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Research paper

N-Phenyl indole derivatives as AT_1 antagonists with anti-hypertension activities: Design, synthesis and biological evaluation

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ABSTRACT

The design, synthesis, *in vitro* and *in vivo* evaluation of 6-substituted benzimidazole with 1, 4-disubsituted or 1, 5-disubsituted indole derivatives as novel angiotensin II receptor antagonists are outlined. Radioligand binding assays showed that several 6-substituted benzimidazole derivatives displayed high affinities binding to the angiotensin II type 1 receptor at the same order of magnitude to telmisartan. The biological evaluation on spontaneously hypertensive rats showed that 2-[4-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole-1-yl]methyl]-1*H*-indol-1-yl]benzoic acid, **1c**, could cause significant decrease on MBP in a dose dependent manner. Its maximal response lowered 53 mmHg of MBP at 5 mg/kg and 64 mmHg of MBP at 10 mg/kg after oral administration, and the significant antihypertensive effect lasted beyond 24 h, which was better than both losartan and telmisartan. A study designed to determine acute toxicity showed that **1c** had low acute toxicity with no significant changes in the weight and no obvious untoward reactions. The encouraging results make **1c** an effective and durable anti-hypertension drug candidate and deserve further investigation for therapeutic application.

1. Introduction

Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. On a worldwide basis hypertension has been ranked third as a cause of disability adjusted life years [1]. The renin angiotensin system (RAS) plays an important role in the regulation of blood pressure and electrolyte/fluid homeostasis [2]. This system consists of a cascade of enzymatic reactions, leading to the production of angiotensin II (AII) [3] which is the final site of action in the RAS. RAS elicits multiple biological effects such as increase in blood pressure, vascular contraction and modulation of central drinking behavior [4]. It is widely accepted that angiotensin II type 1 (AT_1) receptor accounts for a majority of the cardiovascular effects evoked by AII. Losartan (Fig. 1) is the first non-peptide orally active AT_1 receptor antagonist [5]. Since then, a series of angiotensin II receptor blockers (ARBs) were used in clinics for the treatment of hypertension. These ARBs share a common mechanism of action, which block the effects of angiotensin II by selectively antagonizing the AT_1 receptor [6]. Recent investigations suggest that ARBs are also useful for treating congestive heart failure (CHF) and also reducing the cardiovascular disease associated with cardiac and vascular remodeling.

Indole derivatives have been extensively studied as a pharmacophore group because of their wide potential bioactivities [7–9]. Poss [10] developed a series of AII receptor antagonists that contain N-phenyl indole group. **BMS-180560** (Fig. 1) was the most potent

Abbreviations: RAS, renin angiotensin system; AII, angiotensin II; ARBs, angiotensin II receptor blockers; FDA, US Food and Drug Administration; DMAP, 4-(dimethylamino)pyridine; NMR, nuclear magnetic resonance; HRMS, high-resolution mass spectrometry; ESI, electrospray ionization; MS, mass spectrometry; DMSO, dimethylsulfoxide; DMF, N,N-dimethylformamide; THF, tetrahydrofuran; AIBN, azodiisobutyronitrile; NBS, bromosuccinimide; VSMC, vascular smooth muscle cell; IC_{50}, half maximal inhibitory concentration; SHR, spontaneously hypertensive rats; MBP, mean blood pressure; DMEM, Dulbecco's Modified Eagle's Medium; FBS, fetal bovine serum.

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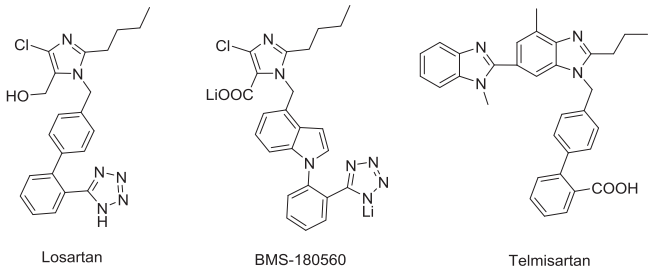

Fig. 1. Non-peptide angiotensin II receptor antagonists.

analog identified in the series, which could cause sustained reduction in blood pressure for over 72 h. In our preliminary work [11], we used N-phenyl indole group instead of biphenyl system as a strategy to generate new potent and long lasting antihypertensive agents.

Telmisartan (Fig. 1) is the most recently marketed drug as an AT_1 receptor antagonist. It has a 24-h antihypertensive efficacy and causes reductions in clinic BP similar to those newer agents in its class [12].

Herein, we report on the design, synthesis, and biological activity of a novel class of potent non-peptide AT_1 receptor antagonists, in which the biphenyl moiety of telmisartan is replaced with N-phenyl indole group. Some of these designed compounds have been authorized as Chinese patent [13]. The dominant conformations of the designed compounds **1c**, **2e**, and **5b** as well as telmisartan were presented in Fig. 2 using computer software Spartan 10. According to their overlay conformations, it is indicated that they align well with each other.

2. Results and discussion

2.1. Chemistry

We developed a general and useful synthesis of indole derivatives with a variety of substituents. In short, this procedure comprised of two coupling parts, one gave the bromide and the other gave the heterocyclic amine. We initially synthesized the halide component which was coupled to the heterocyclic fragment to construct the target molecule.

The synthesis of indole bromides (**11a**,**b**) is outlined in Scheme 1. N-benzoyl protected methylindoles (**10a**,**b**) were prepared from the corresponding commercially available methylindoles (**9a**,**b**) by reacting with benzoyl chloride. They were then brominated with NBS to give the indole bromides (**11a**,**b**). The bromides **11a**,**b** were then used in subsequent synthetic transformations.

The synthesis of **1a**–**e** and **2a**–**e** is outlined in Schemes 2 and 3. The substituted benzimidazoles (**7a**–**e**) were prepared from the commercially available methyl 4-amino-3-methylbenzoate (**6**) by four steps. The phenylamine (**6**) was reacted with alkyl acyl chloride in DCM, nitrated with concentrated nitric acid, hydrogenated with hydrogen and finally cyclized in acetic acid to produce benzimidazoles (**7a**–**e**). The obtained benzimidazoles were converted to the corresponding bis-benzimidazole derivatives (**8a**–**e**) by reacting with 2 M NaOH, and cyclized with N-methylbenzene-1,2-diamine in the presence of polyphosphorous acid. Each bis-benzimidazole derivatives (**8a**–**e**) was reacted with an indole bromide (**11a** or **11b**) to generate bis-benzimidazole indole derivatives (**12a**–**e**, **15a**–**e**). After deprotecting the benzoyl group, the obtained indole derivatives were alkylated with 2-fluorobenzonitrile to produce benzonitrile (**14a**–**e**, **17a**–**e**); which were then hydrolyzed with 5 M NaOH in methanol to yield the final products, **1a**–**e** and **2a**–**e**.

The tetrazole **3** was synthesized by treating benzonitrile **14c** with sodium azide and chlorotributylstannane at 160 °C in DMF, as shown in Scheme 4.

The preparation of **4a**–**c** and **5a**–**c** is outlined in Schemes 5 and 6, which is similar to **1a**–**e** and **2a**–**e**. The commercially available 2-bromopyridine (**18**) was reacted with 3-methylphenylmagnesium bromide (**19**) to give the coupling product, **20**; which was then nitrated with concentrated nitric acid and then hydrogenated to produce amino compound. Acylation of the resulting amino compound with alkyl acyl chloride in DCM, nitration, hydrogenation, and formation of the benzimidazole were performed using the same procedures as described for the preparation of **8a**–**e** to give the benzimidazole derivatives (**21a**–**c**). Coupling the obtained benzimidazole derivatives with indole bromide (**11a**,**b**), deprotection, alkylation, and hydrolyzation of the benzonitrile were also performed using the same procedures as described for the preparation of **1a**–**e** and **2a**–**e** to give the final products, **4a**–**c** and **5a**–**c**.

The aforementioned synthetic route was not amenable to scale-up, where the preparation of heterocyclic amine could be in high yield, but the bromide fragment suffered from low yields coupled with complex manipulative procedures. For this reason, we developed a new method for the preparation of bromide fragment: Indole-4-formaldehyde (or indole-5-formaldehyde) was selected as the starting material to avoid large amounts of by-products compared to the benzylic methyl group. Here, we used indole-4-formaldehyde to present the modified approach. The preparation of 1, 5-disubstituted indole compounds was in a similar manner.

The modified procedure is shown in Scheme 7. Indole-4-

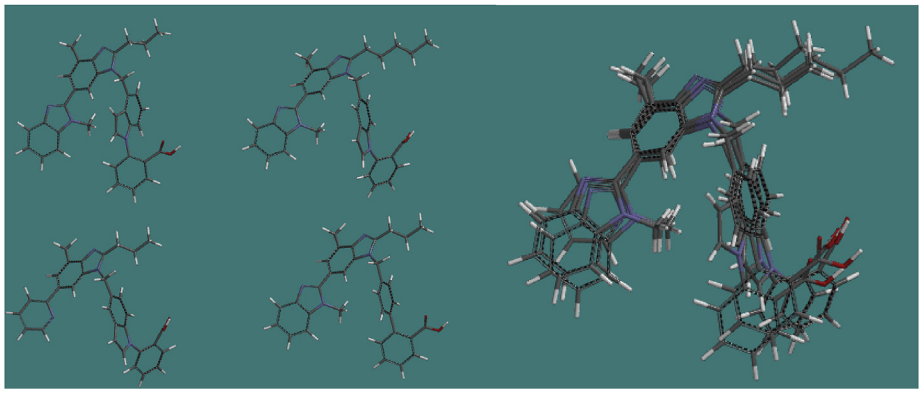

Fig. 2. Energy-minimized conformations of **1c**, **2e**, **5b**, telmisartan and their overlay conformations.