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Synthesis and biological activities of novel nonpeptide angiotensin II receptor antagonists based on benzimidazole derivatives bearing a heterocyclic ring

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ABSTRACT

A series of benzimidazole derivatives bearing a heterocyclic ring imidazole (**1**), 5-chloroimidazole (**2**), 1,2,4-triazol (**3**), and imidazoline (**4**) were synthesized and evaluated for angiotensin II antagonistic activities. The synthetic compounds **1**–**4** were biologically evaluated in vitro using an AT_1 receptor binding assay, where compounds **1** and **3** provided weak binding affinity, compound **2** showed moderate binding affinity, and compound **4** showed good binding affinity. Moreover, compound **4** was found to be almost equipotent with telmisartan in vivo biological evaluation study.

1. Introduction

Angiotensin II (AngII) is an octapeptide produced by the renin–angiotensin system (RAS), which plays an important role in the pathophysiology of hypertension.[1,2] This stimulated many researchers toward designing drugs to block the effects of AngII either by inhibiting the angiotensin-converting enzyme (ACE) or renin or by blocking the AngII receptors.[3–10] AngII receptor antagonists have proved to lower blood pressure effectively,[11] and they are better tolerated than other classes of drugs.[12,13] Losartan,[14,15] the protypical agent of this category, was served as lead for the development of newer AngII receptor antagonists.[16] Carini et al.[17] proposed a structure–activity relationship (SAR) of AT_1 receptor antagonists that suggested activity was improved by the presence of a biphenyl tetrazole group. In fact, dozens of AT_1 receptor antagonists share the same biphenyl tetrazole moiety as a common pharmacophore. However, the tetrazole ring suffers from several insurmountable drawbacks. The duration of losartan is shortened partly due to the N-glucoronidation of tetrazole unit in vivo,[18–20] and the synthesis of tetrazole can be extremely dangerous as it involves explosive azide compounds. Beside, the existence of tetrazole ring also hinders further researches on novel antagonists, because adding another acidic group to the target molecule, which is required in many cases, will result in low oral bioavailability. In 1996, Kohara et al.[21] reported the 5-oxo-1,2,4-oxadiazole ring and its thio analogs are lipophilic bioisosteric replacements for the tetrazole unit, their derivatives exhibit enhanced activity and oral bioavailability. Up to now, relatively few studies have been focused on novel tetrazole replacements, especially groups like heterocyclic rings. Thus, we started our investigation of replacement of the tetrazole ring in AngII receptor antagonists. Besides, the available data from the literature[22] indicated that a benzimidazole derivative, especially 'double benzimidazole', was an excellent group for good binding affinity. Thus, we wish to report herein our synthesis, and in vitro and in vivo biological evaluation of the designed benzimidazole derivatives bearing a heterocyclic ring (Chart 1).

2. Results and discussion

2.1. Chemistry

The preparation of the target molecule **1** was carried out in six steps starting from the 2-cyano-4′-methylbiphenyl **5** as shown in Scheme 1. The imidazoline ring was built by cyclization of the nitrile with ethylenediamine in the presence of sulfur under solvent-free condition. Aromatization of imidazoline **6** to the corresponding imidazole **7** has been performed by direct oxidation of **6** by employing potassium permanganate on silica gel in acetonitrile at room temperature. Tritylation was followed to give the protected imidazole **8**. The key intermediate **9** was prepared by ben-

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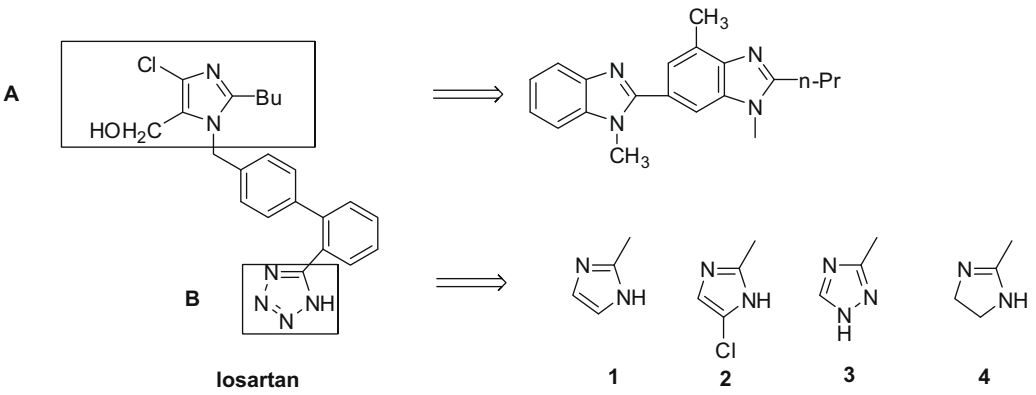
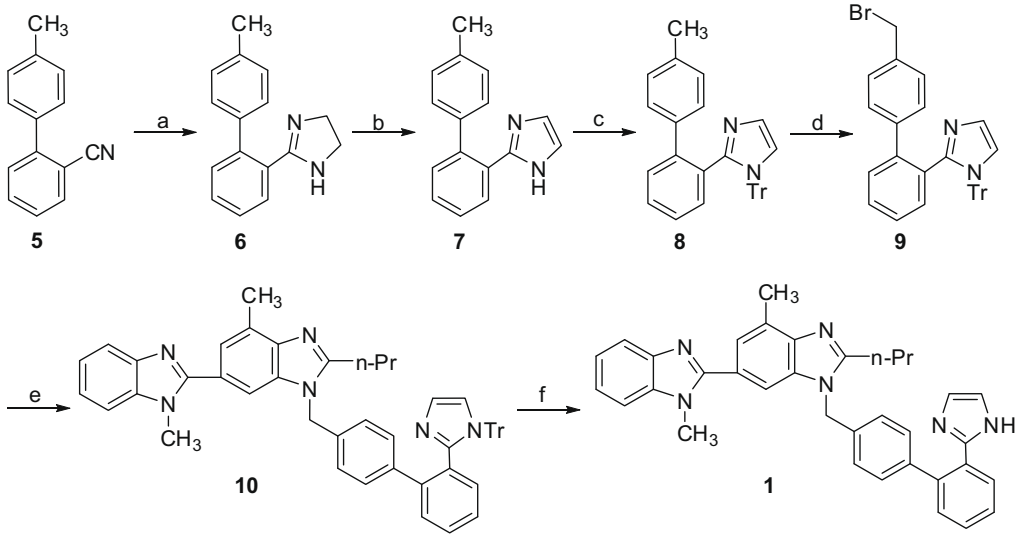


Chart 1. Our AngII receptor antagonists.



Scheme 1. Reagents: (a) $NH_2CH_2CH_2NH_2$, S, reflux; (b) $SiO_2/KMnO_4$, CH_3CN, rt; (c) Ph_3CCl, Et_3N, CH_2Cl_2; (d) NBS, AIBN, CCl_4; (e) 'double benzimidazole' intermediate **25**, NaH, DMF; (f) HCl, THF.

zylic bromination employing NBS/AIBN. Alkylation of **9** with the 'double benzimidazole' intermediate 2-*n*-propyl-4-methyl-6-(1-methylbenzimidazol-2-y1)benzimidazole **25** in the presence of sodium hydride and dimethylformylamine under mild conditions provided triphenylmethyl imidazole **10**, followed by removal of triphenylmethyl protecting group, provided the target molecule **1**.

Scheme 2 demonstrated an alternative and frequently superior route to the target molecule **1** in which the 'double benzimidazole' intermediate **25** was first alkylated with 4′-(bromomethyl)-2-cyanobiphenyl **11** under relatively mild conditions to afford **12**. Likewise, **12** was refluxed with ethylenediamine in the presence of sulfur to give imidazoline **4**, which was further dehydrogenated by potassium permanganate adsorbed on silica gel to form the target compound **1**. Imidazole **1** could be obtained either from the deprotection of the trityl imidazole biphenylylmethyl benzimidazole derivative **10** or from the corresponding nitrile derivative **12** via imidazoline ring formation. The latter method avoids the protection and deprotection of imidazole, thus, the entire route is shortened to four steps and the overall yields are higher. Besides, the latter method is also fit to prepare imidazoline derivative **4**.

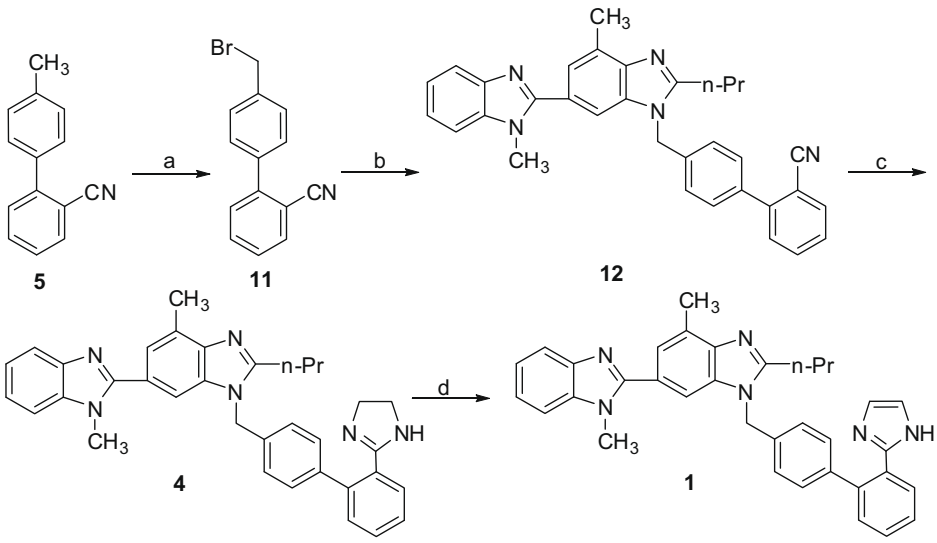
As shown in Scheme 3, the chloro-substituted imidazole **2** was synthesized starting from the 2-cyano-4′-methylbiphenyl **5**, alkaline hydrolysis of **5** in refluxing ethylene glycol for 20 h provided the biphenylcarboxylic acid **13**.[23] This acid was converted, through its acid chloride, to the N-acylated α-aminonitrile **14**. The treatment of compound **14** with 1.0 equiv of triphenylphosphine and 1.0 equiv of carbon tetrachloride at 45 °C in acetonitrile gradually generated 5-chloroimidazole product **15** in 80.2% isolated yield. Tritylation, benzylic bromination, alkylation, and deprotection, as described for the imidazole derivative **1** via method I, afforded **2**.

1,2,4-Triazole derivative **3** was prepared in Scheme 4. Conversion of **5** to the thioamide **19** was performed at room temperature with 70% sodium hydrogen sulfide hydrate and magnesium chloride hexahydrate in dimethylformaide (DMF). Treatment of **19** with methyl iodide gave the activated intermediate **20**, which was elaborated to the 1,2,4-triazole compound **21** by treatment with formic hydrazide in dimethylformamide at elevated temperature. Compound **21** was protected as the trityl derivative **22** and converted to the bromo compound **23**. Reaction of **23** with the 'double benzimidazole' intermediate **25** was then carried out using the conditions described in Scheme 1, followed by removal of triphenylmethyl protecting group, provided the target molecule **3**.

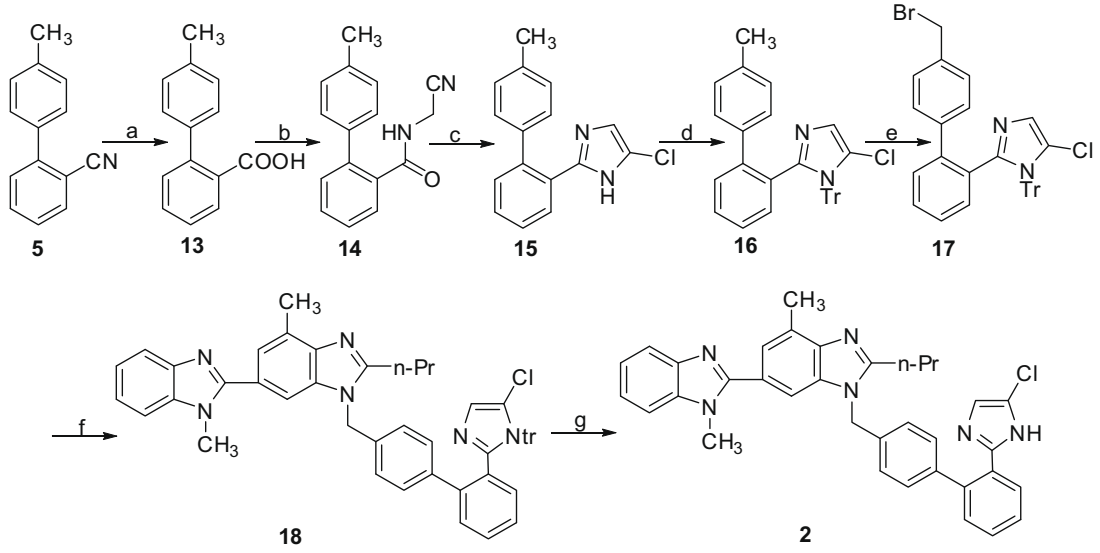
2.2. Biological evaluation

2.2.1. Angiotensin II receptor (AT_1)-binding assay

The prepared compounds **1**–**4** were evaluated for their activity to competitively inhibit [^{125}I]AngII binding to the AT_1 receptor by a



Scheme 2. Reagents: (a) NBS, AIBN, CCl_4; (b) 'double benzimidazole' intermediate **25**, NaH, DMF; (c) $NH_2CH_2CH_2NH_2$, S, reflux; (d) $SiO_2/KMnO_4$, CH_3CN.

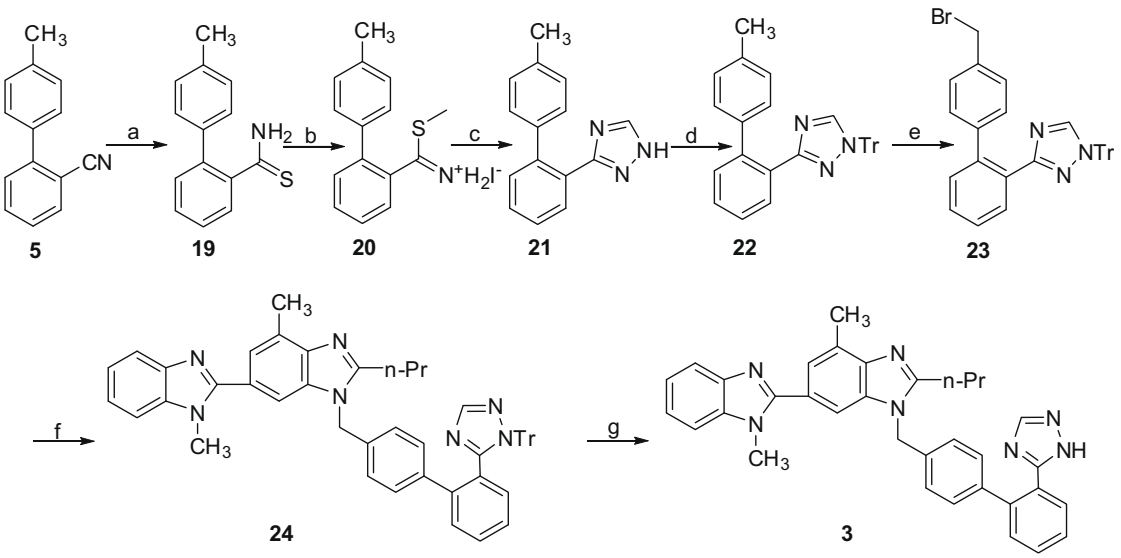


Scheme 3. Reagents: (a) $NaOH/HOCH_2CH_2OH$; (b) $SOCl_2/CHCl_3$, then NaOH, H_2NCH_2CN; (c) PPh_3, CCl_4; (d) Ph_3CCl, Et_3N, CH_2Cl_2; (e) NBS, AIBN, CCl_4; (f) 'double benzimidazole' intermediate **25**, NaH, DMF; (g) HCl, THF.

conventional ligand-binding assay using a bovine adrenal cortex.[24] The results are expressed as IC_{50} values and are listed in Table 1. The heterocyclic ring, imidazole derivative **1** and 1,2,4-triazoles derivative **3** were found to have very similar IC_{50} values. They are relatively nonacidic and as a result do not possess good binding affinities. The acidity of imidazole can be increased through substitution by electron-withdrawing group, such as Cl. With regard to 5-chloroimidazole derivative **2**, the binding affinity surpasses those of the corresponding imidazole derivative **1**. Unfortunately these groups still were not acidic enough to allow for proper binding to the AngII receptor. More interestingly, imidazoline derivative **4** was found to be as potent as the losartan.

2.2.2. Antagonism of AngII-induced pressor response by oral administration in the spontaneously hypertensive dogs

Intravenous administration of angiotensin II (AngII) will stimulate angiotensin II receptor and increase blood pressure. This pressor effect was reversed, with a markedly lowered pressure by addition of the angiotensin II receptor antagonist. Potent inhibition of the pressor response induced by AngII of each test compound was evaluated by extent of increase in blood pressure after 1 h oral administration of the test compounds and intravenous administration of AngII in conscious Beagle dogs (Fig. 1). The smaller of extent of increase in blood pressure, the more potency in vivo of the test compound. The blood pressure (BP) and heart rate after 1 h treatment with the test compounds (2.13 mg/kg, po) and AngII (0.45 μg/kg, iv) were recorded and the data are listed in Tables 2–5. With respect to the heterocyclic ring, the imidazoline derivative **4** which exhibited the highest binding affinities of this series, were also the most potent compounds in vivo. Compound **4** caused significant reduction in conscious Beagle dogs almost approach to the standard drug telmisartan. This suggests that compound **4** is an orally active AT_1 receptor antagonist. The poor in vitro activity of the imidazole derivative **1** and the 1,2,4-triazole **3** was also confirmed in vivo. The 5-chloro-substituted imidazole compound **2** displayed stronger potencies than those of the unsubstituted imid-



Scheme 4. Reagents: (a) 70%NaSH, $MgCl_3{\cdot}6H_2O$, DMF; (b) CH_3I, ether; (c) NH_2NH_2CHO, DMF; (d) Ph_3CCl, Et_3N, CH_2Cl_2; (e) NBS, AIBN, CCl_4; (f) 'double benzimidazole' intermediate **25**, NaH, DMF; (g) HCl, THF.

Table 1
AT_1 receptor binding affinities of compounds **1**–**4**.

Compound	Receptor affinity IC_{50},10^{-7} M[a]
1	14
2	6.8
3	15
4	2.9
Losartan	1.6, 1.5[b], 1.2[c], 0.064[d]
Telmisartan	~0.01[d]

[a] Inhibition of specific binding of [^{125}I]AII (0.2 nM) to bovine adrenal cortex. The IC_{50} value is the concentration of compound which inhibits [^{125}I]AII binding by 50%.
[b] Data taken from Ref. 21.
[c] Data taken from Ref. 25.
[d] Data taken from Ref. 7.

azole derivative **1**, in agreement with their binding affinities. Furthermore, the tested compound except 1,2,4-triazole compound **3** all produced decrease in the basal heart rate.

3. Conclusion

The present study describes the synthesis of a series of benzimidazole derivatives bearing a heterocyclic ring and their biological activities as a novel class of nonpeptide AT_1 receptor antagonists. As demonstrated by in vitro and in vivo results, the imidazoline derivative **4**, displayed almost equal antihypertensive activity to that of the reference compound (telmisartan), whereas the imidazole derivatives **1**, **2** and the triazole derivative **3** showed weak or no antihypertensive activity. We believe that compound **4** has interesting pharmacological properties and can be applied to modification of other antihypertensive drugs. Further work on compound **4** is in progress.

4. Experimental

4.1. General

The melting points were measured in an X-6 melting point apparatus and were uncorrected. ^{1}H and ^{13}C {^{1}H} NMR spectra were recorded on a Bruker Avance 600 NMR spectrometer (600 MHz for ^{1}H, and 150 MHz for ^{13}C) in $CDCl_3$ at 298 K. Chemical shifts (in ppm) of ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded relative to tetramethylsilane (Me_4Si). Mass spectra were obtained on a Finnigan-LCQDECA mass spectrometer (ESI-MS) and ESI-HRMS spectra were recorded on BioTOF Q. Elemental analyses of the new complexes were performed on a Carlo Erba 1106 elemental

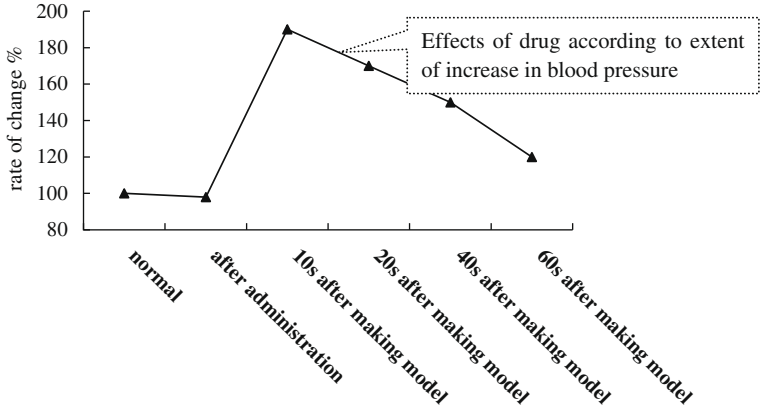


Figure 1. Effect of dosing test compounds on blood pressure and heart rate in Beagle dogs.

Table 2
Effects of compounds **1–4** and telmisartan on AngII-induced mean systolic blood pressure in conscious normotensive Beagle dogs.

Compound	n[a]	Mean systolic blood pressure ± SEM rate of change		
		Normal	Before making model[b]	After making model[c]
Control	7	117.60 ± 21.92	126.96 ± 21.07	179.42 ± 28.40[##]
		100%	108.69 ± 11.47	154.11 ± 20.42
1	6	123.32 ± 17.07	120.50 ± 8.40	184.04 ± 33.80 [##]
		100%	98.67 ± 9.34	151.55 ± 33.31
2	6	141.82 ± 23.04	135.94 ± 29.22	191.75 ± 45.01[#]
		100%	95.75 ± 11.22	135.49 ± 22.74
3	6	127.36 ± 23.76	130.79 ± 17.51	183.44 ± 21.87 [##]
		100%	103.80 ± 8.73	149.11 ± 37.29
4	6	126.82 ± 22.04	121.94 ± 23.22	134.75 ± 22.01[#]
		100%	96.75 ± 11.22	112.49 ± 14.74[*]
Telmisartan	7	125.87 ± 20.63	120.33 ± 21.56	134.87 ± 20.06
		100%	95.78 ± 11.09	107.88 ± 12.29[**]

[a] n is the number of animals treated.
[b] Blood pressure values after 1 h oral administration of the test compounds (2.13 mg/kg po).
[c] Blood pressure values after 1 min of intravenous administration of AngII (0.45 μg/kg, iv).
[#] $p < 0.05$ versus interclass applying observed values, statistically significant.
[##] $p < 0.01$ versus interclass applying observed values, statistically significant.
[*] $p < 0.05$ versus control applying rate of change values, statistically significant.
[**] $p < 0.01$ versus control applying rate of change values, statistically significant.

Table 3
Effects of compounds **1–4** and telmisartan on AngII-induced mean diastolic blood pressure in conscious normotensive Beagle dogs.

Compound	n[a]	Mean diastolic blood pressure ± SEM rate of change		
		Normal	Before making model[b]	After making model[c]
Control	7	89.23 ± 15.40	97.87 ± 21.14	137.71 ± 17.83[##]
		100%	109.35 ± 12.43	156.28 ± 19.25
1	6	87.82 ± 17.98	85.20 ± 16.65	132.02 ± 21.25[##]
		100%	97.96 ± 12.61	156.09 ± 41.98
2	6	101.69 ± 20.43	95.891 ± 8.64	133.61 ± 23.76[#]
		100%	95.28 ± 12.32	133.37 ± 20.11
3	6	94.63 ± 21.08	96.33 ± 16.77	136.17 ± 16.23[##]
		100%	103.14 ± 9.65	151.10 ± 41.80
4	6	96.69 ± 20.43	91.09 ± 8.64	98.61 ± 23.76[#]
		100%	95.28 ± 12.32	107.37 ± 20.11[*]
Telmisartan	7	95.52 ± 23.85	90.66 ± 20.95	94.02 ± 13.97
		100%	96.15 ± 13.89	103.12 ± 26.25[**]

For explanation of footnotes see Table 1.

Table 4
Effect of compounds **1–4** and telmisartan on mean arterial blood pressure in conscious normotensive Beagle dogs.

Compound	n[a]	Mean Arterial Blood Pressure ± SEM rate of change		
		Normal	Before making model[b]	After making model[c]
Control	7	98.69 ± 16.84	107.57 ± 20.31	151.61 ± 19.38[##]
		100%	109.11 ± 11.94	155.44 ± 19.19
1	6	99.65 ± 16.65	96.86 ± 13.18	149.31 ± 23.06[##]
		100%	98.11 ± 10.71	154.06 ± 37.8
2	6	115.06 ± 20.86	109.24 ± 21.68	153.03 ± 29.38[#]
		100%	95.43 ± 11.39	134.26 ± 19.69
3	6	105.54 ± 21.51	107.82 ± 16.70	151.93 ± 17.78[##]
		100%	103.37 ± 9.23	150.17 ± 39.84
4	6	106.06 ± 20.86	102.24 ± 21.68	116.53 ± 29.38[#]
		100%	97.43 ± 11.39	114.26 ± 19.69[*]
Telmisartan	7	105.39 ± 22.00	100.55 ± 20.53	107.64 ± 15.51
		100%	96.13 ± 12.92	104.88 ± 20.58[**]

For explanation of footnotes see Table 1.

analyzer at the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences. Column chromatography (CC) was carried out on silica gel (200–300 mesh, Qingdao Haiyang Chemical Group Co., China). Thin-layer chromatography (TLC) over silica gel 60H (Qingdao Haiyang Chemical Group Co., China) precoated plates. All air-sensitive reactions were conducted in flame- or oven-dried apparatus under a positive pressure of nitrogen. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane was distilled from calcium hydride, and chloroform was passed through an alumina column. Most reagents were purchased from Lancaster and Aldrich. Pentobarbital sodium and telmisartan were kindly provided by the Sichuan Kelun Pharmaceutical, Sinopharm Chemical Reagent Co. Ltd, and Shangxi Chu-

Table 5
Effect of compounds **1**–**4** and telmisartan on mean heart rate in conscious normotensive Beagle dogs.

Compound	n[a]	Mean heart rate ± SEM rate of change		
		Normal	Before making model[b]	After making model[c]
Control	7	144.60 ± 33.73	149.28 ± 40.36	152.03 ± 29.53
		100%	100.75 ± 8.38	105.21 ± 17.14
1	6	150.85 ± 37.41	129.80 ± 34.41	145.55 ± 23.42
		100%	86.20 ± 8.24*	98.87 ± 15.43
2	6	174.37 ± 29.72	142.57 ± 17.94	149.80 ± 15.40
		100%	82.40 ± 6.37**	87.68 ± 14.73
3	6	151.54 ± 52.13	139.94 ± 48.15	152.31 ± 39.51
		100%	93.29 ± 15.88	103.18 ± 14.32
4	6	171.37 ± 29.72	155.57 ± 17.94	149.80 ± 15.40
		100%	84.40 ± 6.37*	94.68 ± 14.73
Telmisartan	7	167.66 ± 37.67	145.87 ± 39.65	150.66 ± 23.22
		100%	86.00 ± 11.28*	92.67 ± 17.18

[a] *n* is the number of animals treated.
[b] Heart rate values after 1 h oral administration of the test compounds (2.13 mg/kg po).
[c] Heart rate values after 1 min of intravenous administration of AngII (0.45 μg/kg, iv).
* $p < 0.05$ versus telmisartan applying rate of change values, statistically significant.
** $p < 0.01$ versus telmisartan applying rate of change values, statistically significant.

anglong Pharmaceutical Co. Ltd, separately. AngII was purchased from Sigma. 2-Cyano-4′-methylbiphenyl (**5**) was purchased from Aldrich. Preparation of 4′-methylbiphenyl-2-carboxylic acid (**13**)[23] and 2-*n*-Propyl-4-methyl-6-(1-methylbenzimidazol-2-y1)benzimidazole (**25**)[22] were performed according to reported procedures.

4.2. Synthesis

4.2.1. Synthesis of 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-imidazole-2-yl) biphenyl (1)

4.2.1.1. 2-(4′-Methylbiphenyl-2-yl)-1*H*-imidazoline (6). This was prepared according to a modified method.[26] A mixture of 2-cyano-4′-methylbiphenyl **5** (15.5 g, 0.08 mol), ethylenediamine (21.5 mL, 0.32 mol), and sulfur (0.64 g, 0.02 mol) was refluxed on an oil bath (120 °C). The progress of the reaction was monitored by TLC (eluent: EtOAc/MeOH, 4:1). After completion of the reaction, the mixture was cooled to room temperature and cold water was added. The reaction mixture was extracted with chloroform and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated and the crude was recrystallized from cyclohexane to afford the pure product **6** (16.0 g, 84.8 %). Mp 109.5–110 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.79 (s, 4H), 6.04 (s, 1H), 7.15–7.16 (d, J = 7.82 Hz, 2H), 7.21–7.22 (d, J = 7.82 Hz, 2H), 7.32–7.33 (d, J = 7.05 Hz, 1H), 7.35–7.40 (m, 2H), 8.02–8.03 (d, J = 7.32 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.3, 49.8, 50.7, 125.5, 127.8, 128.7, 128.8, 130.6, 134.5, 135.2, 136.0, 137.3, 156.8; MS (ESI$^+$) m/z 237.1 (MH^+). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.38; H, 6.77; N, 11.83.

4.2.1.2. 2-(4′-Methylbiphenyl-2-yl)-1*H*-imidazole (7). This was prepared according to a modified method.[27] Compound **6** (4.72 g, 0.02 mol) was dissolved in acetonitrile (250 mL), grinded potassium permanganate (7.9 g, 0.05 mol), and silica gel (10 g) were added to the solution in portions. The course of the reaction was monitored by TLC (eluent: EtOAc/MeOH, 4:1). After completion of the reaction, 10 mL of ethanol was added, and then the mixture was filtered and the precipitated solid was washed with acetonitrile (200 mL). The filtrate was combined and concentrated under vacuum, the residue was purified by Al_2O_3 column chromatography eluting with petroleum ether/EtOAc (1:2) to give the pure product (3.35 g, 71.5%). Mp 176.5–177.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.89 (s, 2H), 7.16–7.17 (d, J = 7.92, 2H), 7.19–7.21 (d, J = 7.92, 2H), 7.27–7.28 (d, J = 7.02 Hz, 1H), 7.36–7.41 (m, 2H), 8.07–8.08 (d, J = 7.32 Hz, 1H), 8.57 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.21, 127.77, 128.45, 128.85, 129.07, 129.49, 129.57, 130.62, 137.64, 138.13, 139.08, 146.21; MS (ESI$^+$) m/z 235.1 (MH^+). Anal.Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.08; H, 6.05; N, 11.91.

4.2.1.3. 1-Triphenylmethyl-2-(4′-methylbiphenyl-2-yl)-1*H*-imidazole (8). This was prepared according to a modified method.[15] To a solution of compound **7** (2.34 g, 0.01 mol) in CH_2Cl_2 (40 mL) was added triethylamine (8 mL). After stirring for 30 min at room temperature, triphenylmethyl chloride (2.79 g, 10 mmol) was added and the mixture was stirred for another 3–4 h. After the evaporation of the solvent, the residue was dissolved in ethyl acetate, washed with solution of NaOH (1N) and dried over anhydrous magnesium sulfate. The crude product was purified by Al_2O_3 column chromatography eluting with petroleum ether/ethyl acetate (1:3) to provide **8** as a white solid (3.62 g, 75.9%). Mp 198.5–200 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.44 (s, 3H), 6.41 (s, 1H), 6.62–6.63 (d, J = 7.92 Hz, 6H), 6.91–6.93 (m 3H), 6.97–7.00 (t, J = 7.74 Hz, 6H), 7.03-7.05 (t, J = 7.47 Hz, 1H), 7.07–7.08 (d, J = 8.04 Hz, 2H), 7.09–7.14 (m, 5H), 7.14–7.16 (t, J = 6.54 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1, 125.3, 126.1, 126.9, 127.3, 128.4, 129.4, 130.3, 130.7, 131.8, 133.2, 136.3, 137.8, 141.4, 142.3, 148.2; MS (ESI$^+$) m/z 477.1 (MH^+). Anal. Calcd for $C_{35}H_{28}N_2$: C, 88.20; H, 5.92; N, 5.88. Found: C, 88.23; H, 5.89; N, 5.86.

4.2.1.4. 1-Triphenylmethyl-2-[4′-(bromomethyl)biphenyl-2-yl]-1*H*-imidazole (9). This was prepared according to a modified method.[15] A solution of compound **8** (3.10 g, 6.5 mmol), *N*-bromoeuccinimide (1.15 g, 6.5 mmol), and dibenzoyl peroxide (0.11 g, 0.45 mmol) in carbon tetrachloride (40 mL) was refluxed for 3 h, cooled to 40 °C, and then filtered. The filtrate was concentrated under vacuum to afford the crude product **9**. The crude product is routinely used without further purification.

4.2.1.5. 4′-{[2-*n*-Propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1-triphenylmethylimidazole-2-yl)biphenyl (10). This was prepared according to a modified method.[15] To a solution of compound **25** (2.37 g, 7.44 mmol) in 20 mL of DMF was added NaH (0.65 g) at 0 °C. After stirring for 1 h at ambient temperature, a solution of compound **9** (3.61 g,

6.5 mmol) in DMF (10 mL) was added and the stirring continued for about 25 h. Following the addition of water (20 mL), the resulting solution was extracted with ethyl acetate (3× 20 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by Al_2O_3 column chromatography (eluant: petroleum ether/ethyl acetate 1:3 and 1:10) to provide product **10** as a light yellow solid (1.56 g, 30.8%). Mp 203.7–205.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.06–1.09* (t, *J* = 7.44 Hz, 3H), 1.89–1.93 (m, 2H), 2.79 (s, 3H), 2.96–2.98 (t, *J* = 7.89 Hz, 2H), 3.74 (s, 3H), 5.45 (s, 2H), 6.41–6.42 (d, *J* = 1.5 Hz, 1H), 6.67–6.68 d, *J* = 7.92 Hz, 6H), 6.89–6.90 (d, *J* = 7.92 Hz, 1H), 6.93–6.94 (t, *J* = 7.80 Hz, 6H), 6.97–6.99 (m, 5H), 7.01–7.07 (m, 5H), 7.10–7.13 (m, 1H), 7.29–7.36 (m,4H), 7.45 (s, 1H), 7.55 (s, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2, 16.9, 21.8, 29.8, 31.9, 47.5, 78.7, 109.4, 119.3, 122.5, 122.7, 123.4, 125.9, 126.6, 127.8, 128.1, 128.9, 129.4, 129.8, 130.0, 134.4, 135.1, 136.6, 140.8, 142.0, 142.6, 143.3, 145.8, 154.8, 156.8, 162.3; MS (ESI) *m*/*z* 780.1 (MH^+). Anal. Calcd for $C_{54}H_{46}N_6$: C, 83.26; H, 5.95; N, 10.79. Found: C, 83.31; H, 5.89; N, 10.73.

4.2.1.6. 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-imidazole-2-yl)biphenyl (1). This was prepared according to a modified method.[15] To a solution of compound **10** (1.00 g, 1.28 mmol) in tetrahydrofuran (25 mL) was added hydrochloric acid (10%, 12.5 mL). After stirring for about 8 h, an excess of aqueous NaOH (10%) was added. The solvent was removed in vacuo, then the resulting solid was washed with chloroform and the organic layers were combined. Following the concentration, the crude product was purified by silica gel column chromatography (eluant: chloroform/methanol 12:1) to afford the title compound **1** (0.62 g, 90.2%). Mp 143.7–145.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.06–1.09* (t, *J* = 7.23 Hz, 3H), 1.86–1.91 (m, 2H), 2.78 (s, 3H), 2.95–2.97 (t, *J* = 7.86 Hz, 2H), 3.87 (s, 3H), 5.41 (s, 2H), 6.68–6.69 (d, *J* = 8.34 Hz, 1H), 7.03–7.05 (d, *J* = 8.04 Hz, 2H), 7.20–7.21 (d, *J* = 7.98 Hz, 2H), 7.28–7.33 (m, 4H), 7.39–7.45 (m, 4H), 7.66–7.67 (d, *J* = 8.04 Hz, 1H), 7.95–7.96 (m, 2H), 9.56 (s 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1, 17.0, 21.8, 29.9, 31.9, 47.3, 109.5, 109.6, 119.3, 122.5, 122.7, 123.4, 123.7, 126.6, 128.1, 128.8, 129.4, 129.5, 129.9, 130.3, 135.0, 135.1, 136.5, 138.6, 140.8, 142.5, 143.3, 145.8, 154.6, 156.6; ESI-HRMS: *m*/*z* calcd for $[C_{35}H_{33}N_6]^+$: 537.6770; found: 537.2761. Anal. Calcd for $C_{35}H_{32}N_6$: C, 78.33; H, 6.01; N, 15.66. Found: C, 78.40; H, 5.95; N, 15.63.

4.2.2. Synthesis of 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-imidazoline-2-yl)biphenyl (4) and4′-{[2-n-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-imidazole-2-yl)biphenyl (1)

4.2.2.1. 2-Cyano-4′-bromomethylbiphenyl (11). The title compound **11** was prepared from 2-cyano-4′-methylbiphenyl **5** using the procedure described in the preparation of compound **9.** The crude product is routinely used without further purification.

4.2.2.2. 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-cyanobiphenyl (12). The title compound **12** was prepared from 2-cyano-4′-bromomethylbiphenyl **11** using the procedure described in the preparation of compound **10.** Compound **12** (60.3%, yield). Mp 181.2–182.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08–1.00 (t, *J* = 7.32 Hz, 3H), 1.89–1.93 (m, 2H), 2.76 (s, 3H), 3.01–3.03 (t, *J* = 7.71 Hz, 2H)), 3.79 (s, 3H), 5.43 (s, 2H), 6.93–6.94 (d, *J* = 7.62 Hz, 2H), 7.12–7.14 (d, *J* = 8.22 Hz, 2H), 7.20 (s, 1H), 7.24–7.26 (m, 1H), 7.30–7.33 (d, *J* = 7.62 Hz, 1H), 7.39–7.40 (d, *J* = 7.98 Hz, 1H), 7.42–7.43 (m, 1H), 7.45–7.46 (m, 2H), 7.62–7.93 (d, *J* = 8.04 Hz, 1H), 7.95–7.96 (m, 1H), 8.03 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1, 16.8, 24.3, 29.2, 32.9, 50.4, 104.6, 109.2, 110.3, 111.2, 117.1, 119.5, 122.5, 123.6, 123.9, 126.4, 127.8, 128.2, 128.5, 129.3, 132.7, 133.6, 134.5, 134.7, 136.4, 138.4, 142.5, 142.8, 153.2, 154.9; MS (ESI) *m*/*z* 496.5 (MH^+). Anal. Calcd for $C_{33}H_{29}N_5$: C, 79.97; H, 5.90; N, 14.13. Found: C, 80.10; H, 5.95; N, 14.03.

4.2.2.3. 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-imidazoline-2-yl)biphenyl (4). The title compound **4** was prepared from compound **12** using the procedure described in the preparation of compound **6.** Compound **4** (80.2%, yield). Mp 98.7–99.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.02–1.05* (t, *J* = 7.35 Hz, 3H), 1.84–1.88 (m, 2H), 2.77 (s, 3H), 2.91–2.93 (t, *J* = 7.83 Hz, 2H), 3.46 (s, 4H), 3.85 (s, 3H), 5.39 (s, 2H), 6.78–7.80 (d, *J* = 7.98 Hz, 2H), 6.82–6.84 (t, *J* = 7.26 Hz,1H), 7.07–7.09 (d, *J* = 7.92 Hz, 2H), 7.14–7.17 (t, *J* = 7.74 Hz, 1H), 7.27–7.32 (m, 1H), 7.34–7.35 (d, *J* = 7.92 Hz, 2H), 7.37–7.39 (s, 1H), 7.43–7.46 (t, *J* = 7.65 Hz, 1H), 7.50 (s, 1H), 7.71–7.75 (dd, *J* = 10.92, 7.56 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2, 17.0, 22.0, 29.9, 31.9, 47.3, 50.8, 109.6, 109.5, 119.3, 122.6, 122.8, 123.4, 123.7, 126.7, 128.2, 128.7, 129.3, 129.6, 129.9, 130.4, 135.0, 135.1, 136.5, 138.6, 140.7, 142.4, 143.4, 145.7, 154.8, 157.0; ESI-HRMS: *m*/*z* calcd for $[C_{35}H_{35}N_6]^+$: 539.6928; found 539.3076. Anal. calcd for $C_{35}H_{34}N_6$: C, 78.04; H, 6.36; N, 15. 60. Found: C, 77.30; H, 6.55; N, 15.93.

4.2.2.4. 2-[4′-[4-methyl-6-(1-methyl-benzoimidazol-2-yl)-2-propyl-benzoimidazol]-1-yl]methylbiphenyl-2-yl]-1*H*-imidazole (1). The title compound **1** was prepared from compound **4** using the procedure described in the preparation of compound **7**. Compound **1** (66.2%, yield). Mp 143.9–144.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.06–1.09* (t, *J* = 7.23 Hz, 3H), 1.86–1.91 (m, 2H), 2.78 (s, 3H), 2.95–2.97 (t, *J* = 7.86 Hz, 2H), 3.87 (s, 3H), 5.41 (s, 2H), 6.68–6.69 (d, *J* = 8.34 Hz, 1H), 7.03–7.05 (d, *J* = 8.04 Hz, 2H), 7.20–7.21 (d, *J* = 7.98 Hz, 2H), 7.28–7.33 (m, 4H), 7.39–7.45 (m, 4H), 7.66–7.67 (d, *J* = 8.04 Hz, 1H), 7.95–7.96 (m, 2H), 9.56 (s 1H).

4.2.3. Synthesis of 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(5-chloro-1*H*-imidazole-2-yl)biphenyl (2)

4.2.3.1. *N*-(2-cyanomethyl)-4′-methylbiphenyl-2-carboxamide (14). This was prepared according to a modified method.[15] A solution of 4′-methylbiphenyl-2-carboxylic acid **13** (5.0 g, 23.6 mmol), thionyl chloride (8.75 mL, 0.12 mol), and 50 mL of chloroform was refluxed for 4 h. The solvent was removed under vacuum, and the residue was concentrated twice from toluene to remove traces of thionyl chloride. The acid chloride thus obtained was dissolved in 25 mL of tetrahydrofuran. This solution was added dropwise in five equal portions, alternating with five equal portions of 1.0 N aqueous sodium hydroxide (23.6 mL, 23.6 mmol), into a solution of 2-aminoacetonitrile hydrochloride (2.16 g, 23.6 mmol) in 1.0 N aqueous sodium hydroxide (23.6 mL, 23.6 mmol) at 0 °C. After 12 h at 25 °C, water (25 mL) was added, and the mixture was extracted with ethyl acetate (3× 50 mL). The organic layers were collected, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum. The residue was recrystallized from methylcyclohexane to furnish **14** as a white solid (5.08 g, 86%). Mp 101.0–102.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *2.37 (s,* 3H), 4.66 (s, 2H), 5.65 (br, 1H), 7.12 (d, *J* = 7.80 Hz, 2H), 7.40–7.37 (t, *J* = 7.85 Hz, 2H), 7.62–7.54 (m,3H), 8.10 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.3, 31.6, 114.8, 127.8, 128.0, 129.5, 131.9, 132.1, 132.7, 133.5, 137.3, 167.6; MS (ESI) *m*/*z* 251.0 (MH^+). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.40; H, 5.95; N, 11.23.

4.2.3.2. 2-(4′-Methylbiphenyl-2-yl)-5-chloroimidazole (15). This was prepared according to a modified method.[28] A solution of compound **14** (3.75 g, 15 mmol) and triphenylphosphine (9.82 g, 37.5 mmol) in acetonitrile (150 mL) was treated with carbon tetrachloride (5.78 g, 37.5 mmol) at 45 °C for 16 h. The reaction mixture was concentrated and the residue was dissolved in 150 mL methylene chloride. To the solution was added 0.5 N sodium hydroxide (150 mL), the two-phase mixture was stirred at room temperature for 10 min. After phase separation, the organic layer was washed with water (2× 60 mL), brine (60 mL), and concentrated, the residue was purified by flash chromatography (silica gel, hexane/$CHCl_3$/EtOAc = 10:2:1) to give desired product **15** (3.23 g, 80.2%). Mp 171.9–173.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (s, 3H), 6.66 (s, 1H), 7.20–7.22 (d, J = 7.68 Hz, 2H), 7.25–7.28 (m, 3H), 7.39–7.44 (m, 2H), 8.13–8.15 (d, J = 7.74 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.3, 112.2, 127.6, 127.9, 128.9, 129.1, 129.4, 129.8, 130.7, 137.7, 138.1, 138.8, 145.0; MS (ESI) m/z 269.0 (MH^+). Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42; Cl, 13.19. Found: C, 71.53; H, 4.89; N, 10.40; Cl, 13.20.

4.2.3.3. 1-Triphenylmethyl-2-(4′-methylbiphenyl-2-yl)-5-chloro-1*H*-imidazole (16). The title compound **16** was prepared from compound **15** using the procedure described in the preparation of compound **8.** Compound **16** (76.2%, yield). Mp 154.8–156.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3H), 6.28 (s, 1H), 6.60–6.61 (d, J = 7.62 Hz, 6H), 6.91–6.93 (t, J = 7.26 Hz, 3H), 6.98–7.01 (t, J = 7.74 Hz, 6H), 7.05–7.07 (t, J = 7.17 Hz, 1H), 7.11–7.17 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.2, 78.7, 120.5, 126.1,127.0, 127.5, 127.9, 128.6, 128.9, 129.1, 129.5, 130.4, 130.6, 131.7, 136.5, 137.5, 141.6, 147.2; MS (ESI) m/z 512.0 (MH^+). Anal. Calcd for $C_{35}H_{27}ClN_2$: C, 82.26; H, 5.32; N, 5.48; Cl, 6.94. Found: C, 82.53; H, 5.39; N, 5.40; Cl, 6.88.

4.2.3.4. 1-Triphenylmethyl-2-(4′-bromomethylbiphenyl-2-yl)-5-chloro-1*H*-imidazole (17). The title compound **17** was prepared from compound **16** using the procedure described in the preparation of **9**. The crude product is routinely used without further purification.

4.2.3.5. 4′-{[2-*n*-Propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(5-chloro-1-(triphenylmethyl)-imidazole-2-yl)biphenyl (18). The title compound **18** was prepared from compound **17** using the procedure described in the preparation of compound **10**. Compound **18** (41.2%, yield). Mp 209.5–212.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.06–1.09 (t,* J = 7.35 Hz, 3H), 1.89–1.95 (m, 2H), 2.79 (s, 3H), 2.96–2.98 (t, J = 7.83 Hz, 2H), 3.74 (s, 3H), 5.46 (s, 2H), 6.30 (s,1H), 6.66–6.67 (d, J = 7.62 Hz, 6H), 6.93–6.96 (t, J = 7.83 Hz, 6H), 6.95–6.98 (m, 2H), 7.03–7.10 (m, 8H), 7.27–7.31 (m, 3H), 7.33–7.36 (m, 1H), 7.46 (s, 1H), 7.56 (s, 1H), 7.78–7.80 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.7, 19.9, 23.5, 30.6, 47.2, 58.3, 110.9, 115.3, 122.3, 123.5, 124.4, 127.3, 128.4, 129.5, 133.4, 134.0, 135.5, 135.6, 138.4, 138.5, 141.8, 153.3, 153.5, 154.5; MS (ESI) m/z 813.5 (MH^+). Anal. Calcd for $C_{54}H_{45}ClN_6$: C, 79.73; H, 5.58; Cl, 4.36; N, 10.33. Found: C, 79.60; H, 5.63; Cl, 4.33; N, 10.36.

4.2.3.6. 4′-[[4-Methyl-6-(1-methyl-benzoimidazol-2-yl)-2-propyl-benzoimidazol]-1-yl]methyl-2-(5-chloroimidazole-2-yl)-biphenyl (2). The title compound **2** was prepared from compound **18** using the procedure described in the preparation of compound **1**. Compound **2** (84%, yield). Mp 147.2–148.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.08–1.10 (t,* J = 7.35 Hz, 3H), 1.82–1.93 (m, 2H), 2.76 (s, 3H), 2.96–2.98 (t, J = 7.86 Hz, 2H), 3.86 (s, 3H), 5.39 (s, 2H), 6.48 (s, 1H), 7.06–7.08 (d, J = 7.98 Hz, 2H), 7.21–7.22 (d, J = 8.04 Hz, 2H), 7.28–7.32 (m, 6H), 7.41–7.42 (m, 2H), 7.57–7.58 (m, 1H), 7.89–7.90 (m,1H), 9.88 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.5, 19.8, 24.5, 29.6, 47.2, 58.3, 110.9, 115.4, 122.6, 123.8, 124.4, 126.8, 128.4, 129.5, 133.4, 133.8, 134.0, 135.5, 135.6, 138.4, 138.5, 141.8, 153.5, 153.3, 154.7; ESI-HRMS: m/z calcd for $[C_{35}H_{32}ClN_6]^+$: 571.1138; found: 571.3809. Anal. Calcd for $C_{35}H_{31}ClN_6$: C, 73.61; H, 5.47; Cl, 6.21; N, 14.72. Found: C, 73.40; H, 5.45; Cl, 6.18; N, 14.63.

4.2.4. Synthesis of 4′-{[2-*n*-propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-1,2,4-triazol-3-yl)biphenyl (3)

4.2.4.1. 4-Methyl-2′-thiocarboxamido-1,1′-biphenyl (19). This was prepared according to a modified method.[29] To a slurry of 70% sodium hydrosulfide hydrate (7.9 g, 99 mmol) and magnesium chloride hexahydrate (10.1 g, 50 mmol) in 100 mL of DMF was added 2-cyano-4′-methylbiphenyl **5** (9.6 g, 50 mmol) in one portion, and the mixture was stirred at room temperature for 2 h. The resulting green slurry was poured into 200 mL water, and the resulting precipitates were collected by filtration. The crude product was resuspended in 1 N HCl and stirred for 20 min, then filtered and washed with water to give the title compound **19** (10.47 g, 92.1%). Mp 135.5–136.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *2.41 (s,* 3H), 6.48 (br s, 2H), 7.32 (m, 7H), 7.91 (dd, J = 9.86, 2.34 Hz, 2H); MS (ESI) m/z 228.3 (MH^+).

4.2.4.2. 4-Methyl-2′-isothiocarboximino-1,1′-biphenyl, methiodide (20). This was prepared according to a method.[30] A solution of 4-methyl-2′-thiocarboxamido-1,1′-biphenyl **19** (2.0 g, 8.8 mmol) in 80 mL of ethyl ether was treated with iodomethane (4.0 mL, 64 mmol). After stirring at room temperature for 24 h, the reaction mixture was filtered. The precipitate was washed with ether (3× 10 mL) and dried under vacuum to give the title compound **20** (2.71 g, 83.5%). Mp 165.7–169.1 °C (dec); ^{1}H NMR (600 MHz, $CDCl_3$): δ *2.41 (s,* 3H), 6.48 (br s, 2H), 7.3 (m, 7H), 7.9 (dd, J = 7.86 Hz, 2H); MS (ESI) m/z 242.1 (M^+).

4.2.4.3. 4-Methyl-2′-(1*H*-1,2,4-triazol-3-yl)-1,1′-biphenyl (21). This was prepared according to a modified method.[30] A stirred solution of 4-methyl-2′-isothiocarboximino-1,1′-biphenyl, methiodide **20** (2.65 g, 6.8 mmol) dissolved 25 mL of dry dimethylformamide under nitrogen atmosphere was treated with formic hydrazide (0.81 g, 14 mmol). The reaction was stirred at room temperature for 16 h, and then heated at 90 °C for 4 h. The cooled reaction mixture was poured into water and extracted with ether. The combined extracts were washed with water (4× 10 mL), dried over magnesium sulfate, filtered, and evaporated under vacuum to give the title compound **21** (0.90 g, 56.3%). Mp 157.1–158.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.48 (br s, 2H), 7.3 (m, 7H), 7.9 (dd, J = 7.86 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.32, 118.54, 127.82, 128.11, 129.01, 129.55, 130.61, 135.22, 135.95, 139.03, 151.23, 159.82; MS (ESI) m/z 236.3 (MH^+).

4.2.4.4. 4-Methyl-2′-(1-triphenylmethyl-1,2,4-triazol-3-yl)-1,1′-biphenyl (22). The title compound **22** was prepared from compound **21** using the procedure described in the preparation of compound **8**. Compound **22** (87.2%, yield). Mp 133.1–134.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.94 (s, 3H), 7.27 (s, 4H), 7.51 (m, 2H), 7.65 (t, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.37, 118.5, 126.2, 127.8, 128.0, 129.2, 129.5, 135.1, 135.4, 139.0, 143.6, 160.1; MS (ESI) m/z 478.5 (MH^+). Anal. Calcd for $C_{34}H_{27}N_3$: C, 85.50; H, 5.70; N, 8.80. Found: C, 85.66; H, 5.49; N, 8.40.

4.2.4.5. 4-Bromomethyl-2′-(1-triphenylmethyl-1,2,4-triazol-3-yl)-1,1′-biphenyl (23). The title compound **23** was prepared from compound **22** using the procedure described in the preparation of **9**. The crude product is routinely used without further purification.

4.2.4.6. 4′-{[2-*n*-Propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1-triphenylmethyl-1,2,4-triazol-3-yl)biphenyl (24). The title compound **24** was prepared from compound **23**, using the procedure described in the preparation of compound **10**. Compound **24** (45%, yield). Mp 250.8–251.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.15 (d, J = 7.89 Hz, 2H), 7.21 (d, J = 7.89 Hz, 2H), 7.34 (m, 1H), 7.44 (m, 2H), 8.05 (s, 1H), 8.15 (dd, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 16.9, 21.8, 30.0, 31.7, 47.0, 78.0, 109.0, 109.5, 119.6, 122.3, 122.4, 123.8, 125.5, 127.5, 127.8, 128.1, 129.0, 129.4, 130.0, 130.2, 130.6, 133.9, 135.1, 136.7, 140.8, 142.0, 143.0, 143.2, 145.9, 154.7, 156.4, 162.3; ESI-HRMS: m/z calcd for $[C_{53}H_{46}N_7]^+$: 780.9795; found: 780.3809.

4.2.4.7. 4′-{[2-*n*-Propyl-4-methyl-6-(1-methylbenzoimidazol-2-yl)benzoimidazol-1-yl]methyl}-2-(1*H*-1,2,4-triazol-3-yl)biphenyl (3). The title compound **3** was prepared from compound **24**, using the procedure described in the preparation of compound **1**. Compound **3** (87%, yield). Mp 197.4–198.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ *1.08–1.10* (t, J = 7.35 Hz, 3H), 1.88–1.94 (m, 2H), 2.76 (s, 3H), 3.01–3.03 (t, J = 7.32 Hz, 2H), 3.79 (s, 3H), 5.43 (s, 2H), 6.92–6.94 (d, J = 7.38 Hz, 2H), 7.12–7.13 (d, J = 8.04 Hz, 2H), 7.20 (s, 1H), 7.25–7.28 (m, 2H), 7.30–7.33 (t, J = 6.60 Hz, 1H), 7.38–7.47 (m, 4H), 7.62–7.63 (d, J = 8.04 Hz, 1H), 7.94–7.98 (m, 1H), 8.03 (s, 1H) 15.86 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1, 17.0, 21.8, 29.9, 31.6, 47.1, 108.9, 109.4, 119.6, 122.3, 122.5, 123.8, 125.5, 128.1, 129.0, 129.4, 129.9, 130.3, 133.8, 135.1, 136.7, 140.8, 143.0, 143.2, 145.8, 154.7, 156.4, 162.3; ESI-HRMS: m/z calcd for $[C_{34}H_{32}N_7]^+$: 538.6651; found: 538.2714.

4.3. Biological activities

4.3.1. Angiotensin II receptor (AT_1)-binding assay

Membrane fractions or bovine adrenal cortex were prepared by modifications of the method of Maeda et al.[31] The freshly isolated bovine adrenal cortex was homogenized in ice-cold medium containing 10 mM sodium phosphate buffer (pH 7.4), 30 mM NaCl, 1 mM $MgCl_2$, 0.1 mM EDTA, 1 mM dithiothreitol (DTT), 1 μM (*p*-amidinophenyl) methanesulfonyl fluoride HCl (*p*-APMSF), and 0.02% NaN_3. The homogenate was layered on a 41% sucrose solution and centrifuged at 95,000g for 60 min. The interfacial band between the supernatant and the sucrose portion was collected. The membrane fraction was washed by centrifugation at 95,000g for 20 min. The pellet obtained was used as the source of AT_1 receptor. Binding of [^{125}I]AngII to membranes was performed at 22 °C for 120 min in 96-well plates. Each 200*u*L incubated solution contained the following (final concentration): 20 mM Tris–HCl (pH 7.4), 120 mM NaCl, 5 mM $MgCl_2$, 0.05% bovine serum albumin (BSA), 1 μM *p*-APMSF, 0.5 mM EDTA, 0.1 mM DTT, 0.1 nM [^{125}I]AngII, the test compound and membrane preparations (10 μg of protein/well). At the end of the incubation, bound complex was trapped on filters (GF/C) and washed with cold Tris buffer (pH 7.4; 3× 250 μL). Filter disks were dried, punched out, and counted in an *r*-counter. Specific binding was defined as total binding minus nonspecific binding, which was estimated in the presence of 1 μM unlabeled AngII. The IC_{50} of an inhibitor was determined as the concentration that displaced the specifically bound [^{125}I]AngII by 50%.

4.3.2. Effects on AngII-induced pressor response in conscious normotensive Beagle dogs

Beagle dogs (~7.5 kg body weight, provided by Laboratory Animal Center, Sichuan Academy of Medical Sciences, test animal certificate number: SCXK (Chuan 2004-15)) were intravenous anesthetized with pentobarbitone–sodium (45 mg/kg, ip) on forward legs, esophagus was cannulated to administration. Wall skin was dissected from hind legs, and separate inferior branch arteria saphena from femoral artery. The artery was cannulated and connected to a pressure transducer (TP-400T, Japan Opto-Electronics) coupled to polygraph (PEG-1000, Japan Opto-Electronics) and a carrier amplifier (PP-101H, Japan Opto-Electronics) for measurement of blood pressure and heart rate and all data were collected using a polygraph data processing system (PEG-1000, Japan Opto-Electronics). The normal blood pressure and heart rate were recorded after stable, and then the test compound (2.13 mg/kg) was orally administered. Blood pressure and heart rate were monitored after 1 h administration of the test compounds so that to study the effect of test compounds on blood pressure and heart rate. Waveforms of blood pressure and heart rate for each dog were recorded after 1 min injection of AngII (0.45 μg/kg). Eight max values were fetched at each of time point and the average value was obtained to avoid data acquisition with experiment error. The blood pressure lowering effects of the test compounds was express as the change rate after 1 h administration of the test compounds and injection of AngII as interclass statistics. The difference between the maximum blood pressure increase before and after drug was reported as the percent (%) inhibition of the AngII pressor effect.

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