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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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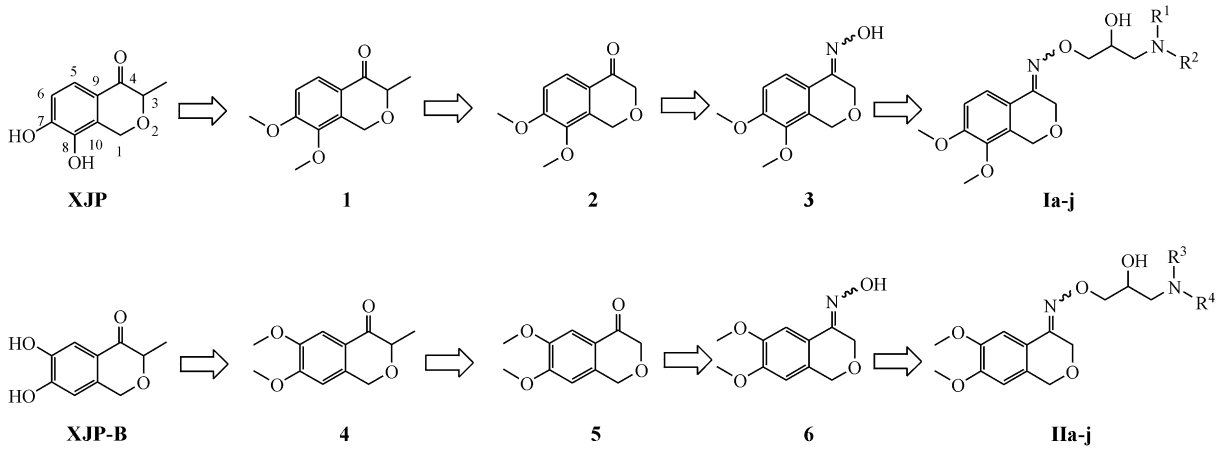

Fig. 1 Strategy for the design of the target compounds from a natural isochroman-4-one

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