2-ylmethoxy) isochroman-4-one (13). White power, yield 82%, mp 98–100 °C; IR (KBr), cm^{-1}: 3001, 2838, 1672, 1602, 1514, 1400, 1279, 1111, 870; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.77–2.79 (m, 1H, $-CH_2-$), 2.92–2.95 (m, 1H, $-CH_2-$), 3.40–3.42 (m, 1H, –CH–), 3.92 (s, 3H, $-OCH_3$), 4.00–4.10 (m, 1H, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.34–4.40 (m, 1H, $-CH_2-$), 4.85 (s, 2H, $-CH_2-$), 6.68 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H); MS(ESI) m/z: 265.1 $[M+H]^+$.



Scheme 3. General synthetic procedure of the target compounds. Reagents and conditions: (a) anhydrous acetone, epichlorohydrin, K_2CO_3, reflux, 75–82%; (b) MeOH, RR′NH, reflux, 75–90%.

Table 1
β_1-Adrenoceptor antagonism in vitro of the synthesized compounds

Compd	Inhibition rate (%)		Compd	Inhibition rate (%)	
	10^{-7} M	10^{-6} M		10^{-7} M	10^{-6} M
Ia	<10	<10	**IIe**	<10	<10
Ib	46.0 ± 4.2	60.7 ± 5.0	**IIf**	14.6 ± 1.4	34.8 ± 3.1
Ic	19.8 ± 2.0	28.9 ± 3.1	**IIg**	22.1 ± 1.4	36.4 ± 3.8
Id	54.7 ± 4.9	79.5 ± 6.2	**IIIa**	<10	<10
Ie	<10	<10	**IIIb**	<10	<10
If	<10	17.3 ± 1.8	**IIIc**	22.4 ± 2.6	47.6 ± 3.8
Ig	<10	<10	**IIId**	44.7 ± 5.0	63.3 ± 5.1
IIa	<10	<10	**IIIe**	36.2 ± 2.6	59.4 ± 4.8
IIb	<10	15.7 ± 1.8	**IIIf**	<10	13.7 ± 2.1
IIc	41.9 ± 3.3	51.9 ± 4.4	**IIIg**	<10	16.4 ± 2.0
IId	42.5 ± 3.9	65.8 ± 4.8	Propranolol	49.7 ± 3.7	73.8 ± 6.8

4.1.2. General procedure for the preparation of compounds Ia–g

Corresponding amine (0.5–0.8 mL) was added to a solution of epoxide **8** (0.264 g, 1 mmol) in methanol (15 mL), respectively. The mixture was refluxed for 2–4 h and then concentrated under reduced pressure, and the residue was recrystallized with *n*-hexane/ethyl acetate (3:1, v/v) to afford compounds **Ia–g** as white solid in yields of 75–88%.

4.1.2.1. 8-(2-Hydroxy-3-(methylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (Ia). White power, yield 77%, mp 109–111 °C; IR (KBr), cm^{-1}: 3276, 2936, 2838, 2802, 1691, 1594, 1491, 1400, 1284, 1270, 1224, 1075, 1030, 793; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.49 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.49 (s, 3H, $-CH_3$), 3.94 (s, 3H, $-OCH_3$), 4.00–4.09 (m, 3H, –CH–, $-CH_2-$), 4.19 (q, 1H, J = 6.7 Hz, –CH–), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.19 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.94 (d, 1H, J = 8.7 Hz, Ar-H), 7.84 (d, 1H, J = 8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.2, 111.0, 77.7, 76.0, 75.8, 68.7, 68.6, 62.8, 55.9, 53.7, 36.4, 15.6; MS (ESI) *m/z*: 296.1 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{15}H_{22}NO_5[M+H]^+$ 296.1492, found 296.1494.

4.1.2.2. 8-(3-Ethylamino-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (Ib). White power, yield 75%, mp 110–112 °C; IR (KBr), cm^{-1}: 2972, 2833, 1691, 1593, 1432, 1400, 1284, 1273, 1123, 1076, 1033, 788; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (t, 3H, J = 7.1 Hz, $-CH_3$), 1.49 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.70–2.87 (m, 4H, $-CH_2-$, $-CH_2-$), 3.93 (s, 3H, $-OCH_3$), 3.80–4.09 (m, 3H, –CH–, $-CH_2-$), 4.19 (q, 1H, J = 6.7 Hz, –CH–), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.19 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.94 (d, 1H, J = 8.6 Hz, Ar-H), 7.84 (d, 1H, J = 8.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.2, 111.0, 77.8, 76.0, 75.8, 68.8, 68.7, 62.9, 55.9, 51.3, 44.1, 15.7, 15.2; MS (ESI) *m/z*: 310.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1652.

4.1.2.3. 8-(2-Hydroxy-3-(propylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (Ic). White power, yield 85%, mp 108–110 °C; IR (KBr), cm^{-1}: 3274, 2944, 2870, 2811, 1690, 1594, 1493, 1399, 1287, 1270, 1230, 1129, 1077, 1026; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, J = 7.4 Hz, $-CH_3$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 1.54–1.57 (m, 2H, $-CH_2-$), 2.56–2.66 (m, 2H, $-CH_2-$), 2.72–2.85 (m, 2H, $-CH_2-$), 3.94 (s, 3H, $-OCH_3$), 3.99–4.09 (m, 3H, –CH–, $-CH_2-$), 4.19 (q, 1H, J = 6.7 Hz, –CH–), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.20 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.94 (d, 1H,

Table 2
Effects on blood pressure of compounds **Id**, **IId** and **IIId** in SHRs[a]

Groups	Dose (mg/kg)	Parameter	Time of observation						
			0 h	0.5 h	1 h	2 h	4 h	6 h	8 h
Control		SAP (mmHg)	177.70 ± 9.81	178.50 ± 10.13	181.20 ± 16.37	172.60 ± 17.30	172.90 ± 10.21	176.70 ± 15.21	174.00 ± 12.10
		DAP (mmHg)	141.10 ± 7.75	138.70 ± 9.20	146.20 ± 13.19	142.90 ± 18.07	141.40 ± 7.11	141.20 ± 7.34	135.30 ± 8.21
		MAP (mmHg)	156.20 ± 12.60	156.20 ± 7.21	158.90 ± 13.65	157.41 ± 9.62	154.40 ± 20.10	155.80 ± 7.97	155.80 ± 11.54
		HR (BPM)	410.90 ± 10.84	406.50 ± 13.15	403.90 ± 12.41	399.50 ± 19.68	403.10 ± 15.92	405.10 ± 24.00	397.20 ± 24.87
Propranolol	20	SAP (mmHg)	175.10 ± 13.22	168.70 ± 12.75	156.80 ± 13.52**	160.60 ± 15.07	158.40 ± 13.06*	161.00 ± 15.20	163.90 ± 18.14
		DAP (mmHg)	138.60 ± 12.23	127.20 ± 10.04	105.50 ± 9.05*	94.10 ± 10.17**	88.30 ± 7.04**	100.30 ± 9.50**	116.90 ± 10.79
		MAP (mmHg)	152.80 ± 16.04	145.00 ± 12.75	122.60 ± 10.07*	116.80 ± 11.10**	108.30 ± 8.92**	120.90 ± 13.07**	132.60 ± 15.25
		HR (BPM)	405.90 ± 17.43	340.00 ± 30.66**	339.90 ± 28.53**	350.60 ± 26.73**	349.60 ± 16.65**	360.10 ± 20.37*	362.30 ± 22.70*
Id	80	SAP (mmHg)	183.30 ± 14.44	175.30 ± 17.41	170.10 ± 10.82	169.00 ± 15.64	170.90 ± 14.03	168.00 ± 11.71	166.30 ± 15.81
		DAP (mmHg)	148.00 ± 11.16	129.60 ± 11.14	114.60 ± 9.59*	109.50 ± 9.10**	117.70 ± 12.76*	124.40 ± 11.32	122.90 ± 12.94
		MAP (mmHg)	159.80 ± 13.46	144.80 ± 12.22	133.10 ± 9.87*	129.30 ± 12.40*	135.40 ± 14.21	138.90 ± 11.63	137.40 ± 9.61
		HR (BPM)	412.90 ± 12.72	383.40 ± 17.82	375.00 ± 19.16*	368.80 ± 19.22*	373.20 ± 20.87*	374.70 ± 20.65*	372.80 ± 26.27*
IId	80	SAP (mmHg)	179.20 ± 12.72	174.10 ± 10.72	164.50 ± 14.36 *	165.70 ± 10.64 *	166.60 ± 14.72 *	164.20 ± 15.58 *	162.60 ± 17.57 *
		DAP (mmHg)	139.30 ± 13.14	113.70 ± 9.11	113.90 ± 10.63	101.00 ± 11.19**	99.80 ± 10.26**	99.00 ± 9.77**	107.70 ± 11.08*
		MAP (mmHg)	151.10 ± 14.97	134.00 ± 10.35	128.80 ± 11.67	122.10 ± 11.73*	118.10 ± 10.52**	121.00 ± 9.25*	124.20 ± 11.20*
		HR (BPM)	407.00 ± 8.06	367.00 ± 12.41*	365.60 ± 16.52*	356.90 ± 10.64*	358.50 ± 15.55*	355.20 ± 22.52*	367.70 ± 24.69*
IIId	80	SAP (mmHg)	176.00 ± 16.70	169.20 ± 13.50	160.90 ± 15.12	152.80 ± 14.61**	141.00 ± 10.90**	150.50 ± 13.48**	158.30 ± 11.34**
		DAP (mmHg)	140.90 ± 11.32	128.70 ± 10.54	102.80 ± 8.80**	84.10 ± 9.73**	83.00 ± 8.35**	91.40 ± 11.73**	98.00 ± 9.30**
		MAP (mmHg)	154.60 ± 12.99	142.20 ± 11.25	123.10 ± 11.10**	103.90 ± 9.96**	97.80 ± 10.46**	114.00 ± 12.44**	119.00 ± 9.59**
		HR (BPM)	408.00 ± 13.61	385.40 ± 20.63	378.30 ± 23.24	365.10 ± 13.57*	361.40 ± 18.62*	370.00 ± 22.45*	372.80 ± 24.44

[a] Data are represented as mean ± SEM (n = **8**). Significance levels.
* p <0.05.
** p <0.01 as compared with the respective control.

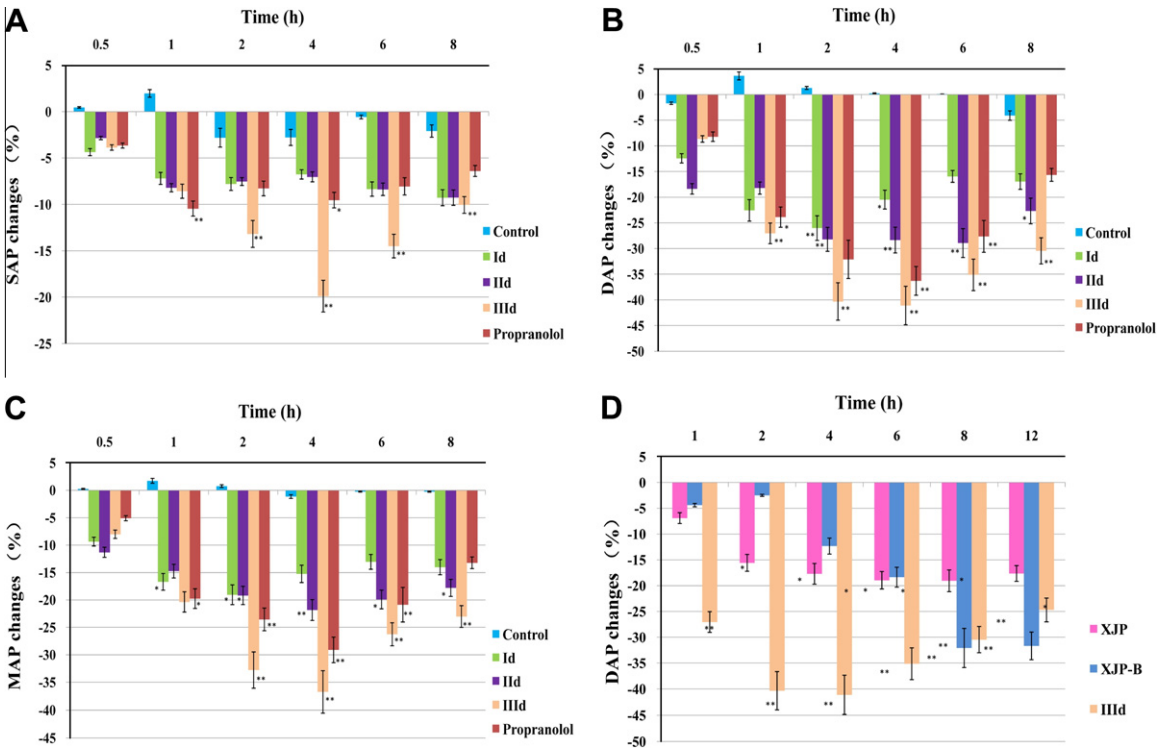


Figure 3. (A) The acute antihypertensive activities of **Id**, **IId**, **IIId** and propranolol in SHRs (SAP, systolic arterial pressure); (B) the acute antihypertensive activities of **Id**, **IId**, **IIId** and propranolol in SHRs (DAP, diastolic arterial pressure); (C) the acute antihypertensive activities of **Id**, **IId**, **IIId** and propranolol in SHRs (MAP, mean artery pressure); (D) the changes of DAP of XJP, XJP-B and **IIId** in SHRs. Data are represented as mean ± SEM (n = **8**). Significance levels *p <0.05 and **p <0.01 as compared with the respective control.

J = 8.7 Hz, Ar-H), 7.84 (d, 1H, J = 8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.2, 111.0, 77.8, 76.0, 75.8, 68.8, 68.7, 62.9, 56.0, 51.7, 51.4; 23.2, 15.7, 11.7; MS (ESI) m/z: 324.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1802.

4.1.2.4. 8-(2-Hydroxy-3-(isopropylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (Id). White power, yield 80%, mp 117–119 °C; IR (KBr), cm^{-1}: 3276, 2962, 2813, 1697, 1595, 1492, 1400, 1288, 1271, 1126, 1076, 1025, 927. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.09 (s, 3H, $-CH_3$), 1.11 (s, 3H, $-CH_3$), 1.49 (d, 3H,

J = 6.6 Hz, $-CH_3$), 2.68–2.75 (m, 1H, –CH–), 2.82–2.87 (m, 2H, $-CH_2-$), 3.96 (s, 3H, $-OCH_3$), 3.98–4.07 (m, 3H, –CH–, $-CH_2-$), 4.19 (q, 1H, J = 6.6 Hz, –CH–), 4.81 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.21 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.94 (d, 1H, J = 8.7 Hz, Ar-H), 7.84 (d, 1H, J = 8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.2, 111.0, 77.8, 76.0, 75.8, 69.0, 62.9, 55.9, 49.0, 23.0, 22.8, 15.7; MS(ESI) m/z: 324.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1800.

4.1.2.5. 8-(3-Butylamino-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (Ie). White power, yield 78%, mp 108–110 °C; IR (KBr), cm^{-1}: 3274, 2929, 2870, 2831, 1697, 1686, 1595, 1491, 1400, 1288, 1271, 1124, 1076; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92 (t, 3H, J = 7.4 Hz, $-CH_3$), 1.26–1.47 (m, 4H, $-CH_2-$, $-CH_2-$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.58–2.86 (m, 4H, $-CH_2-$, $-CH_2-$), 3.88 (s, 3H, $-OCH_3$), 3.90–4.09 (m, 3H, –CH–, $-CH_2-$), 4.19 (q, 1H, J = 6.7 Hz, –CH–), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.19 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.94 (d, 1H, J = 8.7 Hz, Ar-H), 7.84 (d, 1H, J = 8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.2, 111.0, 77.8, 76.0, 75.8, 68.8, 68.7, 62.9, 55.9, 49.6, 32.3, 20.4, 15.7, 14.0; MS (ESI) m/z: 338.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1958.

4.1.2.6. 8-(3-(*tert*-Butylamino)-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (If). White power, yield 77%, mp 99–101 °C; IR (KBr), cm^{-1}: 3298, 2967, 2880, 2836, 1695, 1686, 1594, 1492, 1444, 1363, 1312, 1286, 1222, 1125, 1076, 878; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38–1.50 (m, 12H, $-CH_3$, $-C(CH_3)_3$), 3.01–3.20 (m, 2H, $-CH_2-$), 3.93 (s, 3H, $-OCH_3$), 4.01–4.05 (m, 1H, –CH–), 4.06–4.20 (m, 2H, $-CH_2-$), 4.30–4.35 (q, 1H, J = 6.7 Hz, –CH–), 4.80 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.15 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.92 (d, 1H, J = 8.7 Hz, Ar-H), 7.82 (d, 1H, J = 8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 156.5, 136.1, 124.1, 111.0, 77.7, 76.0, 75.8, 69.3, 62.9, 55.9, 50.3, 44.4, 29.1, 15.7; MS (ESI) m/z: 338.3 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1956.

4.1.2.7. 8-(3-Dimethylamino-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (Ig). White power, yield 76%, mp 56–58 °C; IR (KBr), cm^{-1}: 2983, 2934, 2836, 2777, 1297, 1686, 1594, 1495, 1456, 1400, 1288, 1272, 1127, 1076; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.33 (s, 6H, $-CH_3$, $-CH_3$), 2.38–2.58 (m, 2H, $-CH_2-$), 3.93 (s, 3H, $-OCH_3$), 3.99–4.08 (m, 3H, –CH–, $-CH_2-$), 4.18 (q, 1H, J = 6.7 Hz, –CH–), 4.82 (d, 1H, J = 15.7 Hz, $-CH_2-$), 5.22 (d, 1H, J = 15.7 Hz, $-CH_2-$), 6.93 (d, 1H, J = 8.6 Hz, Ar-H), 7.83 (d, 1H, J = 8.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 195.0, 156.6, 136.1, 124.1, 111.0, 77.7, 75.5, 75.4, 66.8, 62.9, 61.5, 55.9, 45.6, 15.7; MS (ESI) m/z: 310.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1650.

4.1.3. General procedure for the preparation of compounds IIa–g

Corresponding amine (0.5–0.8 mL) was added to a solution of epoxide **9** (0.264 g, 1 mmol) in methanol (15 mL), respectively. The mixture was refluxed for 2–4 h and then concentrated under reduced pressure, and the residue was recrystallized with *n*-hexane/ethyl acetate (3:1, v/v) to give compounds **IIa–g** as white solid in yields of 77–89%.

4.1.3.1. 6-(2-Hydroxy-3-(methylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (IIa). White power, yield 77%, mp 108–110 °C; IR (KBr), cm^{-1}: 2938, 2831, 1685, 1601, 1514, 1443, 1400, 1357, 1275, 1207, 1111, 1039, 868; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.49 (s, 3H, $-CH_3$), 2.74–2.84 (m, 2H, $-CH_2-$), 3.91 (s, 3H, $-OCH_3$), 4.00–4.17 (m, 3H, –CH–, $-CH_2-$), 4.21 (q, 1H, J = 6.7 Hz, –CH–), 4.85 (s, 2H, $-CH_2-$), 6.60 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 154.5, 148.0, 137.4, 122.4, 110.2, 106.1, 78.0, 72.2, 67.8, 66.6, 56.1, 53.7, 36.2, 15.8; MS (ESI) m/z: 296.1 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{15}H_{22}NO_5[M+H]^+$ 296.1492, found 296.1489.

4.1.3.2. 6-(3-Ethylamino-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (IIb). White power, yield 79%, mp 114–116 °C; IR (KBr), cm^{-1}: 2979, 2928, 2821, 1685, 1602, 1513, 1400, 1356, 1274, 1210, 1112; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, 3H, J = 7.2 Hz, $-CH_3$), 1.49 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.91–3.13 (m, 4H, $-CH_2-$, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.08–4.09 (m, 2H, $-CH_2-$), 4.20 (q, 1H, J = 6.7 Hz, –CH–), 4.37–4.40 (m, 1H, –CH–), 4.83 (s, 2H, $-CH_2-$), 6.58 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 154.5, 148.0, 137.4, 122.4, 110.1, 106.1, 78.0, 72.4, 68.0, 66.6, 56.1, 51.5, 44.1, 15.9, 15.3; MS (ESI) m/z: 310.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1645.

4.1.3.3. 6-(2-Hydroxy-3-(propylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (IIc). White power, yield 85%, mp 116–118 °C; IR (KBr), cm^{-1}: 3232, 2968, 2816, 1672, 1601, 1513, 1400, 1355, 1277, 1112, 87; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, J = 7.2 Hz, $-CH_3$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.65 (t, 3H, J = 7.2 Hz, $-CH_2-$), 2.75–2.89 (m, 2H, $-CH_2-$), 3.91 (s, 3H, $-OCH_3$), 4.00–4.13 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.85 (s, 2H, $-CH_2-$), 6.60 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 154.5, 148.0, 137.4, 122.4, 110.1, 106.1, 78.0, 72.3, 68.0, 66.6, 56.1, 51.7, 51.6, 23.2, 15.9, 11.7; MS (ESI) m/z: 324.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1803.

4.1.3.4. 6-(2-Hydroxy-3-(isopropylamino)propoxy)-7-methoxy-3-methylisochroman-4-one (IId). White power, yield 85%, mp 98–100 °C; IR (KBr), cm^{-1}: 3294, 2979, 2940, 1693, 1600, 1512, 1448, 1400, 1356, 1273, 1113, 1010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.72–2.90 (m, 3H, –CH–, $-CH_2-$), 3.91 (s, 3H, $-OCH_3$), 3.98–4.13 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.85 (s, 2H, $-CH_2-$), 6.60 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.8, 154.5, 148.0, 137.3, 122.4, 110.0, 106.1, 78.0, 72.4, 68.1, 66.6, 56.1, 49.1, 48.8, 23.1, 23.0, 15.9; MS (ESI) m/z: 324.2 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1805.

4.1.3.5. 6-(3-Butylamino-2-hydroxypropoxy)-7-methoxy-3 -methylisochroman-4-one (IIe). White power, yield 80%, mp 100–102 °C; IR (KBr), cm^{-1}: 3289, 2956, 2928, 2827, 1677, 1600, 1513, 1400, 1355, 1273, 1212, 1113, 1007; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, J = 7.2 Hz, $-CH_3$), 1.33–1.48 (m, 2H, $-CH_2-$), 1.57 (d, 3H, J = 6.7 Hz, $-CH_3$), 1.63–1.73 (m, 2H, $-CH_2-$), 2.83–2.88 (m, 2H, $-CH_2-$), 2.96–3.12 (m, 2H, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.07–4.09 (m, 2H, $-CH_2-$), 4.21 (q, 1H, J = 6.7 Hz, –CH–), 4.35–4.37 (m, 1H, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.58 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 154.5, 148.0, 137.4, 122.4, 110.1, 106.1, 78.0, 72.3, 68.0, 66.6, 56.1, 51.6, 49.6, 32.3, 20.4, 15.9, 14.0; MS (ESI) m/z: 338.3 $[M+H]^+$; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1962.

4.1.3.6. 6-(3-(*tert*-Butylamino)-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (IIf). White power, yield 83%, mp 112–114 °C; IR (KBr), cm^{-1}: 3289, 2973, 2838, 1682, 1600, 1511, 1400, 1358, 1273, 1210, 1113, 1075, 1010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (s, 9H, $-C(CH_3)_3$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.69–2.74 (m, 1H, $-CH_2-$), 2.83–2.88 (m, 1H, $-CH_2-$), 3.91 (s, 3H, $-OCH_3$), 3.98–4.03 (m, 2H, $-CH_2-$), 4.05–4.13 (m, 1H, –CH–), 4.21 (q, 1H, J = 6.7 Hz, –CH–), 4.85 (s, 2H, $-CH_2-$), 6.60 (s, 1H, Ar-H),

7.50 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 154.5, 148.1, 137.3, 122.4, 110.0, 106.1, 78.0, 72.5, 68.1, 66.6, 56.1, 50.2, 44.4, 29.1, 15.9; MS (ESI) *m/z*: 338.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1964.

4.1.3.7. 6-(3-Dimethylamino-2-hydroxypropoxy)-7-methoxy-3-methylisochroman-4-one (IIg). White power, yield 77%, mp 92–94 °C; IR (KBr), cm^{-1}: 2945, 2821, 2765, 1671, 1602, 1514, 1400, 1356, 1279, 1109, 1041, 878; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.33 (s, 6H, $-CH_3$, $-CH_3$), 2.35–2.40 (m, 1H, $-CH_2-$), 2.51–2.58 (m, 1H, $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 3.97–4.17 (m, 3H, –CH–, $-CH_2-$), 4.21 (q, 1H, J = 6.7 Hz, –CH–), 4.85 (s, 2H, $-CH_2-$), 6.60 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.8, 154.5, 148.1, 137.3, 122.4, 110.0, 106.1, 78.0, 71.9, 66.6, 66.2, 61.6, 56.1, 45.6, 15.9; MS (ESI) *m/z*: 310.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1644.

4.1.4. General procedure for the preparation of compounds IIIa-g

Corresponding amine (0.5–0.8 mL) was added to a solution of epoxide **10** (0.264 g, 1 mmol) in methanol (15 mL), respectively. The mixture was refluxed for 2–4 h and then concentrated under reduced pressure, and the residue was recrystallized with *n*-hexane/ethyl acetate (3:1, v/v) to provide compounds **IIIa–g** as white solid in yields of 75–90%.

4.1.4.1. 7-(2-Hydroxy-3-(methylamino)propoxy)-6-methoxy-3-methylisochroman-4-one (IIIa). White power, yield 78%, mp 142–144 °C; IR (KBr), cm^{-1}: 3317, 3001, 2940, 2821, 1685, 1602, 1511, 1400, 1354, 1272, 1213, 1109, 1013; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.50 (s, 3H, $-CH_3$), 2.77–2.87 (m, 2H, $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.06–4.09 (m, 2H, $-CH_2-$), 4.11–4.16 (m, 1H, –CH–), 4.21 (q, 1H, J = 6.7 Hz, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.65 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.2, 149.0, 136.8, 122.8, 108.3, 107.6, 78.0, 72.1, 67.7, 66.5, 56.0, 53.7, 36.3, 15.9; MS(ESI) *m/z*: 296.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{15}H_{22}NO_5[M+H]^+$ 296.1492, found 296.1493.

4.1.4.2. 7-(3-Ethylamino-2-hydroxypropoxy)-6-methoxy-3-methylisochroman-4-one (IIIb). White power, yield 78%, mp 130–132 °C; IR (KBr), cm^{-1}: 2962, 2928, 2833, 1670, 1603, 1513, 1400, 1357, 1280, 1213, 1109, 1050, 881; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.14 (t, 3H, J = 7.1 Hz, $-CH_3$), 1.51 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.68–2.79 (m, 2H, $-CH_2-$), 2.80–2.92 (m, 2H, $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.05–4.13 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.65 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.3, 149.0, 136.8, 122.7, 108.3, 107.5, 78.0, 72.2, 67.8, 66.5, 56.0, 51.4, 44.1, 15.9, 15.3; MS (ESI) *m/z*: 310.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1641.

4.1.4.3. 7-(2-Hydroxy-3-(propylamino)propoxy)-6-methoxy-3-methylisochroman-4-one (IIIc). White power, yield 85%, mp 134–136 °C; IR (KBr), cm^{-1}: 3276, 2946, 2828, 1670, 1603, 1513, 1400, 1279, 1211, 1111; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (t, 3H, J = 7.1 Hz, $-CH_3$), 1.51 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.64 (t, 3H, J = 7.1 Hz, $-CH_2-$), 2.78–2.93 (m, 4H, $-CH_2-$, $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.06–4.13 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.65 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.3, 149.0, 136.8, 122.7, 108.3, 107.5, 78.0, 72.2, 67.7, 66.5, 56.0, 51.7, 51.5, 23.1, 15.9, 11.7; MS (ESI) *m/z*: 324.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1801.

4.1.4.4. 7-(2-Hydroxy-3-(isopropylamino)propoxy)-6-methoxy-3-methylisochroman-4-one (IIId). White power, yield 90%, mp 134–136 °C; IR (KBr), cm^{-1}: 3271, 2982, 2941, 2833, 1676, 1602, 1512, 1400, 1358, 1278, 1214, 1157, 1111, 1048, 1010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.46–1.52 (m, 9H, $-CH_3$, $-CH_3$, $-CH_3$), 3.18–3.23 (m, 1H, –CH–), 3.34–3.69 (m, 2H, $-CH_2-$), 3.87 (s, 3H, $-OCH_3$), 4.08–4.23 (m, 3H, –CH–, $-CH_2-$), 4.66–4.68 (m, 1H, –CH–),4.81 (s, 2H, $-CH_2-$), 6.65 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.3, 149.0, 136.8, 122.7, 108.3, 107.5, 78.0, 72.3, 67.8, 66.5, 56.0, 49.1, 48.9, 23.1, 23.0, 15.9; MS (ESI) *m/z*: 324.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{17}H_{26}NO_5[M+H]^+$ 324.1805, found 324.1803.

4.1.4.5. 7-(3-Butylamino-2-hydroxypropoxy)-6-methoxy-3 -methylisochroman-4-one (IIIe). White power, yield 80%, mp 100–102 °C; IR (KBr), cm^{-1}: 3276, 2931, 1677, 1603, 1512, 1400, 1278, 1211, 1159, 1110, 1046; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (t, 3H, J = 7.1 Hz, $-CH_3$), 1.33–1.40 (m, 2H, $-CH_2-$), 1.47–1.49 (m, 2H, $-CH_2-$), 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.66–2.70 (m, 2H, $-CH_2-$), 2.80–2.92 (m, 2H, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.06–4.21 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.66 (s, 1H, Ar-H), 7.49 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.3, 149.0, 136.8, 122.7, 108.3, 107.5, 78.0, 72.2, 67.7, 66.5, 56.0, 51.6, 49.6, 32.3, 20.4, 15.9, 14.0; MS (ESI) *m/z*: 338.3 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1962.

4.1.4.6. 7-(3-(*tert*-Butylamino)-2-hydroxypropoxy)-6-methoxy-3-methylisochroman-4-one (IIIf). White power, yield 82%, mp 72–74 °C; IR (KBr), cm^{-1}: 3307, 2965, 2864, 2823, 1683, 1600, 1512, 1450, 1399, 1353, 1274, 1213, 1109, 1043, 1007, 881; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (s, 9H, $-C(CH_3)_3$), 1.51 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.74–2.77 (m, 1H, $-CH_2-$), 2.86–2.92 (m, 1H, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.00–4.13 (m, 3H, –CH–, $-CH_2-$), 4.22 (q, 1H, J = 6.7 Hz, –CH–), 4.84 (s, 2H, $-CH_2-$), 6.65 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.4, 149.0, 136.8, 122.7, 108.3, 107.4, 78.0, 72.5, 72.4, 67.8, 67.7, 66.5, 56.0, 50.4, 44.4, 29.1, 15.9; MS(ESI) *m/z*: 338.3 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{18}H_{28}NO_5[M+H]^+$ 338.1962, found 338.1951.

4.1.4.7. 7-(3-Dimethylamino-2-hydroxypropoxy)-6-methoxy-3-methylisochroman-4-one (IIIg). White power, yield 75%, mp 130–132 °C; IR (KBr), cm^{-1}: 2936, 2828, 2766, 1671, 1600, 1512, 1464, 1374, 1355, 1276, 1210, 1110, 1077, 1002, 881; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, 3H, J = 6.7 Hz, $-CH_3$), 2.04 (s, 6H, $-CH_3$, $-CH_3$), 2.47–2.74 (m, 2H, $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.06–4.09 (m, 2H, $-CH_2-$), 4.11–4.26 (m, 2H, –CH–, –CH–), 4.83 (s, 2H, $-CH_2-$), 6.68 (s, 1H, Ar-H), 7.49 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.9, 153.4, 149.1, 136.7, 122.7, 108.3, 107.6, 78.0, 71.8, 71.7, 66.5, 66.1, 61.7, 56.0, 45.6, 15.9; MS(ESI) *m/z*: 310.2 $[M+H]^+$; HRMS (ESI) *m/z*: calcd for $C_{16}H_{24}NO_5[M+H]^+$ 310.1649, found 310.1646.

4.2. Pharmacological evaluation

4.2.1. β_1-Adrenoceptor blocking test in vitro using the rat isolated left atria

Male Sprague Dawley (SD) rats (250–350 g) were stunned and exsanguinated. The heart was rapidly removed and placed in ice cold Krebs solution that was saturated with 5% CO_2/95% O_2, and the left atria was excised. All procedures were performed in the presence of a modified Krebs solution [composition (mmol/L): $NaHCO_3$, 24; Glucose, 10; KH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KCl, 4.7; NaCl, 118; pH 7.4] which was being vigorously bubbled with 5% CO_2 in oxygen at 37 °C. The left atria was removed from the heart mounted longitudinally between two platinum electrodes

(approximately 3 cm apart, above and below the tissue) under 0.5 g tension in 10 mL organ baths containing Krebs solution and allowed to equilibrate for 30 min. During the equilibration period, the tissues were washed by overflow.

Tissues were electrically stimulated at 2 Hz (3 mesc, 150% threshold potential). 10^{-7} M isoprenaline was added twice until the stable contraction was obtained. The atria were then further treated with new compounds (10^{-7} and 10^{-6} M), and 10^{-7} M isoprenaline was added after 5 min. The contraction change to isoprenaline was observed, then the inhibition ratio was calculated. Propranolol was set as the positive control in the experiment.[17–19]

4.2.2. Antihypertensive effects in SHRs

SHRs were purchased from Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China). After one week of acclimation, 40 SHRs (10-weeks-old, 180–200 g body weight) were randomly divided into 5 groups, namely the SHR model group, propranolol control group, and the compounds **Id**, **IId**, and **IIId** control groups. After oral administration with saline water, propranolol (20 mg/kg), **Id**, **IId** and **IIId** (80 mg/kg) to SHRs respectively, the SAP, DAP, MAP and heart rate (HR) were measured using the tail-cuff method with a blood pressure monitor (BP-2000, Visitech Systems, Inc., US) from 0 to 24 h.[20–22]

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