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Design, synthesis, and biological evaluation of 1,2,4-triazole bearing 5-substituted biphenyl-2-sulfonamide derivatives as potential antihypertensive candidates

Jie Liu [a,c], Qin Liu [a,b], Xue Yang [a,b], Shengtao Xu [a,b], Hengyuan Zhang [a,b], Renren Bai [a,b], Hequan Yao [a,b,*], Jieyun Jiang [d], Mingqin Shen [e], Xiaoming Wu [a,b], Jinyi Xu [a,b,*]

[a] State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, PR China
[b] Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, PR China
[c] Department of Organic Chemistry, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, PR China
[d] Department of Microbiology, Immunology and Molecular Genetics, University of Kentucky College of Medicine, 800 Rose Street, Lexington, KY 40536, USA
[e] Jiangsu Provincial Institute of Traditional Chinese Medicine, Nanjing 210028, PR China

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ABSTRACT

A series of novel 1,2,4-triazole bearing 5-substituted biphenyl-2-sulfonamide derivatives were designed and synthesized to develop new angiotensin II subtype 2 (AT_2) receptor agonists as novel antihypertensive candidates. It was found that **14f** (IC_{50} = 0.4 nM) and **15e** (IC_{50} = 5.0 nM) displayed potent AT_2 receptor affinity and selectivity in binding assays. Biological evaluation in vivo suggested that **14f** is obviously superior to that of reference drug losartan in RHRs, and meanwhile, **14f** has no significant impact on heart rate. The interesting activities of these compounds may make them promising candidates as antihypertensive agents.

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1. Introduction

The renin angiotensin system (RAS) plays a key role in blood pressure regulation and electrolyte homeostasis.[1] The octapeptide angiotensin II (Ang II, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), recognized as the most important bioactive peptide of the RAS, is the endogenous activator of the angiotensin II subtype 1 (AT_1) and the angiotensin II subtype 2 (AT_2) receptors. The AT_1 receptor mediates the well-known physiological effects of Ang II, such as vasoconstriction, aldosterone release, stimulation of sympathetic transmission, and cellular growth.[2–4] AT_1 receptor antagonists (the Sartans) are currently used as effective clinical antihypertensive drugs. The function of the AT_2 receptor subtype, which was cloned more recently and found to share only 32–34% sequence identity with the AT_1 receptor remains elusive and somewhat controversial.[5,6] It has been suggested that it plays a role in mediating antiproliferation, cellular differentiation, apoptosis, and vasodilation.[7–10] One notable feature of the AT_2 receptor is the high level of expression in most fetal tissues, including the brain. The AT_2/AT_1 receptor ratio decreases dramatically after birth,[11,12] which may support a significant involvement of the AT_2 receptor in fetal development. In addition, most remarkably, there is substantial evidence that the AT_2 receptor can offset or counteract the effects mediated by the AT_1 receptor. Correspondingly, AT_2 receptor played the role of a kind of 'natural AT_1 receptor antagonist.'

On the basis of these functions of AT_2 receptor, it has been proposed that the AT_2 receptor could be an important target in the therapeutic area of hypertension and cardiac remodeling. Anders Hallberg initiated a research program aiming to identify nonpeptide and drug-like AT_2 receptor agonists. The nonselective AT_1 receptor agonist **L-162,313** was selected as the lead structure. **L-162,313** is a nonpeptidic structure that shows similar affinities to both the AT_1 receptor and the AT_2 receptor. Furthermore, the compound has been proven to act as an agonist at both the AT_1 receptor and at the AT_2 receptor.[13–15] Recently, the first nonpeptidic selective AT_2 receptor agonist **M024** was designed by introducing a small unsubstituted imidazole in the benzylic position of the **L-162,313**. The unsubstituted imidazole provided a good moiety to obtain high affinity, AT_1/AT_2 selectivity as well as agonism (Fig. 1).[16,17]

Meanwhile, the compounds where the thiophene structure has been replaced with a phenyl maintain affinity and selectivity towards the AT_2 receptor.[18] For example, the compound **L-162,782**

* Corresponding authors. Tel.: +86 025 83271042 (H.Y.), +86 025 83271299 (J.X.).
E-mail addresses: hyao@cpu.edu.cn (H. Yao), jinyixu@china.com (J. Xu).

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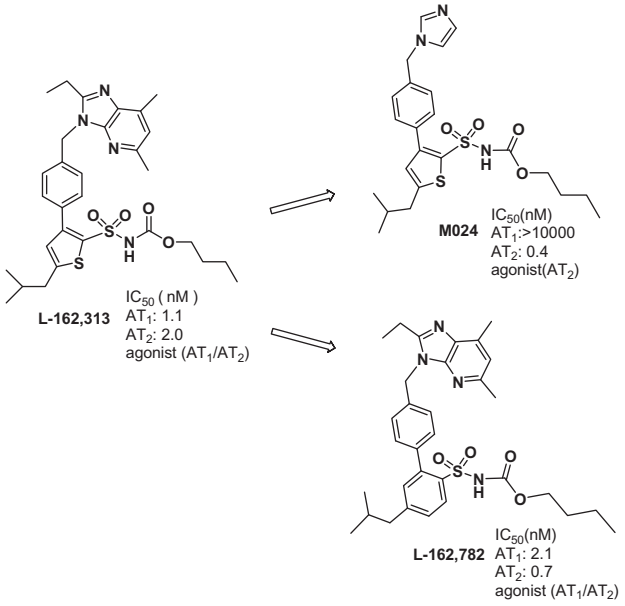

Figure 1. The structures of known AT_1/AT_2 agonists.

showed the high affinities to the AT_1 receptor and AT_2 receptor (Fig. 2).

Previously, we designed and synthesized a series of 1,2,4-triazole derivatives with *N*-phenylpyrrolyl-2-tetrazole moiety. Among them, compound **ATPT** was found to be an orally active AT_1 receptor antagonist, and also found to be more potent than losartan.[19] Furthermore, we disclosed the synthesis and biological evaluation of 4′-[(benzimidazole-1-yl)-methyl]biphenyl-2-sulfonamides derivatives.[20] In an effort to find novel drugs acting on RAS, we became interested in AT_2 receptor agonists with good affinity and selectivity, and focused on the researches of derivatives with diphenyl sulfonamide scaffold. On the basis of SAR information of **M024**,[21] especially we noticed that the replacement of the imidazole in compound **M024** with various substituted or unsubstituted heterocycles rendered analogues with high AT_2 receptor affinity.[22] We decided to use compound **L-162,782** as the lead structure, meanwhile the unsubstituted 1,2,4-triazole group was chosen as replacement for the imidazopyridine ring in the compound **L-162,782**, therefore two modification strategies were achieved. One is by introducing 1,2,4-triazole fragment into the benzylic position of substituted diphenyl sulfonamide scaffold, as well as alteration of the sulfonylcarbamate part (Series I), and the other is the replacement of the bicyclic imidazopyridine ring with amino groups (Series II). Herein, we would like to report some of the synthesized compounds with good AT_2 receptor affinity and selectivity including ligands proven to serve as AT_2 agonists (Fig. 2).

2. Results and discussions

2.1. Chemistry

The synthetic route of the sulfonamides (**3a–b**, **5** and **7**) is shown in Scheme 1. The isobutyl- and methoxyphenylsulfonyl chloride (**2a–b**) were synthesized from their corresponding isobutyl- or methoxybenzene (**1a–b**) with chlorosulfonic acid, while the methylphenylsulfonyl chloride (**4**) was commercially available. These alkyl- or alkoxyphenylsulfonyl chlorides were transformed into the corresponding *t*-butyl protected sulfonamides (**3a–b** and **5**) in excellent yield by treatment with *t*-butylamine in CH_2Cl_2. Meanwhile, compound **6** was achieved from compound **5** through a regioselective bromination with NBS in quite high yield. Subsequent N-alkylation of **6** with diethylamine in CH_2Cl_2 gave another *t*-butyl protected sulfonamide **7**.

The benzeneboronic acids **8a–b**, the key intermediates for the synthesis of the compounds in both series, were prepared in generally good yields through two steps (Scheme 2). Treatment of the *t*-butyl protected sulfonamides (**3a–b**, **5** and **7**) with two equivalents of *n*-BuLi formed the dianions. These anions resided at the position 2′ as directed there by the sulfonamide. The anions were quenched with triisopropylborate and worked up with dilute acid to afford the boronic acid products.

The compounds in series I were prepared as outlined in Scheme 3. The 4-bromo-benzyl-1,2,4-triazole (**11**) was obtained by treating the 1,2,4-triazole (**10**) with K_2CO_3 in THF and subsequently adding 4-bromobenzylbromide (**9**) to give the desired compound in moderate yield. Compound **11** were then coupled with the benzeneboronic acids **8a–d** under Suzuki conditions with $Pd(OAc)_2$ and PPh_3 as catalyst and with NaOH as base to give the *tert*-butyl protected compounds **12a–d** in 26–87% yields. Deprotection by TFA, to give the primary sulfonamides (**13a–d**) followed by reaction with the selected alkyl chloroformates, acyl chlorides and

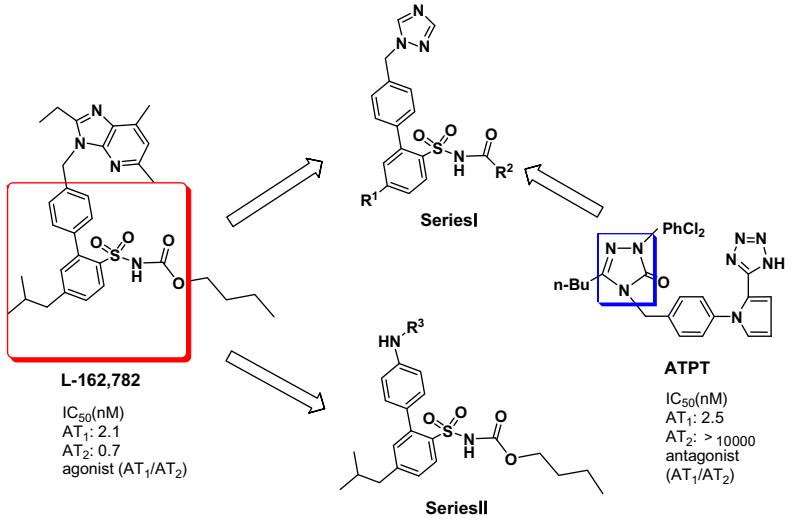

Figure 2. Strategy for the design and optimization of target AT_2 agonists.

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