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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

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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.

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**

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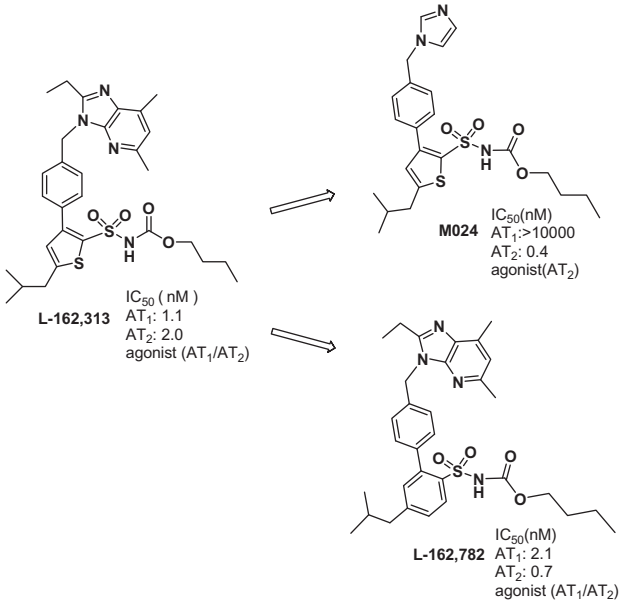


Figure 1. The structures of known AT_1/AT_2 agonists.

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

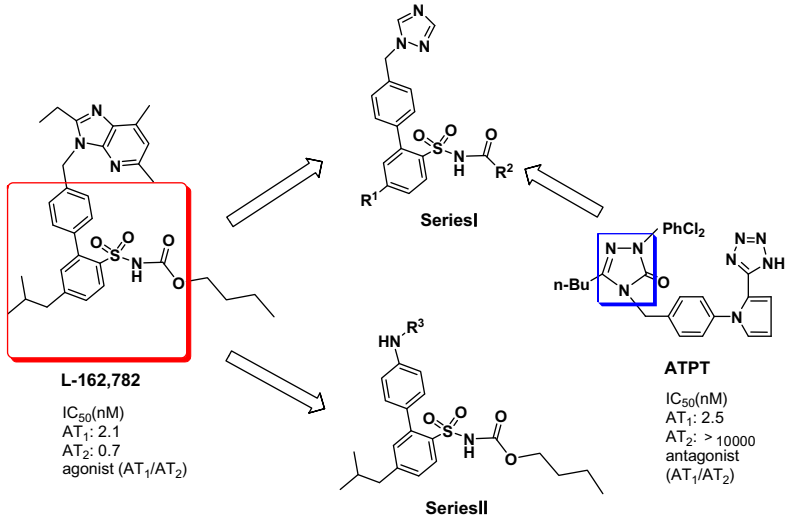
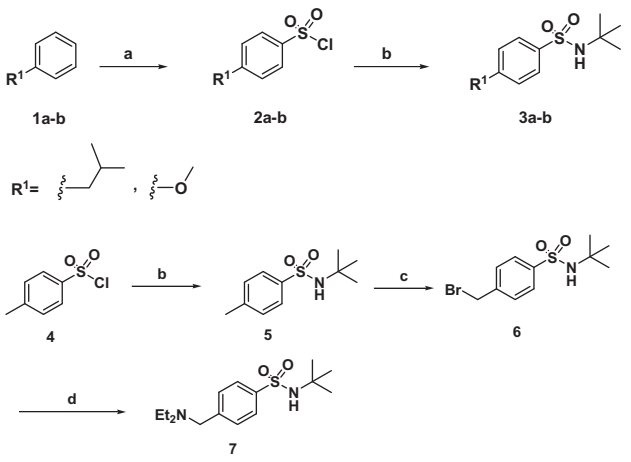
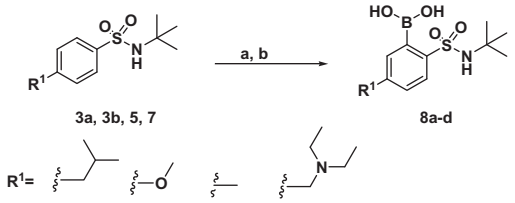


Figure 2. Strategy for the design and optimization of target AT_2 agonists.



Scheme 1. Synthesis of compounds **3a–b** and **7**. Reagents and conditions: (a) chlorosulfonic acid, $CHCl_3$, rt, 1 h; (b) *t*-$BuNH_2$, CH_2Cl_2, rt, 8 h; (c) NBS, AIBN, $CHCl_3$, reflux, 4 h; (d) diethylamine, CH_2Cl_2, rt, 13 h.



Scheme 2. Synthesis of compounds **8a–d**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then −20 °C, 4 h; (b) triisopropylborate, −78 °C, then rt overnight.

benzoyl chlorides, afforded **14a–g**, **15a–f**, **16a–f** and **17a–c** respectively.

The synthesis of series II, outlined in Scheme 4, started with a set of different N-monoalkylated 4-bromoanilines (**18a–d**), which were prepared by selective N-monoalkylation of 4-bromoaniline (**18a**) with alcohols in excellent yields using triphenylphosphine (PPh_3) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dichloromethane at room temperature.[23]

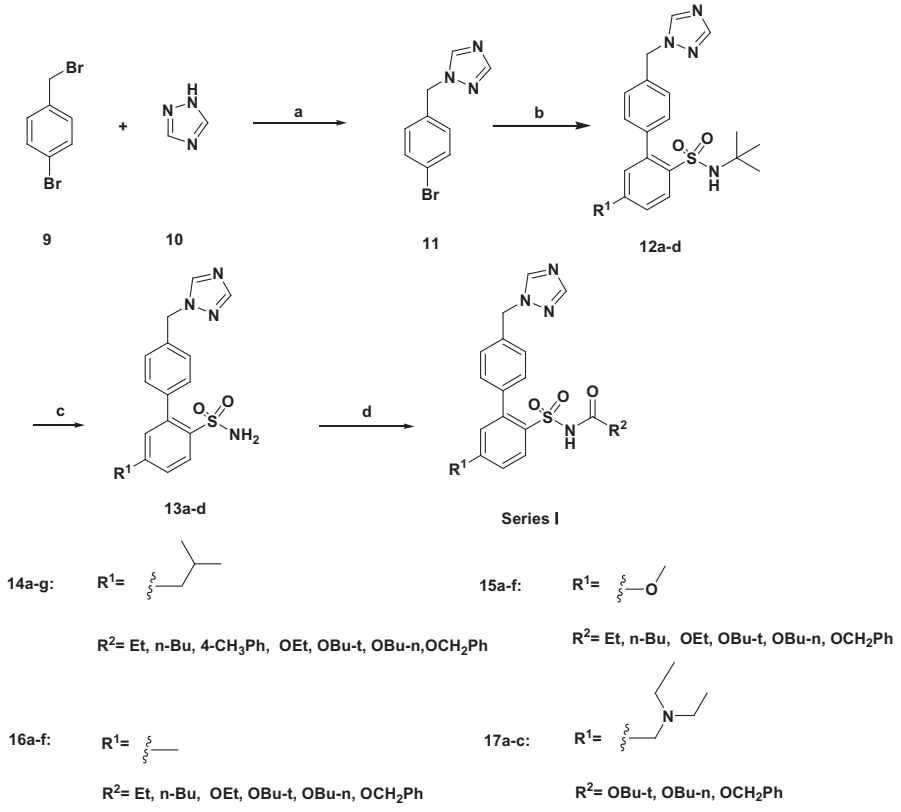
Bromoanilines (**18a–d**) were then coupled with the isobutylbenzeneboronic acid **8a**, prepared under Suzuki conditions[24] with $Pd(OAc)_2$ and PPh_3 as catalyst and with NaOH as base to give the *tert*-butyl protected compounds **19a–d** in moderate yields. Deprotection of compounds **19a–d** by TFA,[25] a milder deprotecting reagent, delivered the primary sulfonamides (**20a–d**) that were subsequently treated with *n*-butyl chloroformate, at ambient temperature, in pyridine to afford the target compounds of series II (**21a–d**).

2.2. Pharmacological evaluation

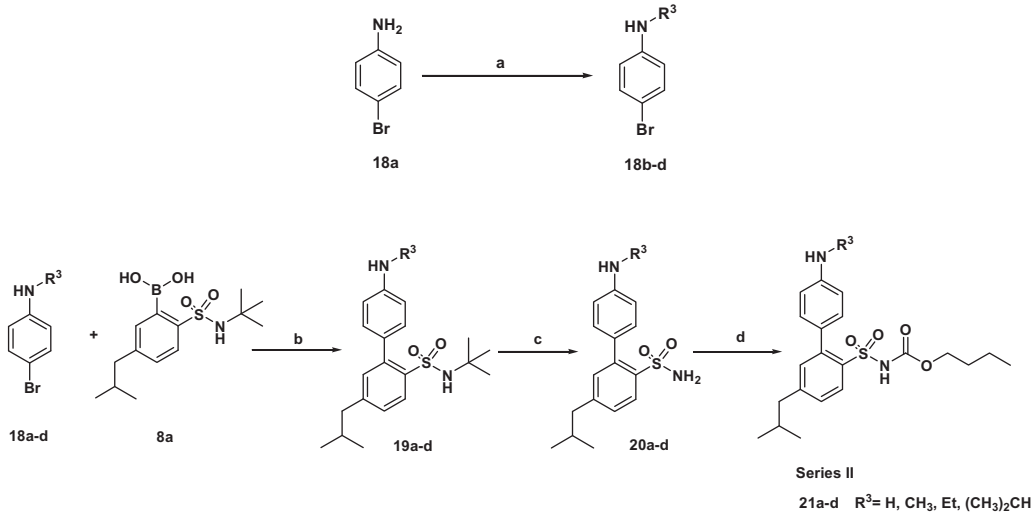
2.2.1. Binding assays

All target compounds were evaluated in radioligand-binding assays by displacement of [^{125}I] Ang II from AT_1 receptors in rat liver membranes and from AT_2 receptors in pig uterus membranes.[26,27] The natural substrate Ang II and the selective AT_1 receptor antagonist losartan were used as reference substances.[28] The affinity results are presented in Table 1.

In series I all compounds exhibited a broad range (potent to inactive) of affinity for AT_2 receptor and none of the compounds possessed any affinity for the AT_1 receptor (Table 1). However, none of the compounds in series II encompassing amine moiety



Scheme 3. Synthesis of compounds **14–17**. Reagents and conditions: (a) K_2CO_3, THF, reflux, 15 h; (b) $Pd(OAc)_2$, PPh_3, NaOH (aq), **8a–d**, ethanol/toluene, reflux, 5 h; (c) TFA, rt, 12 h; (d) alkyl chloroformates or benzoyl chlorides, pyridine, 0 °C, 4 h.



Scheme 4. Synthesis of compounds **21a–d**. Reagents and conditions: (a) alcohols, DDQ, PPh_3, CH_2Cl_2, rt, 2 h; (b) $Pd(OAc)_2$, PPh_3, NaOH (aq), ethanol/toluene, reflux, 5 h; (c) TFA, rt, 12 h; (d) butyl chloroformate, pyridine, 0 °C, 4 h.

showed any AT_1 affinity nor AT_2 affinity. It is suggested that introduction of unsubstituted 1,2,4-triazole group into the benzylic position of substituted diphenyl sulfonamide scaffold provided good AT_2 selectivity and affinity.

The activities of compounds **14a–g** with isobutyl substituent at the 5-position changed obviously with modifications of the sulfonamide side chain. Compound **14f** possessing *n*-butyloxy group clearly demonstrated the most powerful AT_2 affinity (IC_{50} = 0.4 nM). Removing the carbamate oxygen from the side chain gave a compound (compound **14b**) with an 80-fold decrease in affinity for the AT_2 receptor as compared to **14f**. Shortening or branching of the butyloxy group rendered 25 or 140 times decrease of the affinity for the AT_2 receptor (compounds **14d** and **14e**), and surprisingly, introduction of the phenyl groups resulted in totally inactive compounds (compounds **14c** and **14g**). Shortening of the *n*-butyl group (compound **14a**) also brought a twice decrease in affinity for the AT_2 receptor as compared to **14b**. These trends were also observed after replacing the isobutyl substituent with either methoxy group as in **15a–f**, or methyl group in **16a–f**, or diethylaminomethyl group in **17a–c**. On the other hand, in the case of constant sulfonamide side chain, change of substituents at the 5-position of the diphenyl scaffold could also affect the activities of these compounds. For example, among the compounds **14f**, **15e**, **16e** and **17b**, all of these compounds with the *n*-butyloxy group on sulfonamide side chain, **14f** showed best AT_2 affinity, followed the **16e** and **17b** had the lowest affinities with IC_{50} value 16 and 10 nM, respectively. And the potent order of substituent was as follows: *i*-bu > OMe > $MeNEt_2$ > Me. This order was observed after the alteration of the substituent on sulfonamide side chain.

2.2.2. In vivo antihypertensive activities of compounds 14f and 15e

In vitro biological evaluation, compounds **14f** and **15e** showed potent AT_2 receptor affinity and selectivity in binding assays among the titled compounds. Therefore, compounds **14f** and **15e** were selected for further evaluation of antihypertensive effects in SHRs (Table 2). After oral administration of losartan (20 mg/kg), **14f** (20 mg/kg) and **15e** (20 mg/kg) to SHRs, the blood pressure and heart rate were determined from 0 to 8 h. The results showed that **14f** and **15e** reduced the blood pressure significantly and these trends continued throughout the remaining time of the study. The maximum antihypertensive effect on systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) of compound **15e** was approximately equivalent to that of losartan at the same dose. Meanwhile, the maximum antihypertensive effect on SAP and DAP of compound **14f** was prominently more effective than that of losartan. Furthermore, the decreases in MAP by both compounds were significant and the reduction in MAP by **14f** was even more than that of losartan. Heart rates (HR) recorded taken from SHRs proved that **14f** and **15e**, just the same as losartan, did not cause noticeable changes of HR. (Fig. 3) Preliminary in vivo biological evaluation showed that both compounds **14f** and **15e** were promising enough to warrant further investigation.

3. Conclusions

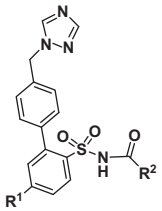
In summary, two series of derivatives with diphenyl sulfonamide scaffold were designed and synthesized to develop new antihypertensive agents with good AT_2 receptor affinity and selectivity. One series of compounds, introducing of unsubstituted 1,2,4-triazole group into the benzylic position of substituted diphenyl sulfonamide scaffold, exhibited a broad range affinity for AT_2 receptor. However, none of the compounds in another series, encompassing amine moiety, showed any AT_1 affinity nor AT_2 affinity. Compound **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 more potent and efficacy than losartan in RHRs, and meanwhile, **14f** has no significant impact on heart rate. It is suggested that merging together unsubstituted 1,2,4-triazole moiety with the biphenyl sulfonamide scaffold, was a successful design strategy to obtain the bioactive conformation of selective nonpeptide AT_2 receptor agonists.

4. Experimental

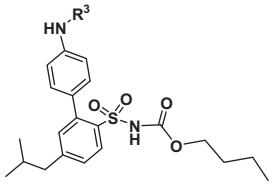
4.1. Chemistry

Reagents and all solvents were purchased from Shanghai Chemical Reagent Company and used without further purification. All of the experiments were monitored by analytical thin-layer chromatography (TLC) performed on silica gel GF254 precoated plates. Column chromatography was carried out using silica gel (200–300 mesh). The purities of all of the compounds (>95%) used

Table 1
Structures and binding assays for the AT_1 receptor and AT_2 receptor of target compounds



Compound	R^1	R^2	AT_2 receptor IC_{50} (nM)	AT_1 receptor IC_{50} (nM)
14a	*i*-Bu	Et	68 ± 5.2	>10,000
14b	*i*-Bu	*n*-Bu	31 ± 4.5	>10,000
14c	*i*-Bu	4-MePh	>10,000	>10,000
14d	*i*-Bu	OEt	10 ± 0.9	>10,000
14e	*i*-Bu	OBu-*t*	55 ± 3.4	>10,000
14f	*i*-Bu	OBu-*n*	0.4 ± 0.07	>10,000
14g	*i*-Bu	OCH_2Ph	>10,000	>10,000
15a	OMe	Et	184 ± 11	>10,000
15b	OMe	*n*-Bu	99 ± 10	>10,000
15c	OMe	OEt	36 ± 2.9	>10,000
15d	OMe	OBu-*t*	170 ± 12	>10,000
15e	OMe	OBu-*n*	5.0 ± 0.7	>10,000
15f	OMe	OCH_2Ph	>10,000	>10,000
16a	Me	Et	223 ± 21	>10,000
16b	Me	*n*-Bu	106 ± 14	>10,000
16c	Me	OEt	64 ± 8.5	>10,000
16d	Me	OBu-*t*	289 ± 18	>10,000
16e	Me	OBu-*n*	16 ± 0.9	>10,000
16f	Me	OCH_2Ph	>10,000	>10,000
17a	Et_2NCH_2	OEt	117 ± 14	>10,000
17b	Et_2NCH_2	OBu-*n*	10 ± 1.1	>10,000
17c	Et_2NCH_2	OCH_2Ph	>10,000	>10,000



Compound	R^3	AT_2receptor IC_{50} (nM)	AT_1 receptor IC_{50} (nM)
21a	H	>10,000	>10,000
21b	Me	>10,000	>10,000
21c	Et	>10,000	>10,000
21d	Pr-*n*	>10,000	>10,000
Losartan		>10,000	85 ± 6.5
PD123,319		29 ± 3.0	>10,000

for biological screening were determined by high-performance liquid chromatography (HPLC) (Agilent, 1260 INFINITY) using a Gemini C18 column (4.6 × 150 mm, 5 μm) eluted with a gradient mixture of acetonitrile/water (1:2). ^{1}H NMR spectra were recorded on Bruker-ACF spectrometer (300 or 500 MHz) in DMSO-d_6. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard. Multiplicities are given as s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet), m (multiplet) and br s (broad signal). IR (in cm^{-1}) spectra in KBr pellets on a Bruker FT-IR TENSOR 27 instrument. Mass spectra were recorded on Agilent LC/MSD TRAP SL spectrometer equipped with an electrospray ionisation (ESI) interface; High-resolution mass spectra were recorded using Agilent QTOF 6520. Melting points were determined using MEL-TEMP II melting point apparatus and are uncorrected.

4.1.1. General procedure for synthesis of compounds 2a–b

Chlorosulfonic acid (0.1 mol) was added slowly to a solution of corresponding isobutyl- or methoxybenzene (**1a** or **1b**) (25.0 mmol) in $CHCl_3$ (30 mL) in an ice cold bath and the mixture was stirred at rt for 45 min. The reaction was poured into ice-cold water (30 mL) and the resulted mixture was extracted twice with CH_2Cl_2 (20 mL). The combined organic layer was washed with saturated brine (30 mL) twice and dried over anhydrous $MgSO_4$, and the solvent was evaporated to give the corresponding compound **2a** or **2b**.

4.1.2. General procedure for synthesis of compounds 3a, 3b and 5

The respective sulfonylchloride (15 mmol) was dissolved in dry CH_2Cl_2 (30 mL). The mixture was cooled on an ice bath and *tert*-butylamine (15 mmol) was added dropwise. After completion of addition, the reaction mixture was left stirring at rt for 8 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (30 mL × 2) and brine (30 mL × 2). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated to achieve the pure compounds **3a**, **3b** and **5** without further purification.

4.1.3. 4-(Bromomethyl)-*N*-*tert*-butylbenzenesulfonamide (6)

Compound **5** (12.6 mmol) was dissolved in $CHCl_3$ (40 mL), then NBS (10.1 mmol) and AIBN (0.288 mmol) were added respectively.

Table 2
Effects on blood pressure in renal antihypertensive rats

Group	Index	Before administration	After administration				
			1 h	2 h	4 h	6 h	8 h
Control	SAP (mmHg)	169.01 ± 9.18	167.68 ± 15.89	169.99 ± 14.64	162.82 ± 13.38	163.63 ± 13.04	168.33 ± 20.27
	Δ		−1.33	0.98	−6.19	−5.38	−0.68
	DAP (mmHg)	137.15 ± 9.31	134.31 ± 14.11	140.36 ± 13.51	135.41 ± 14.66	132.87 ± 6.06	135.06 ± 13.23
	Δ		−2.84	3.21	−1.74	−4.28	−2.09
	MAP (mmHg)	147.77 ± 8.64	145.44 ± 14.33	150.24 ± 13.72	144.54 ± 13.79	143.12 ± 7.26	146.14 ± 14.74
	Δ		−2.33	2.47	−3.23	−4.65	−1.63
	HR (BPM)	387.22 ± 15.36	384.07 ± 18.09	378.56 ± 22.98	378.15 ± 22.25	379.94 ± 21.56	399.88 ± 40.05
	Δ		−3.15	−8.66	−9.07	−7.28	12.66
Losartan	SAP (mmHg)	178.10 ± 10.5	175.30 ± 4.12	172.89 ± 10.1	162.55 ± 11.6	157.87 ± 14.3	164.08 ± 12.1
	Δ		−2.80	−5.21	−15.55*	−20.23**	−14.02*
	DAP (mmHg)	150.15 ± 12.4	142.39 ± 10.04	141.19 ± 9.6	135.90 ± 9.6	132.57 ± 8.1	137.06 ± 10.7
	Δ		−7.76	−8.96	−14.25*	−17.58**	−13.09
	MAP (mmHg)	155.23 ± 13.46	152.18 ± 9.85	147.90 ± 10.87	140.10 ± 12.19	136.11 ± 15.24	140.68 ± 10.74
	Δ		−3.05	−7.33	−15.13*	−19.12**	−14.55*
	HR (BPM)	389.65 ± 12.1	387.65 ± 8.35	382.55 ± 22.1	379.08 ± 28.2	375.60 ± 12.2	376.45 ± 18.9
	Δ		−2.00	−7.10	−10.57	−14.05	−13.20
14f	SAP (mmHg)	171.89 ± 13.91	164.64 ± 11.26	167.63 ± 17.89	157.60 ± 15.50	150.95 ± 14.82	156.67 ± 15.44
	Δ		−7.25	−4.26	−14.29*	−20.94**	−15.22**
	DAP (mmHg)	142.45 ± 13.71	147.38 ± 10.22	138.90 ± 13.54	130.13 ± 12.28	121.09 ± 15.10	128.35 ± 15.40
	Δ		4.93	−3.55	−12.32*	−21.36**	−14.10*
	MAP (mmHg)	152.26 ± 14.96	156.69 ± 7.97	147.48 ± 14.19	138.10 ± 12.19	130.38 ± 14.69	137.17 ± 14.37
	Δ		4.43	−4.78	−14.16*	−21.88**	−15.09**
	HR (BPM)	383.92 ± 32.21	391.17 ± 27.46	378.90 ± 27.91	369.39 ± 27.37	367.23 ± 45.90	369.59 ± 50.47
	Δ		7.25	−5.02	−14.53	−16.69	−14.33
15e	SAP (mmHg)	175.12 ± 10.34	171.71 ± 4.12	170.86 ± 14.39	164.41 ± 13.20	156.18 ± 11.60	165.02 ± 12.09
	Δ		−3.41	−4.26	−10.71*	−18.94**	−10.10*
	DAP (mmHg)	144.67 ± 11.09	140.46 ± 11.55	139.61 ± 12.02	134.35 ± 13.70	127.31 ± 14.58	131.57 ± 12.06
	Δ		−4.21	−5.06	−10.32*	−17.36**	−13.1*
	MAP (mmHg)	155.34 ± 13.58	151.25 ± 8.24	149.72 ± 12.61	145.19 ± 10.66	138.26 ± 15.04	143.15 ± 10.41
	Δ		−4.09	−5.62	−10.15*	−17.08**	−12.19*
	HR (BPM)	385.13 ± 30.11	392.18 ± 24.66	377.49 ± 28.31	371.68 ± 21.80	370.66 ± 32.38	362.23 ± 37.69
	Δ		7.05	−7.64	−13.45	−14.47	−22.90

Each value represents the mean ± SEM (n = 8).
Significance levels $^{*}p < 0.1$ and $^{**}p < 0.05$ as compared with the respective control.
Changes of BP (HR) (Δ) = BP (HR) after administration−BP (HR) before administration.

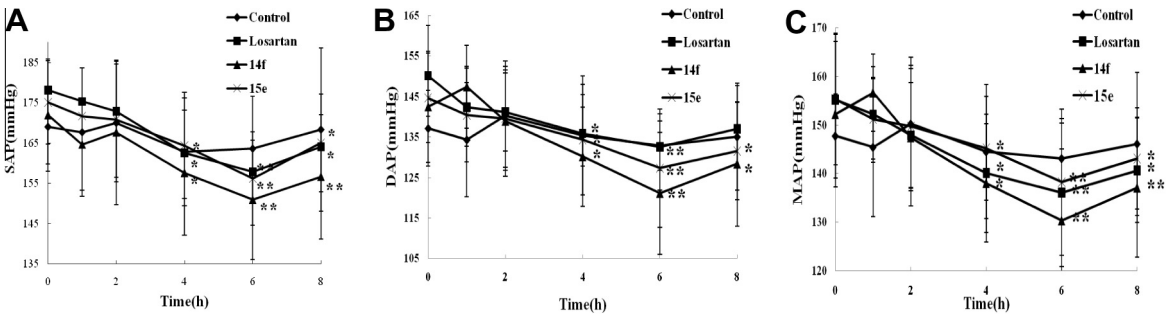


Figure 3. (A) The acute antihypertensive activities of compound **14f**, **15e** and losartan in RHRs (SAP, systolic arterial pressure); (B) The acute antihypertensive activities of compound **14f**, **15e** and losartan in RHRs (DAP, diastolic arterial pressure); (C) the changes of heart rate (HR) of compound **14f**, **15e** and losartan in RHRs. Each value represents the mean ± SEM (n = 8).

The mixture was stirred and allowed to reflux for 4 h. The solvent was removed leaving oil which was dissolved in ethyl acetate (30 mL) and washed with water (30 mL). After drying over anhydrous $MgSO_4$ and evaporating under reduced pressure, the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:5, v/v) as eluent to afford **6** as yellow oil in 92.4% yield.

4.1.4. *N-tert*-Butyl-4-[(diethylamino)methyl]benzenesulfonamide (7)

Compound **6** (20.1 mmol) was dissolved in CH_2Cl_2 (30 mL) then diethylamine (0.101 mol, 9.7 mL) was added dropwise. The reaction mixture was left stirring at rt for 13 h. Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH (30:1, v/v) as eluent to afford **7**.

Yellow oil, yield 49.3%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.239 (9H, s), 1.425 (6H, t, J = 7.2 Hz), 3.132 (4H, q, J = 7.5 Hz), 4.289 (2H, s), 5.583 (1H, s, NH), 7.910 (2H, d, J = 8.4 Hz), 7.997 (2H, d, J = 8.4 Hz).

4.1.5. General procedure for synthesis of compounds 8a–d

To a cooled (−78 °C) solution of compounds **3a**, **3b**, **5** and **7** in dry THF (30 mL) was added n-BuLi (2.5 M/L) under nitrogen and the reaction was stirred for 1 h. The temperature was raised to −20 °C and kept for 3 h and subsequently decreased to −78 °C.

Triisopropyl borate was then added. The reaction mixture was stirred over night at room temperature. The reaction mixture was cooled (0 °C) and treated with an excess of 2 M HCl solution. The mixture was extracted with EtOAc (20 mL × 2) and the combined organic phase was washed with water and brine. The organic layer was dried with $MgSO_4$, filtered and evaporated. The crude product was then purified by silica gel column chromatography using ethyl acetate/petroleum ether as eluent to afford **8a–d**.

4.1.6. 2-(*N*-*tert*-Butylsulfamoyl)-5-isobutylphenylboronic acid (8a)

According to the general procedure compound **3a** (14.6 mmol) was dissolved in dry THF (30 mL) and reacted with *n*-BuLi (2.5 M in hexane, 29.3 mmol) and triisopropyl borate (17.6 mmol). The compound **8a** was obtained as Yellow oil in 56.3% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.863 (6H, d, J = 6.6 Hz), 1.079 (9H, s, *t*-Bu), 1.858 (1H, m, CH), 2.544 (2H, d, J = 6.9 Hz, CH_2CH), 6.825 (1H, s, NH), 7.271 (1H, d, J = 4.2 Hz, H-4), 7.381 (1H, s, H-6), 7.721 (1H, d, J = 7.8 Hz, H-3), 8.356 (2H, s, $B(OH)_2$).

4.1.7. 1-(4-Bromobenzyl)-1*H*-1,2,4-triazole (11)

THF (30 mL) was added to K_2CO_3 (7.341 mmol) and the mixture was stirred for 5 min. 1,2,4-triazole **10** (29 mmol) was then added and the mixture was stirred for 1 h. 4-Bromobenzyl bromide **9** (7.5 mmol) dissolved in DMF (5 mL) was added dropwise and the mixture was heated to reflux and stirred for 15 h before water (15 mL) was added. The mixture was extracted with ether (3 × 10 mL) and each extract was washed with water (3 × 10 mL). The combined ether layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified on silica gel with $CHCl_3$/MeOH (40:1) as eluent to get white solid **11** in 82% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.307 (2H, s, CH_2), 7.144 (2H, d, J = 8.4 Hz, Ar-H), 7.511 (2H, d, J = 8.4 Hz, Ar-H), 7.498 (1H, s, 3*H*), 8.098 (1H, s, 5*H*);

EI-MS, m/z: 237, M: [M+2] = 1:1.

4.1.8. General procedure for synthesis of compounds 12a–d

Compounds **8a–d** (2.55 mmol), **11** (2.55 mmol), toluene (15 mL), ethanol (12 mL), NaOH (1.56 M, 7 mL), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.204 mmol), was mixed under N_2. The mixture was warmed to reflux for 5 h. The mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by silica gel column chromatography using $CHCl_3$/MeOH as an eluent to give **12a–d**.

4.1.8.1. 4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-*N*-*tert*-butyl-5-isobutylbiphenyl-2-sulfonamide (12a).

Yellow oil, yield 86.6%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.905 (6H, d, J = 6.6 Hz), 0.987 (9H, s), 1.897 (1H, m), 2.535 (2H, d, J = 7.2 Hz), 3.515 (1H, s, NH), 7.048 (1H, d, J = 1.5 Hz, H-4), 7.238 (1H, d, J = 0.9 Hz, H-6), 7. 343 (2H, d, J = 4.2 Hz, Ar-H), 7.529 (2H, d, J = 8.1 Hz, Ar-H), 7.995 (1H, s, 3*H*), 8.051 (1H, d, J = 8.1 Hz, H-3), 8.149 (1H, s, 5*H*).

4.1.9. General procedure for synthesis of compounds 14a–g, 15a–f, 16a–f and 17a–c

TFA (4 mL) was added **12a–d** (2.5 mmol) and stirred the mixture under N_2 atmosphere for 12 h at rt. The reaction mixture was evaporated and most TFA was removed leaving oil which was dissolved in ethyl acetate (15 mL) and washed with water (10 mL). After drying over anhydrous $MgSO_4$ and evaporating under reduced pressure to achieve the compounds **13a–d** without further purification. The crude **13a–d** were dissolved in pyridine (4 mL), and followed by the respective alkyl chloroformates, acyl chlorides and benzoyl chlorides (2.0 mmol) were added on an ice bath. The reaction mixture was stirred for 4 h at 0 °C under N_2 atmosphere. Evaporation and the residue taken in ethyl acetate (15 mL), washed with HCl (1 M) followed by water, brine and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$/MeOH as an eluent to give **14a–g**, **15a–f**, **16a–f** and **17a–c**.

4.1.9.1. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonyl}propionamide (14a).

White solid, yield. 28.9% mp 144–146 °C. IR (film, cm^{-1}): 2957, 2926, 2024, 1704, 1467, 1333, 1141; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.818 (6H, d, J = 5.1 Hz, $(CH_3)_2$CH), 0.905 (3H, t, J = 5.1 Hz, CH_3), 2.008 (2H, q, J = 7.5, 15 Hz, CH_2), 1.830–1.972 (1H, m, $(CH_3)_2CH$), 2.542 (2H, d, J = 6.9 Hz, CH_2CH), 5.438 (s, 2H, CH_2), 7.039 (1H, d, J = 1.2 Hz), 7.337 (4H, dd, J = 3.9, 2.7 Hz), 7.998 (1H, s), 8.195 (2H, d, J = 8.1 Hz), 8.292 (1H, s); ESI-MS, m/z: 425 [$(M-H)^-$], 427 [$(M+H)^+$]. HR-MS (ESI, M+H) m/z: calcd for $C_{22}H_{27}N_4O_3S$: 427.1804, found 427.1806.

4.1.9.2. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonyl}pentanemide (14b).

White solid, yield 31.5% mp 100–102 °C. IR (film, cm^{-1}): 3439, 2957, 2024, 1717, 1336, 1138; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.885 (3H, t, J = 6.9 Hz, CH_3), 0.942 (6H, d, J = 6.6 Hz, $(CH_3)_2$CH), 1.452–1.477 (m, 2H, CH_3CH_2), 1.879–1.961 (4H, m), 1.187–1.211 (1H, m, $(CH_3)_2$-*CH*), 2.539 (2H, d, J = 6.0 Hz, CH_2CO), 5.435 (2H, s), 7.038 (1H, s), 7.232–7.358 (5H, m), 7.965 (1H, s), 8.199 (1H, dd, J = 1.5, 6.6 Hz), 8.248 (1H, s); ESI-MS, m/z: 453.3 [$(M-H)^-$], 455 [$(M+H)^+$].HR-MS (ESI, M+H) m/z: calcd for $C_{24}H_{31}N_4O_3S$: 455.2117, found 455.2114.

4.1.9.3. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonyl}-4-methylbenzamide (14c).

White solid, yield 12.1%. mp 100–102 °C.

IR (film, cm^{-1}): 3438, 2956, 2024, 1752, 1607, 1228, 1163; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.925 (6H, d, J = 6.3 Hz), 1.913 (1H, m), 2.142 (3H, s, CH_3), 2.436 (2H, d, J = 7.4 Hz), 5.164 (2H, s), 7.114 (1H, s), 7.204–7.228 (m, 2H), 7.268–7.302 (m, 4H), 7.368–7.402 (m, 4H),7.908 (1H, s), 8.106 (1H, s), 8.228 (1H, d, J = 7.0 Hz); ESI-MS, m/z: 487.2[$(M-H)^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{27}H_{29}N_4O_3S$: 489.6092, found 489.6095.

4.1.9.4. Ethyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonylcarbamate (14d).

White solid, yield 55.2%. mp 96–98 °C. IR (film, cm^{-1}): 3415, 2957, 2025, 1744, 1340, 1161, 1144, 576; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.844 (6H, d, J = 6.6 Hz, $(CH_3)_2$CH), 1.064 (3H, t, J = 6.9 Hz, CH_3CH_2), 1.785–1.874 (1H, m, $(CH_3)_2CH$), 2.476 (2H, d, J = 7.2 Hz, CH_2CH), 4.014 (2H, q, J = 7.2, 7.2 Hz, CH_2CH_3), 5.300 (2H, s, CH_2–Ar), 6.978 (1H, d, J = 1.5 Hz), 7.148 (2H, d, J = 8.1 Hz), 7.240–7.288 (3H, m), 7.853 (1H, s), 8.039 (s,1H), 8.103 (1H, d, J = 8.1 Hz), 8.473 (1H, s); ESI-MS, m/z: 442 [$(M-H)^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{22}H_{27}N_4O_4S$: 443.1753, found 443.1751.

4.1.9.5. *tert*-Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonylcarbamate (14e).

White solid, yield 45.2%. mp 97–100 °C. IR (film, cm^{-1}): 3418, 2958, 2925, 2024, 1739, 1515, 1341, 1139; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.844 (6H, d, J = 6.6 Hz), 1.229 (9H, s, *t*-Bu), 1.773–1.811 (1H, m), 2.486 (2H, d, J = 7.2 Hz), 5.330 (2H, s), 6.993 (1H, s), 1.171 (1H, s), 7.199 (2H, d, J = 2.4 Hz), 7.273 (1H, d, J = 3.0 Hz), 7.315 (2H, d, J = 6.3 Hz), 7.892 (1H, s), 8.058 (1H, s), 8.084 (1H, s); ESI-MS, m/z: 469.3 [$(M-H)^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{24}H_{31}N_4O_4S$: 471.2066, found 471.2065.

4.1.9.6. Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonylcarbamate (14f).

White solid, yield

40.9%. mp 78–80 °C. IR (film, cm^{-1}): 3417, 2958, 2930, 2024, 1743, 1510, 1342, 1160, 1144; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.767 (3H, t, J = 7.5 Hz, CH_3), 0.842 (6H, d, J = 6.6 Hz), 1.335–1.350 (2H, m, CH_3CH_2), 1.809–2.022 (1H, m), 2.480 (2H, d, J = 7.2 Hz, CH_2CH), 3.948 (2H, t, J = 6.6 Hz, CH_2O), 5.342 (2H, s), 6.993 (1H, d, J = 1.5 Hz), 7.117 (1H, s), 7.217–7.299 (5H, m), 7.918 (1H, s), 8.074 (1H, s), 8.095 (1H, d, J = 3.6 Hz); ESI-MS, m/z: 469.3 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{24}H_{31}N_4O_4S$: 471.2066, found 471.2068.

4.1.9.7. Benzyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-isobutylbiphenyl-2-ylsulfonylcarbamate (14g). White solid, yield 31.1%. mp 100–102 °C. IR (film, cm^{-1}): 3419, 3033, 2957, 2926, 2025, 1745, 1510, 1342, 1160, 1144; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.895 (6H, d, J = 8.4 Hz), 1.854–1.944 (m, 1H), 2.546 (2H, d, J = 7.2 Hz), 5.022 (2H, s, CH_2O), 5.327 (2H, s, CH_2), 6.998 (1H, s), 7.111–7.198 (5H, m), 7.274 (1H, s),7.307–7.328 (3H, m), 7.730 (1H, s), 8.126 (1H, s), 8.166 (2H, d, J = 7.5 Hz); ESI-MS, m/z: 503 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{27}H_{29}N_4O_4S$: 505.1910, found 505.1912.

4.1.9.8. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]- 5-methoxybiphenyl-2-ylsulfonyl}propionamide (15a). White solid, yield 30.2%. mp 181–185 °C. IR (film, cm^{-1}): 3440, 3113, 3033, 2353, 2024, 1706, 1599, 1477, 1324, 1146; ^1H NMR ($CDCl_3$, 300 MHz): δ δ (ppm) 0.972 (3H, t, J = 7.5 Hz, CH_3CH_2), 1.969 (2H, q, J = 7.5, 7.5 Hz, CH_3CH_2), 3.862 (s, 3H, CH_3O), 5.425 (2H, s), 6.730 (1H, d, J = 2.1 Hz), 7.023 (1H, dd, J = 2.7, 6.3 Hz), 7.209–7.304 (4H, m), 7.950 (1H, s), 8.225 (1H, s), 8.248 (1H, d, J = 3.9 Hz), 8.669 (1H, s); ESI-MS, m/z: 399.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{19}H_{21}N_4O_4S$: 401.1284, found 401.1285.

4.1.9.9. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-methoxybiphenyl-2-ylsulfonyl}pentanamide (15b). White solid, yield 45.1%. mp 94–98 °C. IR (film, cm^{-1}): 3417, 3122, 2959, 2932, 2871, 2025, 1715, 1595, 1130,1138; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.864 (3H, t, J = 4.5 Hz, CH_3CH_2), 1.195–1.219 (m, 2H, CH_3CH_2), 1.414–1.463 (m, 2H, $CH_2CH_2CH_2$), 1.941 (3H, t, J = 7.2 Hz, CH_2CH_2CO), 3.864 (3H, s, CH_3O), 5.429 (2H, s), 6.732 (1H, d, J = 2.4 Hz), 7.023 (1H, dd, J = 2.4, 6.3 Hz), 7.238–7.311 (3H, m), 7.956 (1H, s), 7.227 (1H, s), 7.256 (1H, s), 8.758 (1H, s); ESI-MS, m/z: 427 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{21}H_{25}N_4O_4S$: 429.1597, found 429.1599.

4.1.9.10. Ethyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methoxybiphenyl-2-ylsulfonylcarbamate (15c). White solid, yield 27.3%. mp 155–158 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.160 (3H, t, J = 6.9 Hz, CH_3CH_2), 3.869 (s, 3H, CH_3O), 4.068 (2H, q, J = 7.2, 7.2 Hz, CH_3CH_2CO), 5.433 (2H, s), 6.744 (1H, d, J = 1.5 Hz), 6.965–7.023 (1H, q, J = 2.4, 5.1 Hz), 7.337–7.397 (4H, m), 8.029 (1H, s), 8.182 (1H, d, J = 9.0 Hz), 8.370 (1H, s); ESI-MS, m/z: 415.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{19}H_{21}N_4O_5S$: 417.1233, found 417.1231.

4.1.9.11. *tert*-Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methoxybiphenyl-2-ylsulfonylcarbamate (15d). White solid, yield 23.4%. mp 94–96 °C. IR (film, cm^{-1}): 3368, 3129, 2973, 2024, 1744, 1592, 1317, 1156; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.235 (9H, s, *t*-Bu), 3.862 (3H, s), 5.425 (2H, s), 6.788 (1H, s), 6.961 (1H, d, J = 8.7 Hz), 7.325 (2H, d, J = 7.8 Hz), 7.486 (2H, d, J = 7.2 Hz), 7.997 (1H, s), 8.070 (1H, d, J = 9.0 Hz), 8.198 (1H, s); ESI-MS, m/z: 443.2 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{21}H_{25}N_4O_5S$: 445.1546, found 445.1548.

4.1.9.12. Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methoxybiphenyl-2-ylsulfonylcarbamate (15e). White solid, yield 34.1%. mp 108–110 °C. IR (film, cm^{-1}): 3482, 3120, 2959, 2933, 2025, 1751, 1512, 1331; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.900 (3H, t, J = 9.3 Hz), 1.192–1.257 (2H, m), 1.447–1.541 (2H, m), 3.871 (3H, s, CH_3O), 4.052 (2H, t, J = 6.6 Hz, CH_2CH_2O), 5.408 (2H, s), 6.760 (1H, d, J = 2.7 Hz), 7.017 (1H, dd, J = 2.4, 6.3 Hz), 7.248 (1H, s), 7.268 (1H, d, J = 3 Hz), 7.348 (2H, d, J = 8.1 Hz), 7.981 (1H, s), 8.161 (1H, s), 8.203 (1H, d, J = 9.0 Hz); ESI-MS, m/z: 443.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{21}H_{25}N_4O_5S$: 445.1546, found 445.1547.

4.1.9.13. Benzyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methoxybiphenyl-2-ylsulfonylcarbamate (15f). White solid, yield 37.2%. mp 164–167 °C. IR (film, cm^{-1}): 3437, 3032, 2941, 2024, 1748, 1593; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.429 (3H, s, CH_3O), 5.017 (2H, s, CH_2O), 5.265 (2H, s), 7.014 (1H, s), 7.158–7.183 (m, 4H), 7.260–7.320 (m, 6H), 7.867 (1H, s), 8.050 (1H, s), 8.128 (1H, d, J = 8.1 Hz); ESI-MS, m/z: 477.2 [(M−H)$^-$].HR-MS (ESI, M+H) m/z: calcd for $C_{24}H_{23}N_4O_5S$: 479.1389, found 479.1391.

4.1.9.14. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonyl}propionamide (16a). White solid, yield 31.3%. mp 88–90 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.981 (3H, t, J = 7.5 Hz, CH_3CH_2), 1.982 (2H, q, J = 7.5 Hz, J = 7.5 Hz, CH_3CH_2), 3.445 (s, 3H, CH_3), 5.439 (2H, s), 7.079 (1H, d, J = 1.2 Hz), 7.023 (1H, dd, J = 2.7, 6.3 Hz), 7.231–7.259 (2H, m), 7.322–7.373 (2H, m), 7.400 (1H, dd, J = 1.8, 7.8 Hz), 8.200 (1H, d, J = 8.4 Hz), 8.252 (1H, s), 8.661 (1H, s). ESI-MS, m/z: 383.2 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{19}H_{21}N_4O_3S$: 385.1334, found 385.1331.

4.1.9.15. *N*-{4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonyl}pentanamide (16b). White solid, yield 38.0%. mp 91–93 °C. IR (film, cm^{-1}): 3391, 2957, 2024, 1702, 1512, 1468, 1334, 1142; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.832 (3H, t, J = 6.6 Hz), 1.235–1.431 (m, 4H), 1.937 (t, 2H), 2.429 (s, 3H), 5.429 (s, 2H), 7.069 (s, 1H), 7.262–7.376 (m, 4H), 7.968 (s, 1H), 8.179 (1H, d, J = 7.8 Hz), 8.266 (1H, s), 8.418 (1H, s); ESI-MS, m/z: 411.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{21}H_{25}N_4O_3S$: 413.1647, found 413.1651.

4.1.9.16. Ethyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonylcarbamate (16c). White solid, yield 26.3%. mp 89–90 °C. IR (film, cm^{-1}): 3452, 3004, 2784, 2669, 2024, 1736, 1507, 1333, 1236, 1145; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.143 (t, 3H, J = 7.2 Hz), 2.438 (3H, s), 4.066 (2H, q, J = 6.9, 7.2 Hz), 5.397 (2H, s), 7.093 (1H, s), 7.242–7.262 (m, 2H), 7.242–7.332 (m, 3H), 7.967 (1H, s), 8.136 (1H, d, J = 1.5 Hz), 8.167 (1H, s); ESI-MS, m/z: 399.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{19}H_{21}N_4O_4S$: 401.1284, found 401.1286.

4.1.9.17. *tert*-Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonylcarbamate (16d). Colorless oil, yield 23.4%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.256 (9H, s, *t*-Bu), 2.405 (3H, s), 5.406 (2H, s), 6.708 (1H, s), 7.011 (1H, d, J = 8.5 Hz), 7.332–7.420 (4H, m), 8.008 (1H, s), 8.098 (1H, d, J = 8.9 Hz), 8.159 (1H, s). ESI-MS, m/z: 427.1 [(M−H)$^-$]. HR-MS (ESI, M+H) m/z: calcd for $C_{21}H_{25}N_4O_4S$: 429.1597, found 429.1595.

4.1.9.18. Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonylcarbamate (16e). White solid, yield 32.4%. mp 92–94 °C. IR (film, cm^{-1}): 3441, 2960, 2872, 2024, 1743, 1510, 1341, 1160, 1143, 889; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.861 (3H, t, J = 7.5 Hz), 1.143–1.256 (2H, m), 1.429–1.608 (2H, m), 2.435 (3H, s), 4.015 (2H, t, J = 6.6 Hz), 5.377 (2H, s), 7.079 (1H, s), 7.214–7.241 (2H, d, J = 6.6 Hz), 7.265–7.364 (3H, m), 7.938 (1H, s), 8.138 (s, 1H), 8.166 (s, 1H) ESI-MS, m/z: 427.1

[(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{21}H_{25}N_4O_4S$: 429.1597, found 429.1599.

4.1.9.19. Benzyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-methylbiphenyl-2-ylsulfonylcarbamate (16f). White solid, yield 34.2%. mp 145–147 °C. IR (film, cm^{-1}): 3464, 3035, 2627, 2024, 1744, 1508, 1337, 1229, 1154, 885, 786; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.855 (3H, s, CH_3), 5.026 (2H, s, CH_2O), 5.289 (2H, s), 7.019 (1H, s), 7.158–7.183 (m, 2H), 7.248–7.253 (m, 2H), 7.271–7.305 (m, 4H), 7.315–7.330 (m, 3H), 7.868 (1H, s), 8.019 (1H, s), 8.156 (1H, d, J = 7.9 Hz); ESI-MS, *m/z*: 461.1 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{24}H_{23}N_4O_4S$: 463.1440, found 463.1442.

4.1.9.20. Ethyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-[(diethylamino)methyl]biphenyl-2-ylsulfonylcarbamate (17a). Yellow oil, yield 14.3%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.082 (6H, t, J = 6.4 Hz, $(CH_3CH_2)_2N$), 1.468 (3H, s), 2.560 (d, 4H, J = 6.1 Hz, $(CH_3CH_2)_2N$), 3.508 (2H, d, J = 7.2 Hz), 4.096 (2H, q, J = 7.0, 7.2 Hz), 5.520 (2H, s), 7.738–7.764 (m, 4H), 7.805–7.829 (m, 3H), 8.011 (1H, s), 8.102 (1H, d, J = 8.1 Hz), 8.201 (1H, s). ESI-MS, *m/z*: 470.2 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{23}H_{30}N_5O_4S$: 472.2019, found 472.2016.

4.1.9.21. Butyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-[(diethylamino)methyl]biphenyl-2-ylsulfonylcarbamate (17b). Yellow oil, yield 14.3%.

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.902 (3H, t, J = 7.0 Hz), 1.078 (6H, t, J = 6.0 Hz, $(CH_3CH_2)_2N$), 1.166–1.287 (2H, m), 1.321–1.514 (2H, m), 2.450 (d, 4H, J = 6.2 Hz, $(CH_3CH_2)_2N$), 3.798 (2H, d, J = 7.0 Hz), 4.115 (2H, t, J = 6.8 Hz), 5.680 (2H, s), 7.633–7.678 (m, 4H), 7.705–7.729 (m, 3H), 7.908 (1H, s), 8.002 (1H, d, J = 8.0 Hz), 8.101 (1H, s). ESI-MS, *m/z*: 498.5 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{25}H_{34}N_5O_4S$: 500.2332, found 500.2334.

4.1.9.22. Benzyl 4′-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-[(diethylamino)methyl]- biphenyl-2-ylsulfonylcarbamate (17c). Colorless oil, yield 18.2%. ^1H NMR (DMSO, 300 MHz): δ (ppm) 0.980 (6H, t, J = 7.2 Hz), 3.603 (4H, t, J = 18.9, 24 Hz), 4.997 (2H, s), 5.516 (2H, s), 6.832–6.841 (2H, d, J = 2.7 Hz), 7.035–7.080 (4H, d, J = 2.7 Hz), 7.229–7.305 (5H, m), 7.379–7.406 (3H, m), 7.956 (1H, s), 8.009 (1H, d, J = 8.4 Hz), 8.666 (1H, s). ESI-MS, *m/z*: 532.3 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{28}H_{32}N_5O_4S$: 534.2175, found 534.2177.

4.1.10. General procedure for synthesis of compounds 18b–d

The respective alcohol (10.0 mmol) was added to a mixture of PPh_3 (12.0 mmol), DDQ (12.0 mmol), and 4-bromoanilines **18a** (10.0 mmol) in CH_2Cl_2 (30 mL). The reaction was stirred at room temperature for 2 h. Then, the solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether as eluent to afford **18b–d**.

4.1.11. General procedure for synthesis of compounds 19a–d

Compound **18a–d** (2.55 mmol), **8a** (2.55 mmol), toluene (15 mL), ethanol (12 mL), NaOH (1.56 M, 7 mL), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.204 mmol), was mixed under N_2. The mixture was warmed to reflux for 5 h. The mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by silica gel column chromatography using $CHCl_3$/MeOH as an eluent to give **19a–d**.

4.1.12. General procedure for synthesis of compounds 21a–d

TFA (4 mL) was added **19a–d** (2.5 mmol) and stirred the mixture under N_2 atmosphere for 12 h at rt. The reaction mixture was evaporated and most TFA was removed leaving oil which was dissolved in ethyl acetate (15 mL) and washed with water (10 mL). After drying over anhydrous $MgSO_4$ and evaporating under reduced pressure to achieve the compounds **20a–d** without further purification. The crude **20a–d** was dissolved in pyridine (4 mL), and followed by *n*-butyl chloroformate (2.0 mmol) were added on an ice bath. The reaction mixture was stirred for 4 h at 0 °C under N_2 atmosphere. Evaporation and the residue taken in ethyl acetate (15 mL), washed with HCl (1 M) followed by water, brine and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$/MeOH as an eluent to give **21a–d**.

4.1.12.1. Butyl 4′-amino-5-isobutylbiphenyl-2-ylsulfonylcarbamate (21a). Yellow oil, yield 22.4%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.868 (3H, t, J = 4.5 Hz), 0.920 (6H, d, J = 3.0 Hz), 1.191–1.221 (2H, m), 1.416–1.472 (2H, m), 1.882–1.923 (1H, m), 2.539 (2H, d, J = 4.2 Hz), 3.988 (3H, t, J = 3.9 Hz), 6.730 (2H, d, J = 5.1 Hz), 7.088 (1H, d, J = 0.9 Hz), 7.128–7.150 (m, 2H), 7.250–7.269 (m, 1H), 8.116 (1H, d, J = 4.8 Hz). ESI-MS, *m/z*: 403.1 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{21}H_{29}N_2O_4S$: 405.1848, found 405.1851.

4.1.12.2. Butyl 5-isobutyl-4′-(methylamino)biphenyl-2-ylsulfonylcarbamate (21b). Yellow oil, yield 12.1%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.821–1.864 (5H, m), 0.879–0.962 (10H, m), 1.890–1.934 (1H, m), 2.548 (2H, d, J = 4.2 Hz), 3.353 (3H, s), 7.107 (1H, t, J = 1.8, 1.5 Hz), 7.237–7.367 (m, 5H), 8.148 (1H, d, J = 8.4 Hz). ESI-MS, *m/z*: 417.4 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{22}H_{31}N_2O_4S$: 419.2005, found 419.2002.

4.1.12.3. Butyl 5-isobutyl-4′-(ethylamino)biphenyl-2-ylsulfonylcarbamate (21c). Yellow oil, yield 10.3%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.832 (3H, t, J = 4.5 Hz), 0.923 (6H, d, J = 3.1 Hz), 1.174–1.198 (2H, m), 1.467–1.489 (2H, m), 1.869–1.937 (1H, m), 2.563 (2H, d, J = 2.1 Hz), 7.269–7.298 (m, 1H), 7.312–7.367 (m, 5H), 8.142 (1H, d, J = 8.4 Hz). ESI-MS, *m/z*: 431.1 [(M−H)⁻].HR-MS (ESI, M+H) *m/z*: calcd for $C_{23}H_{33}N_2O_4S$: 433.2161, found 433.2165.

4.1.12.4. Butyl 5-isobutyl-4′-(isopropylamino)biphenyl-2-ylsulfonylcarbamate (21d). Yellow oil, yield 20.2%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.856 (3H, t, J = 4.5 Hz), 0.939 (6H, d, J = 3.0 Hz), 0.948 (6H, d, J = 3.2 Hz),1.256–1.296 (2H, m), 1.467–1.537 (2H, m), 1.879–1.969 (1H, m), 2.550 (d, 2H, J = 4.2 Hz), 7.154 (2H, d, J = 5.1 Hz), 7.266 (1H, d, J = 0.9 Hz), 7.433–7.502 (m, 3H), 8.038 (1H, d, J = 2.1 Hz). ESI-MS, *m/z*: 445.2 [(M−H)⁻]. HR-MS (ESI, M+H) *m/z*: calcd for $C_{23}H_{33}N_2O_4S$: 447.2318, found 447.2315.

4.2. Pharmacological evaluation

4.2.1. Rat liver membrane AT_1 receptor-binding assay

AT_1 receptor affinity assay was determined using rat liver membrane as described previously by Wallinder, et al.[21] and Dudley et al.[26]

4.2.2. Porcine myometrial membrane AT_2 receptor-binding assay

Porcine myometrial membranes were prepared from porcine uteri according to the method by Nielsen et al.[27]

A presumable interference by binding to AT_1 receptors was blocked by addition of 1 μM losartan. Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris–HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to

10 mg of the original tissue weight, [^{125}I]Ang II (80,000–85,000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25 °C for 1.5 h. At the end of incubation, bound complex was trapped on filters (GF/C) and washed with cold Tris buffer (pH 7.4; 3 × 250 μL), and transferred to tubes. The radioactivity was measured in a 1470 Wizard *r*-counter. The characteristics of the Ang II-binding AT_2 receptor were determined by using six different concentrations (0.03–5 nmol/L) of the labeled [^{125}I]Ang II. Nonspecific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]Ang II. The IC_{50} of an inhibitor was determined as the concentration that displaced the specifically bound [^{125}I]Ang II by 50%. All determinations were performed in triplicate.

4.2.3. Antihypertensive effects in the spontaneously hypertensive rats (RHRs)

Male SHRs were purchased from Vital River Laboratory Animal Technology Co. Ltd, (Beijing, China). After one week of acclimation, 32 SHRs (10-weeks-old, 180–200 g body weight) were randomly divided into four groups, namely the SHR model group, the losartan control group, the compounds **14f** and **15e** control groups. After oral administration with saline water, losartan (20 mg/kg), **14f** (20 mg/kg) and **15e** (20 mg/kg) to SHRs respectively, the SAP, DAP and heart rate (HR) were measured using the tail-cuff method with a blood pressure monitor (BP-2000, Visitech Systems, Inc., US) from 0 to 8 h.[29]

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