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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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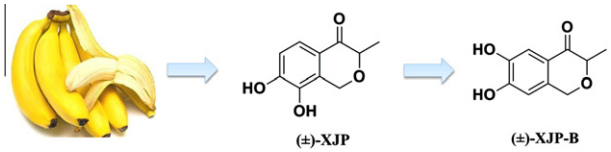

Figure 1. The structures of (±)-XJP and (±)-XJP-B.

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-

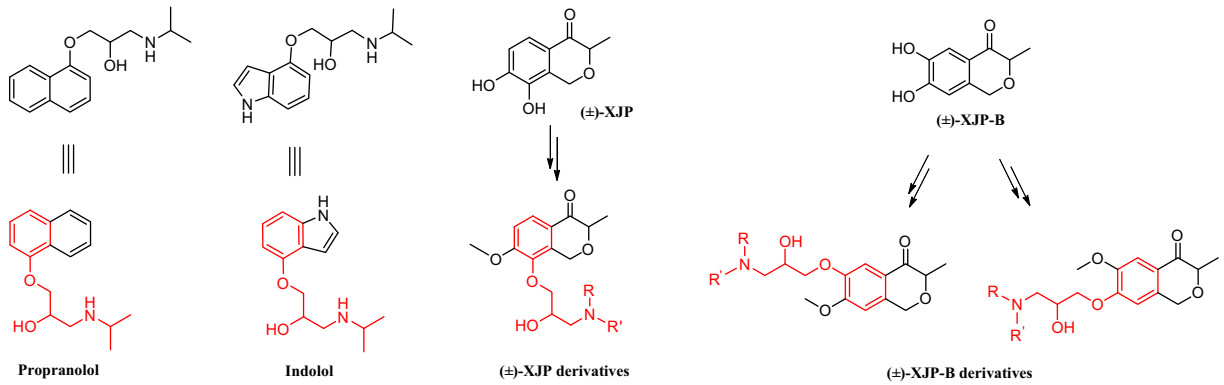

Figure 2. Strategy for the design of β-receptor blockers derived from natural isochroman-4-one.