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Synthesis and *β*-adrenergic blocking activity of oxime ether hybrids derived from a natural isochroman-4-one

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[ABSTRACT] AIM: In a search for new cardiovascular drug candidates, a series of novel oxime ethers derived from a natural isochroman-4-one were synthesized. **METHOD:** Compounds **3** and **6**, derived from the natural antihypertensive compound 7, 8-dihydroxy-3-methyl-isochroman-4-one (XJP), were designed and synthesized. Subsequently, a series of novel isochroman-4-one oxime ether hybrids were prepared by hybridizing various *N*-substituted isopropanolamine functionalities to isochroman-4-one oxime. Furthermore, β_1-adrenergic blocking activities of the synthesized compounds were assayed using the isolated rat left atria. **RESULTS:** Twenty target compounds were obtained, and the preliminary structure-activity relationships were deduced. The most promising compound **Ic** exhibited β_1-adrenoceptor blocking activity (inhibition: 52.2%) at 10^{-7} mol·L^{-1}, which was superior to that of propranolol (inhibition: 49.7%). **CONCLUSION:** The results suggested that natural product XJP/isopropanolamine moiety hybrids may provide a promising approach for the discovery of novel cardiovascular drug candidates.

[KEY WORDS] Isochroman-4-one derivatives; Oxime ethers; Hybrids; *β*-Adrenergic blocking activity; Antihypertensive activity

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1 Introduction

Cardiovascular disease affects millions of people around the world, causing loss of lives, and a heavy economic burden [1]. During the past few decades, enormous effects have been made in the development of new antihypertensive agents. Antihypertensive products from plants are an important resource to find new leads for further structure modification [2-4]. The banana peel has been widely used as a folk medicine for the treatment of hypertension, ulceration, etc [5]. 7, 8-Dihydroxy-3-methyl-isochroman-4-one (XJP, Fig. 1), isolated from the banana, *Musa sapientum* L. peel extract, is a structurally unique polyphenolic compound possessing potent antihypertensive and antioxidant activities [6-8]. In previous studies from our laboratory, XJP significantly decreased blood pressure in a dose-dependent manner. In both acute and therapeutic antihypertensive tests of conscious renal hypertensive rats (RHRs), the maximum antihypertensive effect of XJP at the dose of 100 mg·kg^{-1} was comparable to that of captopril at the dose of 25 mg·kg^{-1} [9]. In the further structure modification studies, XJP-B (Fig. 1), an analogue of XJP, was synthesized which was more active than XJP in spontaneously hypertensive rats (SHRs) [10].

Searching for new isochroman-4-one derivatives and analogues with potential cardiovascular protection properties has remained an interest for a long time. In order to overcome the instability and to enhance the bioavailability of these polyphenols [11], the hydroxymethylated products of XJP and

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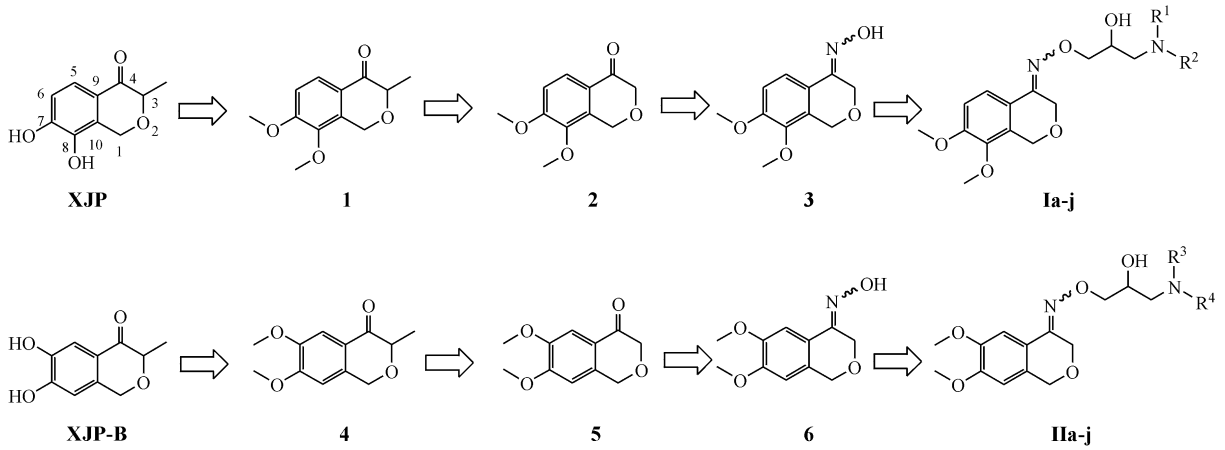


Fig. 1 Strategy for the design of the target compounds from a natural isochroman-4-one

XJP-B were firstly synthesized. Furthermore, the methyl group at the 3-position of isochroman-4-one was removed to reduce the number of chiral centers and decrease the impact on the propanolamine side chain. In this paper, compounds **2** and **5** were chosen as the key scaffolds for further modification, and then compounds **3** and **6** were designed and synthesized.

β-Adrenoreceptor antagonists have been used clinically for the treatment of cardiovascular disease for many years [12]. It is well-known that an aryloxypropanolamine unit is the chemical feature required for *β*- adrenergic blocking activity [13]. In addition, a few compounds with *β*- adrenergic blocking activities have been described in which the characteristic propanolamine side chain is attached to the oxygen of an oxime function [14-17]. The insertion of the C=N-O group in the molecule did not abolish *β*-adrenoreceptor activity, and, in some cases, led to potent *β*-antagonists [18-20]. In previous studies, the hybrids XJP and XJP-B bearing isopropanolamine moiety on the phenolic oxygen exhibited powerful β_1-adrenoceptor blocking effects [21]. Based on the above results, it appeared interesting to introduce various *N*-substituted isopropanolamine functionalities to the oxygen of the oxime derivatives of compounds **3** and **6** to obtain novel isochroman-4-one oxime ethers. Herein, the synthesis and biological evaluation of these oxime ether hybrids derived from isochroman-4-one are reported.

2 Experimental

2.1 *Chemistry*

2.1.1 *General*

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 are uncorrected. IR spectra were recorded in KBr on a Nicolet Impact 410 grating infrared spectrometer (ν_{max} in cm^{-1}) and ^1H NMR spectra were recorded with a 300 MHz spectrometer in the indicated solvents (TMS as internal standard): the values of the chemical shifts are expressed in δ values and the coupling constants (*J*) in Hz. High-resolution mass spectra were recorded using an Agilent QTOF 6520 instrument. Purity of all tested compounds was ⩾ 95%, as estimated by HPLC analysis. The major peak of the compounds analyzed by HPLC accounted for ⩾ 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 (200−300 mesh).

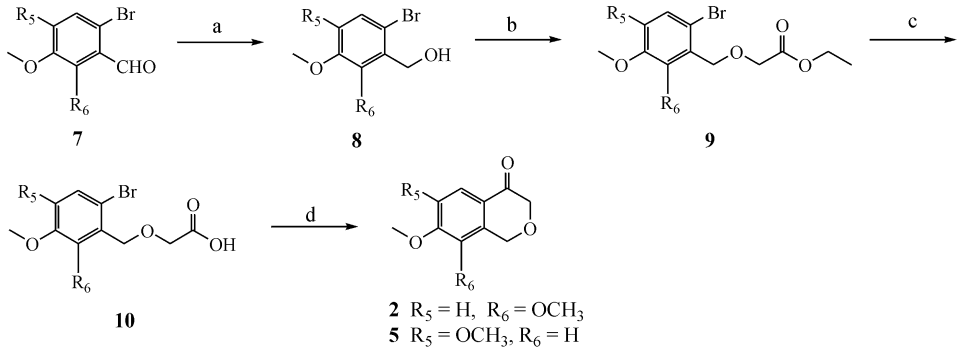
2.1.2 *Synthesis of the target compounds* ***Ia−j*** *and* ***IIa−j***

Isochroman-4-one derivatives **2** and **5** were synthesized as shown in Scheme 1. Substituted benzaldehyde **7** was reduced by sodium borohydride to the corresponding benzyl alcohol **8**. Subsequent alkylation of **8** with ethyl bromoacetate in the presence of NaH followed by saponification of the ethyl ester provided acid **10**, which was treated with *n*-butyllithium in THF at −85 °C to provide ring-closing isochroman-4-one derivatives **2** and **5**.

The synthetic route of the target compounds **Ia−j** and **IIa−j** is depicted in Scheme 2. The ketones **2** and **5** were converted, by mixing with hydroxylamine hydrochloride, in a mixture of methanol and water (1 : 1, *V*/*V*) at room temperature, to yield the oximes **3** and **6**, respectively. Oximes were then treated with epichlorohydrin in the presence of NaH to give corresponding epoxides **11** and **12**. Subsequent ring opening of the epoxides with various amines afforded the target compounds **Ia−j** and **IIa−j**, respectively.

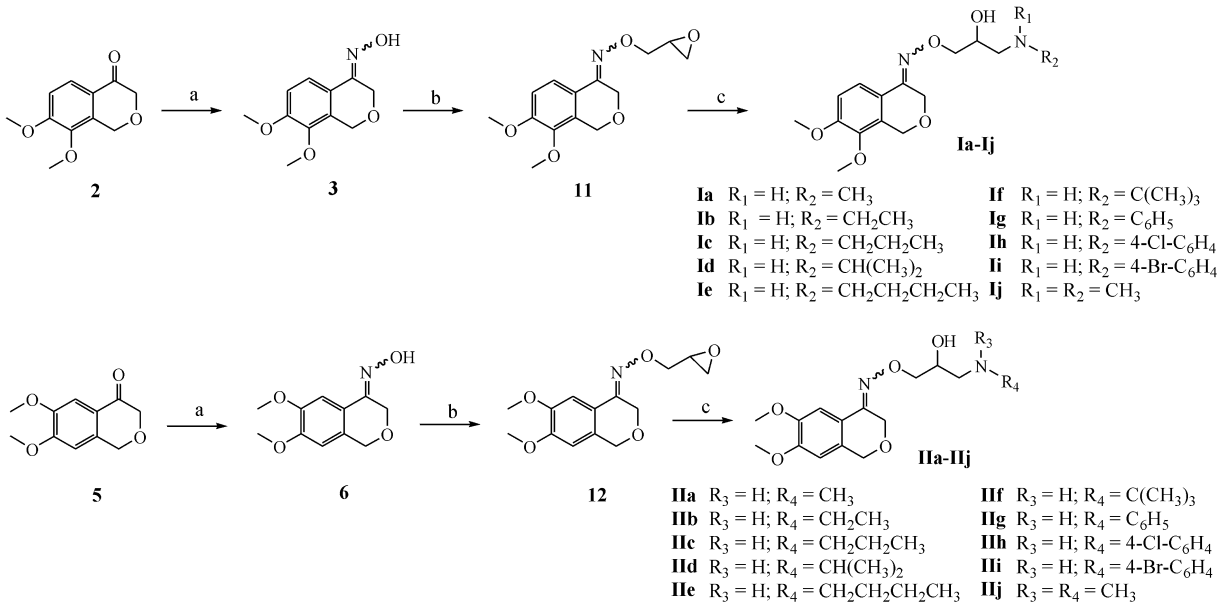
2.2 *β_1-Adrenoceptor antagonism assay*

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 ($mmol \cdot L^{-1}$): $NaHCO_3$, 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 and mounted longitudinally between two platinum electrodes (approximately 3 cm apart, above and below the



Reagents and conditions: (a) anhydrous MeOH, $NaBH_4$, 0 °C, 85%–95%; (b) anhydrous DMF, NaH, 0 °C, 70%–75%; (c) MeOH, 10% NaOH, rt, then 10% HCl, 80%–85%; (d) *n*-BuLi, anhydrous THF, −85 °C to rt, 50%–55%

Scheme 1 Synthesis of the isochroman-4-one derivatives 2 and 5



Reagents and conditions: (a) $H_2NOH{\cdot}HCl$, $MeOH/H_2O$, 73%–78%; (b) anhydrous DMF, NaH, epichlorohydrin, 0 °C, 75%–82%; (c) MeOH, RR'NH, reflux, 75%–90%

Scheme 2 Synthesis of the target compounds Ia−j and IIa−j

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 msec, 150% threshold potential). Isoprenaline (10^{-7} mol·L^{-1}) was added twice until a stable contraction was obtained. The atria were then further treated with the new compounds (10^{-7}, 10^{-6} mol·L^{-1}), and 10^{-7} mol·L^{-1} isoprenaline was added after 5 min. The contraction change to isoprenaline was observed, and the inhibition ratio was calculated. Propranolol was set as the positive control in the experiment [16].

3 Results and Discussion

3.1 *Chemistry*

Intermediates **2** and **5** were synthesized according to reported routes from this laboratory [9].

7, 8-Dimethoxyisochroman-4-one (**2**) White powder, yield 50%, mp 107–109 °C; IR (KBr) cm^{-1}: 2 937, 2 818, 1 693, 1 597, 1 493, 1 455, 1 440, 1 347, 1 288, 1 231, 1 126, 1 079, 1 029, 980; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (s, 3H, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$), 4.29 (s, 2H, $-CH_2$-), 4.94 (s, 2H, $-CH_2$-), 6.96 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 209.1 $[M + H]^+$.

6, 7-Dimethoxyisochroman-4-one (**5**) White powder, yield 55%, mp 160–162 °C; IR (KBr) cm^{-1}: 3 003, 2 845, 1 684, 1 676, 1 600, 1 513, 1 400, 1 362, 1 335, 1 285, 1 232, 1 150, 1 051, 778; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.93 (s, 3H, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$), 4.32 (s, 2H, $-CH_2$-), 4.84 (s, 2H, $-CH_2$-), 6.63 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H); ESI-MS *m/z* 209.0 $[M + H]^+$.

*General procedure for the preparation of compounds **3** and **6***

A suspension of the ketone **2** (0.208 g, 1.00 mmol) and hydroxylamine hydrochloride (0.178 g, 3.4 mmol) in 20 mL of a mixture of methanol and water (1 : 1, *V*/*V*) was stirred at room temperature for 6 h. The mixture was evaporated to dryness in vacuum and the oxime **3** was collected, washed with water and purified. Compound **6** was prepared by the above method.

7, 8-Dimethoxyisochroman-4-one oxime (**3**) White powder, yield 78%, mp 129−131 °C; IR (KBr) cm^{-1}: 2 992, 2 837, 1 602, 1 497, 1 400, 1 336, 1 278, 1 232, 1 115, 1 069, 1 040, 970, 886, 812; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.83 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.76 (s, 2H, -OCH_2-), 4.78 (s, 2H, -OCH_2-), 6.88 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* $[M + H]^+$.

6, 7-Dimethoxyisochroman-4-one oxime (**6**) White powder, yield 73%, mp 134−136 °C; IR (KBr) cm^{-1}: 2 932, 2 837, 1 603, 1 514, 1 467, 1 364, 1 288, 1 219, 1 068, 968, 903, 856; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.90 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 4.64 (s, 2H, -CH_2-), 4.80 (s, 2H, -CH_2-), 6.58 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H); ESI-MS *m/z* 224.1 $[M + H]^+$.

*General procedure for the preparation of compounds **11** and **12***

NaH (0.08 g, 60% in oil, 2 mmol) was added to a solution of compound **3** (0.223 g, 1 mmol) in anhydrous DMF (10−12 mL) and the mixture was stirred at 0 °C for 30 min. Then epichlorohydrin (0.32 mL, 4 mmol) was added and the mixture was stirred at 0 °C for another 3 h. After filtration and concentration under reduced pressure, the extract was purified by flash column chromatography with *n*-hexane/ethyl acetate (5 : 1, *V*/*V*) as eluent, compound **11** was afforded as a white solid in 82% yield. Compound **12** was prepared by the above method.

4-[(2, 3-Epoxypropyl)oximino]-7, 8-dimethoxyisochroman (**11**) White powder, yield 75%, mp 106−108 °C; IR (KBr) cm^{-1}: 2 993, 2 939, 2 836, 1 618, 1 594, 1 400, 1 278, 1 225, 1 073, 1 053, 950; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.65−2.68 (m, 1H, -OCH_2-), 2.85−2.88 (m, 1H, -OCH_2-), 3.28−3.32 (m, 1H, -OCH-), 3.82 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.07-4.13 (m, 1H, -OCH_2-), 4.31−4.37 (m, 1H, -OCH_2-), 4.72 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.86 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.69 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 280.1 $[M + H]^+$.

4-[(2, 3-Epoxypropyl)oximino]-6, 7-dimethoxyisochroman (**12**) White powder, yield 78%, mp 108−110 °C; IR (KBr) cm^{-1}: 2 944, 2 875, 2 821, 1 599, 1 507, 1 467, 1 367, 1 297, 1 246, 1 227, 1 156, 1 046, 1 029, 906, 867; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.66−2.69 (m, 1H, -CH_2-), 2.87 (t, 1H, *J* = 4.5 Hz, -CH_2-), 3.30−3.33 (m, 1H, -CH-), 3.89 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 4.08−4.14 (m, 1H, -CH_2-), 4.35−4.40 (m, 1H, -CH_2-), 4.62 (s, 2H, -CH_2-), 4.75 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.41 (s, 1H, Ar-H); ESI-MS *m/z* 280.1 $[M + H]^+$.

*General procedure for the preparation of compounds **Ia−j** and **IIa−j***

The corresponding amine (0.2−0.5 mL) was added to a solution of epoxide **11** (0.279 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 petroleum ether/acetone (3 : 1, *V*/*V*) to afford compounds **Ia**−**j** as white solids in yields of 75%−88%. Compounds **IIa**−**j** were prepared by the above method.

4-[1-(3-Methylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ia**) White powder, yield 80%, mp 109−111 °C; IR (KBr) cm^{-1}: 3 298, 2 929, 2 851, 2 787, 2 594, 1 508, 1 400, 1 373, 1 250, 1 229, 1 217, 1 156, 1 054, 1 033, 973, 868; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.49 (s, 3H, -CH_3), 2.64−2.79 (m, 2H, -CH_2-), 3.91 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3), 4.06−4.11 (m, 1H, -CH-), 4.20 (d, 2H, *J* = 5.1 Hz, -CH_2-), 4.63 (s, 2H, -CH_2-), 4.75 (s, 2H, -CH_2-), 6.57 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H); ESI-MS *m/z* 311.2 $[M + H]^+$;

4-[1-(3-Ethylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ib**) White powder, yield 84%, mp 122−124 °C; IR (KBr) cm^{-1}: 3 264, 2 944, 2 831, 1 596, 1 517, 1 399, 1 370, 1 297, 1 259, 1 228, 1 151, 1 051, 1 025, 873; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.39 (t, 3H, *J* = 7.1 Hz, -CH_3), 2.65−2.79 (m, 2H, -CH_2-), 2.80−3.31 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 4.03−4.13 (m, 1H, -CH-), 4.18 (d, 2H, *J* = 5.1 Hz, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.73 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H); ESI-MS *m/z* 325.2 $[M + H]^+$.

4-[1-(3-Propylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ic**) White powder, yield 80%, mp 118−120 °C; IR (KBr) cm^{-1}: 3 269, 2 954, 2 870, 2 836, 1 594, 1 514, 1 459, 1 400, 1 368, 1 258, 1 228, 1 216, 1 158, 1 057, 1 041, 936, 871; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (t, 3H, *J* = 7.4 Hz, -CH_3), 1.47−1.59 (m, 2H, -CH_2-), 2.55−2.83 (m, 4H, -CH_2-, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 4.01−4.09 (m, 1H, -CH-), 4.18 (d, 2H, *J* = 5.1 Hz, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.73 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.30 (s, 1H, Ar-H); ESI-MS *m/z* 339.2 $[M + H]^+$.

4-[1-(3-Isopropylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Id**) White powder, yield 85%, mp 105−107 °C; IR (KBr) cm^{-1}: 3 274, 2 959, 2 851, 1 494, 1 508, 1 466, 1 400, 1 366, 1 291, 1 247, 1 230, 1 121, 1 047, 1 029, 868, 763; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.07 (s, 3H, -CH_3), 1.09 (s, 3H, -CH_3), 2.53−2.67 (m, 1H, -CH-), 2.79−2.86 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 3.97−4.03 (m, 1H, -CH-), 4.18 (d, 2H, *J* = 5.1 Hz, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.73 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H); ESI-MS *m/z* 339.2 $[M + H]^+$.

4-[1-(3-Butylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ie**) White powder, yield 75%, mp 92−94 °C; IR (KBr) cm^{-1}: 3 264, 2 959, 2 919, 2 870, 2 811,

1 596, 1 512, 1 466, 1 370, 1 258, 1 228, 1 215, 1 155, 1 113, 1 056, 1 028, 946, 867; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, *J* = 6.7 Hz, -CH_3), 1.27–1.65 (m, 6H, -CH_2-, -CH_2-, -CH_2-), 3.37–3.79 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 3.95–4.37 (m, 3H, -CH-, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.71 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H); ESI-MS *m/z* 353.2 $[M + H]^+$.

4-[1-(3-*tert*-Butylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**If**) White powder, yield 78%, mp 106–108 °C; IR (KBr) cm^{-1}: 2 959, 2 841, 1 594, 1 508, 1 470, 1 400, 1 370, 1 251, 1 228, 1 214, 1 155, 1 119, 1 058, 1 039, 950, 871; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.11 (s, 9H, -$C(CH_3)_3$), 2.57–2.79 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 3.93–3.96 (m, 1H, -CH-), 4.18–4.20 (m, 2H, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.73 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.37 (s, 1H, Ar-H); ESI-MS *m/z* 353.2 $[M + H]^+$.

4-[1-(3-Phenylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ig**) White powder, yield 76%, mp 101–103 °C; IR (KBr) cm^{-1}: 3 328, 2 969, 2 900, 2 836, 1 605, 1 508, 1 363, 1 299, 1 253, 1 228, 1 216, 1 050, 913, 768; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.18–3.41 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.23–4.33 (m, 3H, -CH-, -CH_2-), 4.62 (s, 2H, -CH_2-), 4.74 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 6.68–6.77 (m, 3H, Ar-H), 7.19 (t, 2H, *J* = 7.8 Hz, Ar-H), 7.33 (s, 1H, Ar-H); ESI-MS *m/z* 373.2 $[M + H]^+$.

4-{1-[3-(4-Chlorophenylamino)-2-hydroxypropyl]-oxyimino}-7, 8-dimethoxyisochroman (**Ih**) White powder, yield 75%, mp 122–124 °C; IR (KBr) cm^{-1}: 3 510, 3 362, 2 939, 2 841, 1 600, 1 512, 1 494, 1 400, 1 367, 1 256, 1 225, 1 151, 1 053, 1 029, 765; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.46–3.80 (m, 2H, -CH_2-), 3.90 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 4.11–4.28 (m, 3H, -CH-, -CH_2-), 4.60 (s, 2H, -CH_2-), 4.66 (s, 2H, -CH_2-), 6.55 (d, 1H, *J* = 9.5 Hz, Ar-H), 7.30–7.40 (m, 4H, Ar-H), 7.63 (d, 1H, *J* = 8.4 Hz, Ar-H); ESI-MS *m/z* 407.1 $[M + H]^+$.

4-{1-[3-(4-Bromophenylamino)-2-hydroxypropyl]-oxyimino}-7, 8-dimethoxyisochroman (**Ii**) White powder, yield 77%, mp 118–120 °C; IR (KBr) cm^{-1}: 3 511, 3 362, 2 929, 2 831, 1 599, 1 511, 1 491, 1 400, 1 367, 1 299, 1 255, 1 225, 1 154, 1 117, 1 053, 1 028, 952; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.26–3.39 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.12–4.27 (m, 2H, -CH_2-), 4.32–4.36 (m, 1H, -CH-), 4.60 (s, 2H, -CH_2-), 4.70 (s, 2H, -CH_2-), 6.55 (d, 1H, *J* = 9.5 Hz, Ar-H), 6.91 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.21–7.36 (m, 3H, Ar-H), 7.54 (d, 1H, *J* = 8.5 Hz, Ar-H); ESI-MS *m/z* 451.1 $[M + H]^+$.

4-[1-(3-Dimethylamino-2-hydroxypropyl)-oxyimino]-7, 8-dimethoxyisochroman (**Ij**) White powder, yield 75%, mp 101–103 °C; IR (KBr) cm^{-1}: 3 008, 2 939, 2 836, 2 777, 1 596, 1 507, 1 463, 1 451, 1 370, 1 333, 1 257, 1 227, 1 155, 1 123, 1 054, 1 023, 947, 870; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.32 (s, 6H, -CH_3, -CH_3), 2.36–2.50 (m, 2H, -CH_2-), 3.89 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.02–4.08 (m, 1H, -CH-), 4.18 (d, 2H, *J* = 4.9 Hz, -CH_2-), 4.61 (s, 2H, -CH_2-), 4.74 (s, 2H, -CH_2-), 6.56 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H); ESI-MS *m/z* 325.2 $[M + H]^+$.

4-[1-(3-Methylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIa**) White powder, yield 80%, mp 109–111 °C; IR (KBr) cm^{-1}: 3 138, 2 999, 2 831, 1 609, 1 470, 1 382, 1 260, 1 217, 1 123, 1 059, 1 045, 973; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.35 (s, 3H, -CH_3), 2.64–2.73 (m, 2H, -CH_2-), 3.81 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.04–4.07 (m, 1H, -CH-), 4.21 (d, 2H, *J* = 5.1 Hz, -CH_2-), 4.73 (s, 2H, -CH_2-), 4.75 (s, 2H, -CH_2-),6.84 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.62 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 311.2 $[M + H]^+$.

4-[1-(3-Ethylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIb**) White powder, yield 75%, mp 103–105 °C; IR (KBr) cm^{-1}: 3 127, 2 993, 2 826, 1 623, 1 475, 1 400, 1 278, 1 109, 1 071, 947; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.13 (t, 3H, *J* = 7.1 Hz, -CH_3), 2.64–2.71 (m, 2H, -CH_2-), 2.73–2.81 (m, 2H, -CH_2-), 3.82 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.02–4.06 (m, 1H, -CH-), 4.17 (d, 2H, *J* = 4.8 Hz, -CH_2-), 4.70 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.85 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.64 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 325.1 $[M + H]^+$.

4-[1-(3-Propylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIc**) White powder, yield 83%, mp 85–87 °C; IR (KBr) cm^{-1}: 3 134, 2 974, 2 944, 1 654, 1 577, 1 560, 1 498, 1 400, 1 343, 1 282, 1 122, 1 069, 954; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.85 (t, 3H, *J* = 7.4 Hz, -CH_3), 1.41 (q, 2H, *J* = 7.1 Hz, -CH_2-), 2.48 (t, 2H, *J* = 7.1 Hz, -CH_2-), 2.59 (q, 2H, *J* = 5.4 Hz, -CH_2-), 3.71 (s, 3H, -OCH_3), 3.75-3.80 (m, 1H, -CH-), 3.84 (s, 3H, -OCH_3), 3.97–4.07 (m, 2H, -CH_2-), 4.62 (s, 2H, -OCH_2-), 4.66 (s, 2H, -OCH_2-), 7.03 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.57 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 339.2 $[M + H]^+$.

4-[1-(3-Isopropylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IId**) White powder, yield 80%, mp 81–83 °C; IR (KBr) cm^{-1}: 3 274, 2 969, 2 831, 1 613, 1 594, 1 497, 1 462, 1 400, 1 345, 1 276, 1 232, 1 072, 1 049, 1 019, 953, 807; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.07 (s, 3H, -CH_3), 1.09 (s, 3H, -CH_3), 2.64 (t, 1H, *J* = 6.0 Hz, -CH-), 2.77–2.83 (m, 2H, -CH_2-), 3.82 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 3.98–4.02 (m, 1H, -CH-), 4.16 (d, 2H, *J* = 4.8 Hz, -CH_2-), 4.70 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.85 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.65 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 339.2 $[M + H]^+$.

4-[1-(3-Butylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIe**) White powder, yield 76%, mp 88–90 °C; IR (KBr) cm^{-1}: 3 165, 2 969, 2 860, 2 836, 1 566, 1 498, 1 458, 1 400, 1 343, 1 283, 1 228, 1 120, 1 073, 1 023, 961, 816; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.86 (t, 3H, *J* = 7.5 Hz, -CH_3), 1.25–1.41 (m, 4H, -CH_2CH_2-), 2.45–2.49 (m, 2H, -CH_2-), 2.50–2.61 (m, 2H, -CH_2-), 3.72 (s, 3H, -OCH_3),

3.71−3.79 (m, 1H, -OCH-), 3.84 (s, 3H, -OCH_3), 3.97−4.09 (m, 1H, -CH-), 4.62 (s, 2H, -OCH_2-), 4.66 (s, 2H, -OCH_2-), 7.04 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.58 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 353.2 $[M + H]^+$.

4-[1-(3-*tert*-Butylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIf**) White powder, yield 77%, mp 100−102 °C; IR (KBr) cm^{-1}: 3 293, 2 959, 2 826, 1 621, 1 589, 1 496, 1 400, 1 343, 1 279, 1 228, 1 109, 1 070, 1 033, 1 016, 952, 846; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.19 (s, 9H, -$(CH_3)_3$), 2.69−2.88 (m, 2H, -CH_2-), 3.81 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.06−4.12 (m, 1H, -CH-), 4.16−4.21 (m, 2H, -CH_2-), 4.69 (s, 2H, -OCH_2-), 4.73 (s, 2H, -OCH_2-), 6.85 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.65 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 353.2 $[M + H]^+$.

4-[1-(3-Phenylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIg**) White powder, yield 79%, mp 97−99 °C; IR (KBr) cm^{-1}: 3 308, 2 919, 2 836, 1 606, 1 497, 1 400, 1 279, 1 112, 1 070, 1 051, 950, 753; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.20−3.40 (m, 2H, -CH_2-), 3.82 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.21−4.27 (m, 3H, -CH_2-, -CH-), 4.71 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.70−6.78 (m, 3H, Ar-H), 6.86 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.19 (t, 2H, *J* = 7.7 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 373.1 $[M + H]^+$.

4-{1-[3-(4-Chlorophenylamino)-2-hydroxypropyl]-oxyimino}-6, 7-dimethoxyisochroman (**IIh**) White powder, yield 82%, mp 107−109 °C; IR (KBr) cm^{-1}: 3 288, 2 944, 2 836, 1 601, 1 498, 1 400, 1 279, 1 112, 1 071, 1 041, 952, 807; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.18−3.32 (m, 2H, -CH_2-), 3.82 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.19−4.26 (m, 3H, -CH_2-, -CH-), 4.70 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.60 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.86 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.12 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.61 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 407.1 $[M + H]^+$.

4-{1-[3-(4-Bromophenylamino)-2-hydroxypropyl]-oxyimino}-6, 7-dimethoxyisochroman (**IIi**) White powder, yield 78%, mp 118−120 °C; IR (KBr) cm^{-1}: 3 274, 2 993, 2 939, 2 836, 1 595, 1 497, 1 400, 1 278, 1 111, 1 072, 1 042, 952, 806; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.18−3.33 (m, 2H, -CH_2-), 3.82 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.20−4.28 (m, 3H, -CH_2-, -CH-), 4.70 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.58 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.86 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.26 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.61 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 451.0 $[M + H]^+$.

4-[1-(3-Dimethylamino-2-hydroxypropyl)-oxyimino]-6, 7-dimethoxyisochroman (**IIj**) White powder, yield 75%, mp 64−66 °C; IR (KBr) cm^{-1}: 2 993, 2 959, 2 944, 2 831, 1 589, 1 500, 1 458, 1 429, 1 348, 1 286, 1 116, 1 072, 1 027, 965, 834; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.35 (s, 6H, -$(CH_3)_2$), 2.35−2.48 (m, 2H, -CH_2-), 3.81 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.01−4.06 (m, 1H, -CH-), 4.16 (d, 2H, *J* = 4.9 Hz, -CH_2-), 4.71 (s, 2H, -OCH_2-), 4.74 (s, 2H, -OCH_2-), 6.85 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.66 (d, 1H, *J* = 8.7 Hz, Ar-H); ESI-MS *m/z* 325.1 $[M + H]^+$.

3.2 *β_1-Adrenoceptor antagonism assay and structure- activity relationships analysis*

β_1-Adrenergic blocking activities of the synthesized compounds were assayed using the isolated rat left atria. As shown in Table 1, selecting the natural isochroman-4-one scaffold as the aromatic ring remained significant β-adrenoceptor blocking activity in the designed derivatives. However, the methoxy substituent position on isochroman-4-one caused a moderate effect on the β_1-adrenergic blocking activity. Generally, 7, 8-dimethoxy substituted derivatives (**Ia-If**) had stronger β_1-adrenergic blocking activities than 6, 7-dimethoxy substituted derivatives (**IIa-IIf**). The substituents on the terminal amine of the side chain had a profound effect on the β_1-adrenergic blocking activity. Direct

Table 1 Antagonistic activity on β_1-adrenoceptor of the synthesized compounds

Compd.	Inhibition (%)		Compd.	Inhibition (%)	
	10^{-7} mol·L^{-1}	10^{-6} mol·L^{-1}		10^{-7} mol·L^{-1}	10^{-6} mol·L^{-1}
Ia	< 10	< 10	**IIa**	< 10	< 10
Ib	19.5 ± 1.7	26.6 ± 2.1	**IIb**	< 10	< 10
Ic	52.2 ± 2.6	62.9 ± 4.6	**IIc**	15.3 ± 1.2	27.0 ± 2.5
Id	24.5 ± 1.9	43.3 ± 3.7	**IId**	11.1 ± 1.4	14.6 ± 1.7
Ie	22.4 ± 2.5	32.6 ± 2.9	**IIe**	15.3 ± 1.2	20.7 ± 2.5
If	10.8 ± 1.2	15.9 ± 1.8	**IIf**	16.2 ± 1.8	31.1 ± 3.2
Ig	< 10	< 10	**IIg**	< 10	< 10
Ih	< 10	< 10	**IIh**	< 10	< 10
Ii	< 10	< 10	**IIi**	< 10	< 10
Ij	< 10	< 10	**IIj**	< 10	< 10
Propranolol	49.7 ± 3.7	73.8 ± 6.8			

aromatic substitution on the terminal amine led to almost complete abolition of the β_1-antagonist properties, indicating that a large steric hindrance at this position is not tolerated. In addition, the activities of this kind of aryl-substituted compound may also be influenced by their poor solubility. Substitution of the terminal amine by various alkyl groups usually led to β_1-adrenergic blocking activity, except **Ia**, **Ij**, **IIa**, **IIb** and **IIj**. It was considered that it could be attributed to the size of the *N*-substituted group. With increased lengthening of the carbon chain of the alkyl group, the β_1-adrenergic blocking activity had greater changes. *N*-Methyl analogues (**Ia**, **Ij**, **IIa** and **IIj**) were either poorly active or inactive. While increasing the length of the *N*-substituted alkyl group enhanced the activity. However, large groups, such as *n*-butyl or aryl groups, led to a significant decrease in the activity.

The compounds bearing a *N*-isopropyl or a *N*-propyl moiety (**Ic**, **Id)** exhibited moderate to strong β_1-adrenergic blocking activity, suggesting that a *N*-alkyl substituent with a three carbon chain may play a crucial role in β_1-adrenergic blocking activity. Of all the compounds, the most promising compound **Ic** exhibited β_1-adrenoceptor blocking activity (inhibition: 52.2%) at 10^{-7} mol·L^{-1}, which was superior to that of propranolol (inhibition: 49.7%).

4 Conclusions

In conclusion, the synthesis and *in vitro* β_1-adrenoceptor blocking effects of a new series of isochroman-4-one oxime ether hybrids are described. Compound **Ic** bearing the *N*-propyl substituted isopropanolamine moiety exhibited the most powerful β_1-adrenoceptor blocking effects, and was comparable or superior to the reference drug propranolol at different concentrations. The results of the biological evaluation elucidate that the isochroman-4-one skeleton can successfully remain intact for significant β_1-adrenoceptor blocking activity. Furthermore, the results also indicated that oxime ethers containing the C=N-O group were well tolerated, and that introduction of an imino group in the side chain of β-blocking agents did not abolish the β-adrenoceptor activity. These findings may provide new insights into the further development of natural isochroman-4-one derivatives as candidates for the treatment of cardiovascular disease.

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天然活性产物异色满-4-酮肟醚类衍生物的合成及其 β-肾上腺素受体阻断活性

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【摘　要】 **目的**：为探索寻找新型心血管药物候选化合物，设计合成了一系列全新结构的异色满-4-酮肟醚类衍生物。**方法**：首先设计合成了天然降压活性产物 3-甲基-7, 8-二羟基异色满-4-酮（XJP）的类似物 **3** 和 **6**，然后通过醚键在肟羟基上引入经典 β-受体阻断剂侧链异丙醇胺基团，合成了一系列异色满-4-酮肟醚类新化合物；采用离体大鼠左心房测试了目标化合物对 β_1-肾上腺素受体的阻断作用。**结果**：获得了 20 个具有肟醚异丙醇胺结构的目标化合物；其 β_1-受体的阻断活性测试结果表明，化合物 **Ic** 活性最强，在 10^{-7} mol·L^{-1} 浓度下对 β_1-受体的抑制率为 52.2%，优于阳性药普萘洛尔(49.7%)；初步获得了构效关系信息。**结论**：对活性天然产物 XJP 结构修饰的结果可为新型心血管药物分子设计提供研究思路。

【关键词】 异色满-4-酮衍生物；肟醚；杂合体；β-受体阻断活性；抗高血压活性

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