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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of new sartan derivatives

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Abstract

As prodrugs series of new sartan-derived molecules were designed, synthesized, and evaluated. Most of the synthesized compounds could decrease blood pressure efficiently in spontaneously hypertensive rats. It could be ratiocinated that the original drugs could be released from the prodrugs exactly at the connecting position catalyzed by the hydrolyzation enzymes. The maximal response of mean blood pressure (MBP) lowered 70.2 ± 5.0 mmHg (compound $\mathbf{I_1}$) and 61.2 ± 1.0 mmHg (compound $\mathbf{II_1}$) at 10 mg/kg after oral administration, and the antihypertensive effect lasted beyond 24 h, which performed better than Losartan and were similar with Telmisartan. Pharmacokinetics test results of $\mathbf{I_1}$ were consistent with its antihypertension effects in vivo. The safety was confirmed by the influence on the rats' heart rates and other symptoms which could not be observed during the whole process. Therefore, compounds $\mathbf{I_1}$ and $\mathbf{II_1}$ could be considered potential antihypertension drug candidates.

Keywords Hypertension · Antihypertension · Prodrug · AT_1 receptor blockers

Introduction

Hypertension is the main risk factor in cerebrovascular disease, coronary heart disease, and renal vascular disease [1, 2]. The renin-angiotensin system plays a vital role in regulating blood pressure (BP) and fluid balance [3]. AT_1 receptor blockers (ARBs or sartans) act as antihypertensive drugs by blocking Angiotensin II to stimulate AT_1 receptors. Several ARBs have been developed, such as Losartan, Candesartan, and Telmisartan, one of the most widely used ARBS in clinics with high potency, long-lasting, and low toxicity [4–6]. However, long-term use of sartans could cause symptoms such as nausea and headache, so it is still necessary to develop effective, bioavailable, and safe antihypertension drugs [7–9].

Hypertension is mostly caused by a combination of heterogeneous factors such as genetic background and renal or endocrine disorders, and clusters often with other chronic kidney disease or cardiovascular disease, such as heart failure, thrombosis, myocardial infarction, ischemic stroke, etc. [10]. Thus one-drug therapy is usually insufficient for most patients. The use of two drug combination therapy was recommended in the 2018 ESC/ESH guideline; namely, an angiotensin receptor blocker (ARB) is usually matched with a calcium channel blocker (CCB) or diuretic as the initial treatment to control BP [11] because of the existence of complementary effects between different antihypertension drugs [12]. In addition, hypertension patients with atherogenic dyslipidemia are recommended to administrate antihypertension drugs together with Aspirin or Statins to reduce the incidence of cardiovascular events. However, for the patients receiving two or more pills, their adherence to treatment in practice is about 25–65%, complying with the prescribed treatment regimen [13].

Single-pill combination (SPC) therapy with two or more drugs in a single tablet has been used to simplify the treatment by reducing the number of pills to be taken. It has shown better BP control than those given two or more drugs

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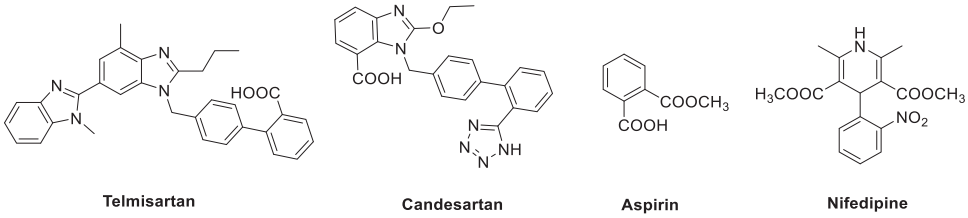
Fig. 1 Structure of drugs



separately and can maintain all or most of the expected effects of the different agents contained [14]. For example, as an SPC of sacubitril and valsartan, Entresto has a good BP reduction effect and can significantly reduce hospitalization or mortality in patients with heart failure [15]. Conjugation of two drug molecules with suitable linkers into one new molecule is another strategy for treating patients with one or several cardiovascular-related diseases [16]. As a prodrug, this new molecule usually has dual activities with a higher bioavailability and lower toxicity than the simple combination of two drugs [17]. Here series of new sartan-derived molecules conjugated with cardiovascular drugs, namely, Telmisartan and Candesartan with antithrombotic agent Aspirin and CCB Nifedipine, Telmisartan with Candesartan, and Telmisartan with itself, were synthesized, and their antihypertension activities were evaluated as prodrugs (Fig. 1).

Results and discussion

Chemistry

The preparation of compounds (**I_1, I_2, I_3, II_1**) is depicted in Scheme 1. The hydrogen of −COOH of Telmisartan was replaced by the chloride methyl group to obtain compound **2**, while the hydroxyethyl group gave compound **5**. Compound **2** was reacted with carboxylic acid compounds (**1**, **3**, **4**) to give compounds **I_1**–**I_3**. Compound **II_1** was generated after **5** with compound **1** under the existence of DCC and DMAP.

The preparation of compounds **III_1** and **III_2** is described in Scheme 2. The commercially available compound **6** was reacted with chloromethyl sulfurochloridate under $Bu_4N^+ \cdot HSO_4$ as catalyst and $NaHCO_3$ as a base to obtain compound **7**. Compound **7** was reacted with K_2CO_3 and NaI followed with carboxylic acid (**1**, **3**) in DMF to generate compounds **III_1** and **III_2**.

Biological evaluation

In vivo antihypertension effects

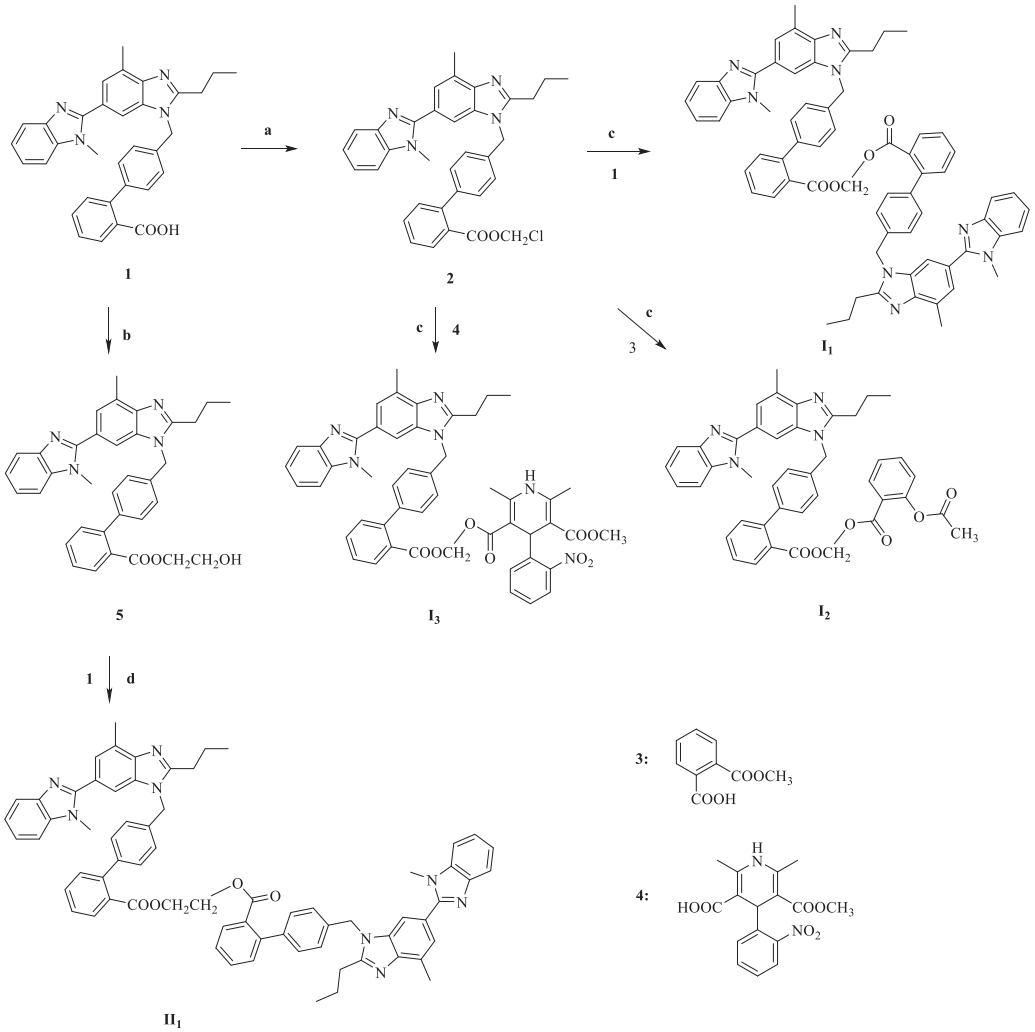
The antihypertensive efficiency of compounds **I_1**, **I_2**, **I_3**, **II_1** and **III_1**, **III_2** (5 and 10 mg/kg) was investigated in SHRs (spontaneously hypertensive rats) after oral administration with Losartan and Telmisartan (10 mg/kg) as positive control drugs (Fig. 2). All compounds could decrease BP significantly at 5 and 10 mg/kg dosages. Among them, the change of MBP in compound **II_1** was 61.2 ± 0.1 mmHg at 3 h, and **I_1** was 70.2 ± 5.0 mmHg at 3 h, which was higher than Losartan and almost equal to Telmisartan (72.2 ± 2.3) at 10 mg/kg. The antihypertensive effects of **I_1** and **II_1** were sustained for at least 24 h. It could be ratiocinated that the original drugs could be released from the prodrugs exactly at the connecting position through hydrolyzation by the mammalian metabolism enzymes to take their antihypertension effects [18]. No influence on the rats' heart rate and no symptoms such as nausea and diarrhea were observed, which confirmed the safety of new compounds.

Pharmacokinetics test

Liquid chromatography-mass spectrometry (LC-MS) method was used to monitor the concentration of compound **I_1** in plasma which showed the highest antihypertensive activity after oral administration (10 mg/kg). The mean plasma concentration-time curve of **I_1** is shown in Fig. 3. The bioavailability of compound **I_1** after oral administration was 48.01% ($F = AUC_{0-t}(test)/AUC_{0-t}(reference) \times 100\%$), which was almost the same with Telmisartan (48.8%), and the $AUC_{0\text{-}78}$ of compound **I_1** (688.50 ± 20.88 h) was also similar with Telmisartan (649.00 ± 8.07 h, $p < 0.05$). These results were consistent with its antihypertension effects in vivo.

Conclusions

As prodrugs series of novel sartan derivatives was prepared. Most of them could decrease BP efficiently in SHRs. It could be ratiocinated that the original drugs could be released from the prodrugs exactly at the connecting position catalyzed by the hydrolyzation enzymes. The safety was confirmed by the influence on the rats' heart rates and other symptoms which could not be observed during the whole process. Pharmacokinetics test results of compound **I_1** were consistent with its antihypertension effects in vivo. Compounds **I_1** and **II_1** could reduce BP more effectively than Losartan, thus **I_1** and **II_1** could be considered potential



Scheme 1 Reagents and reaction conditions: (a) Chloromethyl sulfurochloridate, $Bu_4N^+{\cdot}HSO_4^-$, $NaHCO_3$, H_2O, DCM, rt, 1 h, 72%; (b) $HOCH_2CH_2OH$, DCC, DMAP, DCM, rt, 2.5 h, 81%; (c) K_2CO_3, NaI, DMF, rt, 2 h; 77%; (d) DCC, DMAP, DCM, rt, 2.5 h, 89%

antihypertension drug candidates and deserve further investigation. Other effects, such as the antithrombotic effects of Aspirin and the synergistic effects of two drugs released from their prodrugs, will be further studied.

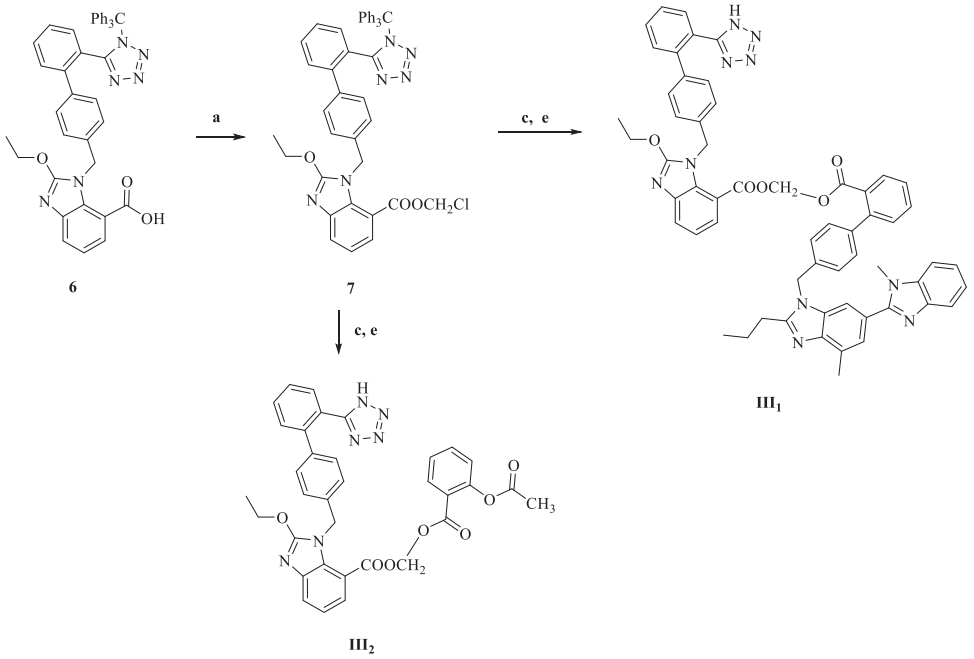
Experimental section

Chemistry

Most of the reagents were bought from commercial suppliers and used without purification. The progress of reactions was monitored through thin layer chromatography. In total, 300–400 meshes silica gel was selected for the purification in column chromatography. An electrothermal melting point apparatus was applied to measure melting points (m.p.). ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) spectra were recorded on a spectrometer with $CDCl_3$ or DMSO-d_6 as solvent and Me_4Si as internal standard. ESI-MS spectra were tested on a Micro-mass-triple-quadrupole-mass spectrometer.

General procedure for the synthesis of chloromethyl 4′-((1,7′-dimethyl-2′ -propyl-1H,3′H-[2,5′-bibenzo[d]imidazol]-3′-yl) methyl)-[1,1′-biphenyl]-2-carboxylate (2)

4'-((1,7'-Dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid (2 g, 3.89 mmol) was reacted with chloromethyl sulfurochloridate (0.03 ml, 4 mmol) under the existence of $Bu_4N^+{\cdot}HSO_4$ (6.6 g, 19.45 mmol) and $NaHCO_3$ (1.6 g, 19.45 mmol) in the mixed solution of DCM (50 ml) and H_2O (50 ml) at rt. After stirred for 1 h, the reaction was quenched with water (100 ml) and extracted with EtOAc (100 ml × 3). The mixed organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain an off-white



Scheme 2 Reagents and reaction conditions: (a) Chloromethyl sulfurochloridate, $Bu_4N^+ \cdot HSO_4^-$, $NaHCO_3$, H_2O, DCM, rt, 1 h, 72%; (b) $HOCH_2CH_2OH$, DCC, DMAP, DCM, rt, 2.5 h, 81%; (c) K_2CO_3, NaI, DMF, rt, 2 h; 77%; (d) DCC, DMAP, DCM, rt, 2.5 h, 89%; (e) HCl, MeOH, rt, 2 h, 80%

solid, purified by column chromatography [eluent: petroleum ether/ethyl acetate (4:1, v/v)] to give the pure product **2** as a white solid in 72% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.87 (ddd, $J = 17.9$, 7.4, 2.6 Hz, 2H, PhH), 7.65–7.51 (m, 2H, PhH), 7.48–7.37 (m, 3H, PhH), 7.37–7.30 (m, 3H, PhH), 7.26–7.21 (m, 2H, PhH), 7.12 (d, $J = 8.1$ Hz, 2H, PhH), 6.34 (s, 2H, $-O-CH_2-Cl$), 5.49 (s, 2H, $-CH_2$-Ph), 3.85 (s, 3H, $-NCH_3$), 3.01–2.92 (m, 2H, $-CH_2CH_2CH_3$), 2.78 (s, 3H, $-CH_3$), 1.90 (h, $J = 7.4$ Hz, 2H, $-CH_2CH_2CH_3$), 1.07 (t, $J = 7.3$ Hz, 3H, $-CH_2CH_2CH_3$). MS (ESI) *m/z* calcd for: $C_{34}H_{31}ClN_4O_2$ $[M + H]^+$: 564.1; found: 564.0.

2-Hydroxyethyl4′-((1,7′-dimethyl-2′-propyl-1H,3′H-[2,5′-bibenzo[d]imidazole]-3′-yl)methyl)-[1,1′-biphenyl]-2-carboxylate (5)

The mixture of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (500 mg, 0.97 mmol), $HOCH_2CH_2OH$ (30 mg, 0.48 mmol), DCC (400 mg, 1.94 mmol), DMAP (12.5 mg, 0.1 mmol) and dimethylformamide (50 ml) was stirred for 2.5 h, then extracted with EtOAc (50 ml × 3). The organic phase was dried over $MgSO_4$, and concentrated under a reduced pressure. The obtained residue was purified by column chromatography [eluent: petroleum ether/EtOAc (2:1, v/v)] to provide the pure **5** as a white solid. Yield: 81%; m.p.: 213-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.86 (d, $J =$ 1.5 Hz, 1H, PhH), 7.82–7.74 (m, 1H, PhH), 7.72–7.57 (m, 3H, PhH), 7.53 (dp, $J = 7.3$, 2.3 Hz, 4H, PhH), 7.43 (d, $J = 1.5$ Hz, 1H, PhH), 7.35–7.17 (m, 4H, PhH), 5.34 (d, $J = 1.2$ Hz, 2H, $-CH_2$-Ph), 4.40 (t, $J = 3.0$ Hz, 2H, $-CH_2CH_2$-OH), 3.86 (s, 3H, $-NCH_3$), 3.80 (s, 3H, $-CH_3$), 2.60 (t, $J = 7.9$ Hz, 2H, $-CH_2CH_2$-OH), 2.49 (h, $J = 9.5$ Hz, 2H, $-CH_2CH_2CH_3$), 1.58 (h, $J = 7.9$ Hz, 2H, $-CH_2CH_2CH_3$), 0.88 (t, $J = 8.0$ Hz, 3H, $-CH_2CH_2CH_3$). MS (ESI) *m/z* calcd for: $C_{35}H_{34}N_4O_3$ $[M + H]^+$: 559.1; found: 559.1.

Chloromethyl2-ethoxy-1-((2′-(1-trityl-1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl) methyl) -1H-benzo[d] imidazole-4-carboxylate (7)

2-Ethoxy-1-((2'-(1-trityl-1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid (2 g, 2.93 mmol) was reacted with chloromethyl sulfurochloridate (0.03 ml, 4 mmol) under the existence of $Bu_4N^+ \cdot HSO_4$ (6.6 g, 19.45 mmol) and $NaHCO_3$ (1.6 g, 19.45 mmol) in the mixed solution of DCM (50 ml) and H_2O (50 ml) at rt. After stirred for 1 h, the reaction was quenched with water (100 ml) and extracted with EtOAc (100 ml × 3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain an off-white solid which was purified by column chromatography [eluent: petroleum ether/ethyl acetate (4:1, v/v)] to give the pure product **7**. Yield: 72.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.81 (dd, $J = 7.4$, 1.6 Hz, 1H, PhH), 7.73 (dd, $J = 7.5$, 1.7 Hz, 1H, PhH), 7.52 (m, $J = 7.2$, 4.7, 2.2 Hz, 4H, PhH), 7.49 (dd, $J = 7.5$, 2.0 Hz, 1H, PhH), 7.42–7.28 (m, 15H, PhH), 7.18 (m, $J = 11.2$, 7.4, 2.0 Hz, 2H, PhH), 7.08–6.96 (m, 2H, PhH), 5.34 (d, $J = 1.5$ Hz, 2H, $-CH_2$-Ph), 4.67 (s, 2H, $-O$-CH_2-Cl), 4.38 (q, $J =$ 8.0 Hz, 2H, $-OCH_2CH_3$), 2.39 (t, 3H, $-OCH_2CH_3$). MS (ESI) *m/z* calcd for: $C_{44}H_{35}ClN_6O_3$ $[M + H]^+$: 731.1; found: 731.1.

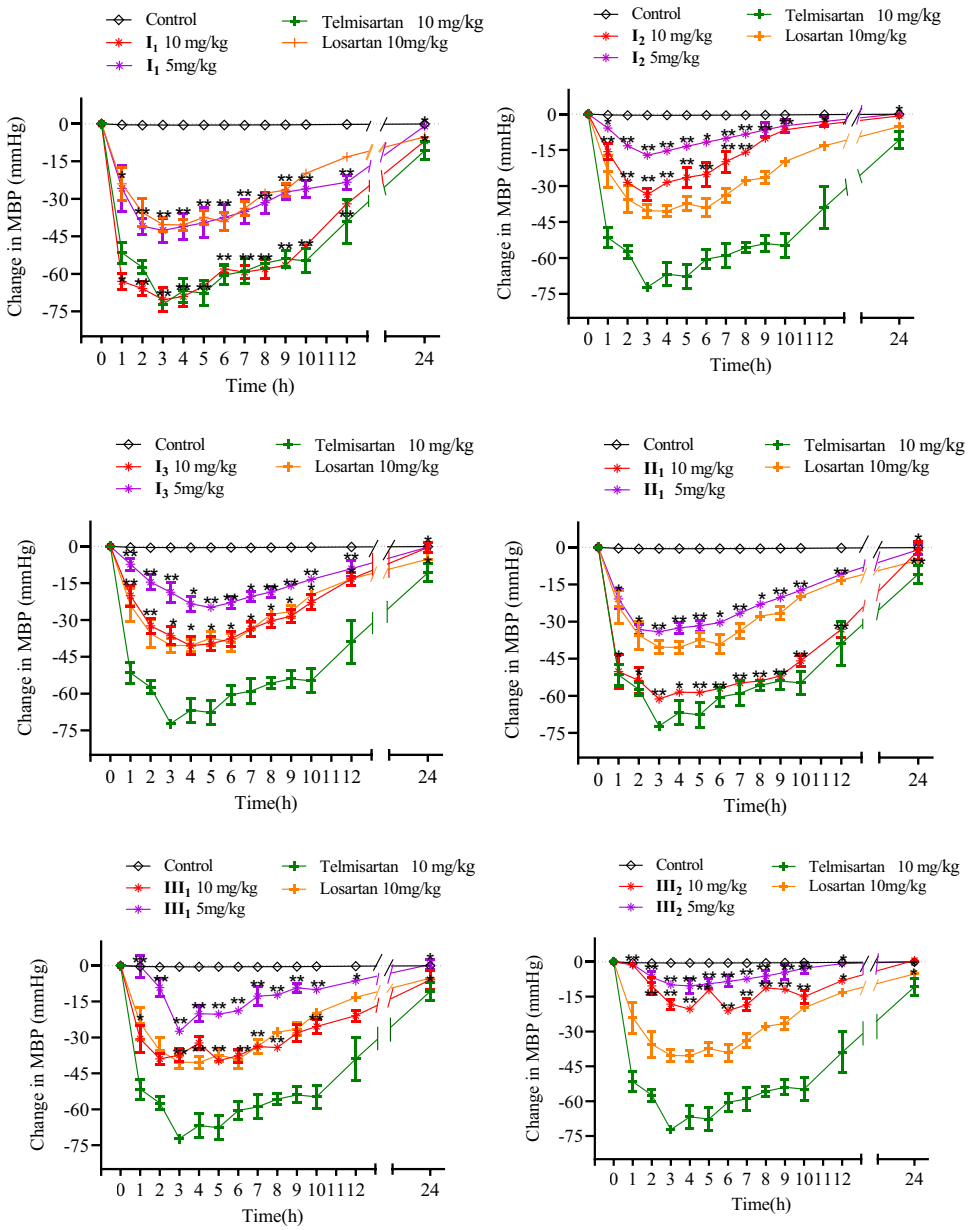


Fig. 2 Effects of compound $\mathbf{I_1}$–$\mathbf{I_3}$, $\mathbf{II_1}$ and $\mathbf{III_1}$, $\mathbf{III_2}$ on MBP of SHRs ($n = 6$, $^*p < 0.05$, $^{**}p < 0.01$ vs. negative control); and compound $\mathbf{I_1}$ and $\mathbf{II_1}$ on MBP ($^*p < 0.05$, $^{**}p < 0.01$ vs. Losartan)

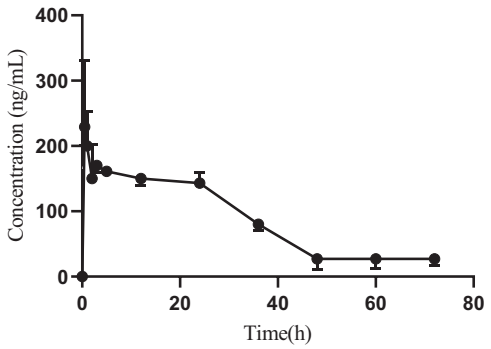


Fig. 3 Plasma concentrations of compound $\mathbf{I_1}$ in rats after signal oral administration at 10 mg/kg ($n = 6$, mean ± SD)

General procedure for the synthesis of I_1–I_3

A mixture of K_2CO_3 (270 mg, 1.95 mmol), NaI (292.3 mg, 1.95 mmol), compound **2** (220 mg, 0.39 mmol) and DMF (50 ml) was stirred for 0.5 h at rt, then **4** (129.6 mg, 0.39 mmol), or **1** (200 mg, 0.39 mmol) or **3** (70 mg, 0.39 mmol) was added slowly to the reaction mixture. After stirring for another 1.5 h at rt, 100 ml water was added to the mixture and extracted with EtOAc (100 ml × 2). The organic phase was dried with $MgSO_4$ and concentrated in vacuo to obtain an off-white solid, purified by column chromatography [eluent: petroleum ether/EtOAc (4:1, v/v)] to provide a pure white solid product ($\mathbf{I_1}$–$\mathbf{I_3}$).

Methylene-bis(4′-((1,7′-dimethyl-2′-propyl-1H,3′H-[2,5′-bibenzo[d]imidazol] -3′-yl) methyl)-[1,1′-biphenyl]-2-carboxylate) (I_1)

Compound $\mathbf{I_1}$ was prepared following the above general procedure. Yield: 77.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (m, J = 17.9, 7.4, 2.6 Hz, 4H, PhH), 7.64–7.50 (m, 4H, PhH), 7.48–7.38 (m, 6H, PhH), 7.36–7.30 (m, 6H, PhH), 7.26–7.22 (m, 4H, PhH), 7.12 (d, J = 8.1 Hz, 4H, PhH), 5.71 (s, 2H, −O-CH_2-O-), 5.51 (s, 4H, −CH_2-Ph), 3.85 (s, 6H, −NCH_3), 3.03–2.91 (m, 4H, −$CH_2CH_2CH_3$), 2.78 (s, 6H, −CH_3), 1.90 (h, J = 7.4 Hz, 4H, −$CH_2CH_2CH_3$), 1.07 (t, J = 7.3 Hz, 6H, −$CH_2CH_2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.72, 156.07, 153.97, 142.62, 142.44, 141.51, 139.28, 136.60, 136.12, 134.70, 132.21, 130.86, 129.68, 128.86, 128.65, 128.22, 127.49, 126.30, 123.28, 121.98, 121.73, 118.63, 110.28, 109.10, 79.98, 45.97, 39.96, 39.76, 31.50, 28.68, 20.59, 16.41, 13.74. MS (ESI) m/z calcd for: $C_{67}H_{61}N_8O_4$ $[M + H]^+$: 1041.5; found: 1041.4.

((2-Acetoxybenzoyl)oxy)methyl 4′-((1,7′-dimethyl-2′-propyl-1H,3′H- [2,5′-bibenzo [d] imidazol] -3′-yl)methyl)-[1,1′-biphenyl]-2-carboxylate (I_2)

Compound $\mathbf{I_2}$ was prepared with the above general procedure. Yield: 71.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.90 (dd, J = 7.9, 1.7 Hz, 1H, PhH), 7.80 (dd, J = 7.8, 1.3 Hz, 1H, PhH), 7.71 (ddd, J = 15.6, 7.5, 1.6 Hz, 2H, PhH), 7.64 (tdd, J = 7.6, 5.1, 1.5 Hz, 2H, PhH), 7.59–7.54 (m, 1H, PhH), 7.54–7.45 (m, 2H, PhH), 7.38 (ddd, J = 8.8, 7.7, 1.3 Hz, 2H, PhH), 7.31–7.17 (m, 5H, PhH), 7.10 (d, J = 8.1 Hz, 2H, PhH), 5.93 (d, J = 17.2 Hz, 2H, −O-CH_2-O-), 5.51 (d, J = 16.6 Hz, 2H, −CH_2-Ph), 3.82 (s, 3H, −NCH_3), 2.88 (dd, J = 9.0, 6.2 Hz, 2H, −$CH_2CH_2CH_3$), 2.65 (s, 3H, −$COOCH_3$), 2.18 (s, 3H, −CH_3), 1.79 (p, J = 7.4 Hz, 2H, −$CH_2CH_2CH_3$), 0.99 (t, J = 7.3 Hz, 3H, −$CH_2CH_2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.09, 167.68, 167.25, 159.08, 152.90, 152.43, 150.94, 141.86, 141.47, 137.42, 136.46, 135.57, 134.63, 134.34, 133.90, 132.79, 131.83, 130.58, 130.51, 129.38, 128.69, 128.06, 127.22, 126.98, 126.87, 126.78, 124.22, 122.70, 122.64, 122.30, 119.60, 111.15, 109.52, 82.70, 46.76, 31.40, 29.01, 20.92, 20.15, 18.56, 13.53. MS (ESI) m/z calcd for: $C_{43}H_{39}N_4O_6$ $[M + H]^+$: 707.3; found: 707.4.

3-(((4′-((2′-Ethyl-1,7′-dimethyl-1H, 3′H-[2,5′-bibenzo[d] imidazol] -3′-yl) methyl)-[1,1′-biphenyl]-2-carbonyl)oxy) methyl) 5-methyl 2,6-dimethyl-4- (3-nitrophenyl) -1,4-dihydropyridine -3,5-dicarboxylate (I_3)

Compound $\mathbf{I_3}$ was prepared with the above general procedure. Yield: 77.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H, PhH), 7.90 (dp, J = 4.4, 2.3 Hz, 2H, PhH), 7.75 (d, J = 1.5 Hz, 1H, PhH), 7.65–7.62 (m, 1H, PhH), 7.61–7.53 (m, 3H, PhH), 7.52–7.47 (m, 2H, PhH), 7.44–7.38 (m, 2H, PhH), 7.35 (d, J = 7.7 Hz, 1H, PhH), 7.28–7.17 (m, 4H, PhH), 7.12 (d, J = 8.1 Hz, 2H, PhH), 5.75–5.63 (m, 2H, −O-CH_2-O-), 5.61 (d, J = 5.4 Hz, 2H, −CH_2-Ph), 3.82 (s, 3H, −NCH_3), 3.52 (s, 3H, −$COOCH_3$), 2.91 (t, J = 7.6 Hz, 2H, −$CH_2CH_2CH_3$), 2.64 (s, 3H, Ph-CH_3), 2.28 (d, J = 8.8 Hz, 6H, Ph-CH_3), 1.81 (q, J = 7.5 Hz, 2H, −$CH_2CH_2CH_3$), 0.99 (t, = 7.4 Hz, 3H, −$CH_2CH_2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.84, 165.89, 164.82, 156.15, 153.96, 149.52, 148.93, 147.57, 146.06, 141.47, 139.38, 136.56, 136.08, 134.71, 133.90, 129.52, 128.97, 128.62, 128.24, 127.43, 126.28, 123.22, 122.02, 121.77, 121.50, 121.15, 118.55, 110.32, 109.17, 101.65, 99.33, 78.99, 50.85, 46.03, 31.68, 28.72, 20.66, 18.48, 18.15, 16.42, 13.78. MS (ESI) m/z calcd for: $C_{50}H_{47}N_6O_8$ $[M + H]^+$: 859.2; found: 859.3.

General procedure for the synthesis of II_1

A mixture of compounds **5** (877.0 mg, 1.57 mmol) and **1** (808 mg, 1.57 mmol), DCC (323.9 mg, 1.57 mmol), DMAP (191.8 mg, 1.57 mmol), and dimethylformamide (50 ml) was stirred for 2.5 h. The mixture was extracted with EtOAc (50 ml × 2), and the organic phase was collected and drained with $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was purified by column chromatography [eluent: petroleum ether/EtOAc (2:1, v/v)] to provide the pure $\mathbf{II_1}$ as a white solid.

Ethane-1,2-diylbis (4′-((1,7′-dimethyl-2′-propyl-1*H*, 3′*H*-[2,5′-bibenzo [d] imidazol]-3′-yl) methyl)-[1,1′-biphenyl]-2-carboxylate) (II_1)

Compound $\mathbf{II_1}$ was prepared as the above general procedure. Yield: 89.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.70 (s, 2H, PhH), 7.66–7.56 (m, 4H, PhH), 7.52 (ddd, J = 7.5, 5.9, 1.6 Hz, 4H, PhH), 7.47 (s, 2H, PhH), 7.37 (t, J = 7.6 Hz, 2H, PhH), 7.31 (d, J = 7.7 Hz, 2H, PhH), 7.27–7.13 (m, 8H, PhH), 7.03 (d, J = 7.9 Hz, 4H, −O-CH_2-CH_2-O-), 5.52 (s, 4H, −CH_2-Ph), 3.97 (s, 4H, −$CH_2CH_2CH_3$), 3.79 (s, 6H, −NCH_3), 2.84 (t, 4H),2.62 (s, 6H, Ph-CH_3), 1.77 (h, J = 7.4 Hz, 4H, −$CH_2CH_2CH_3$), 0.94 (t, J = 7.3 Hz, 6H, −$CH_2CH_2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.16, 156.07, 153.99, 142.65, 142.49, 141.00, 139.67, 136.61, 135.98, 134.71, 131.58, 130.54, 130.14, 129.30, 128.53, 128.21, 127.39, 126.16, 123.33, 121.96, 118.64, 110.27, 109.09, 62.13, 45.94, 31.64, 28.68, 20.60, 16.41, 13.74. MS (ESI) m/z calcd for: $C_{68}H_{63}N_8O_4$ $[M + H]^+$: 1054.5; found: 1055.4.

General procedure for the synthesis of compounds III_1 and III_2

A mixture of compound **7** (285.1 mg, 0.39 mmol), DMF (50 ml), K_2CO_3 (270 mg, 1.95 mmol), and NaI (292.3 mg,

1.95 mmol) was stirred for 0.5 h at rt, then **1** (200 mg, 0.39 mmol) or **3** (70 mg, 0.39 mmol) was added. The mixture was stirred for another 1.5 h at rt followed by the addition of 100 ml water and extracted with EtOAc (100 ml × 2). The combined organic layer was dried over $MgSO_4$ and concentrated. In order to give a white solid, the solid residue was purified by column chromatography [eluent: petroleum ether/EtOAc (4:1, v/v)]. Then solid was dissolved in 50 ml MeOH with a 3 M hydrochloric acid solution (3 ml). The mixture was stirred for 1 h. The solvent was removed, and the residue was purified by column chromatography [elution: petroleum ether/EtOAc (1:1, v/v)] to provide the pure product $\mathbf{III_1}$ or $\mathbf{III_2}$ as a white solid.

((4′-((1,7′-Dimethyl-2′-propyl-1H,3′H-[2,5′-bibenzo[d] imidazol]-3′-yl)methyl)-[1, 1′-biphenyl]-2-carbonyl)oxy) methyl-1-((2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo [d] imidazole-7-carboxylate ($\mathbf{III_1}$)

Compound $\mathbf{III_1}$ was prepared as the above procedure. Yield: 81.9%.^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.90 (dd, $J = 7.5$, 1.7 Hz, 1H, PhH), 7.86 (dd, $J = 7.5$, 1.7 Hz, 1H, (2H) PhH), 7.81–7.75 (m, 1H(3H), PhH), 7.67 (dt, $J = 7.5$, 1.7 Hz, 1H, PhH), 7.66–7.59 (m, 4H), 7.59–7.55 (m, 3H, PhH), 7.55–7.51 (m, 2H, PhH), 7.51–7.47 (m, 2H, PhH), 7.44 (t, $J = 7.5$ Hz, 1H, PhH), 7.35–7.27 (m, 2H, PhH), 7.21 (s, 2H, PhH), 7.12–7.06 (m, 2H, PhH), 7.05–6.99 (m, 2H, −O-CH_2-O-), 5.34 (d, $J = 1.2$ Hz, 4H, -CH_2-Ph), 4.38 (q, $J = 8.0$ Hz, 2H, −CH_2CH_3), 3.69 (s, 3H, −NCH_3), 2.60 (t, $J = 7.9$ Hz, 2H, −$CH_2CH_2CH_3$), 2.49 (s, 3H, Ph-CH_3), 1.59 (p, $J = 7.9$ Hz, 2H, −$CH_2CH_2CH_3$), 1.51 (t, $J = 8.0$ Hz, 3H, −CH_2CH_3), 0.88 (t, $J = 8.0$ Hz, 3H, −$CH_2CH_2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.68, 167.34, 159.08, 158.36, 154.61, 152.90, 152.43, 141.86, 141.47, 140.38, 138.26, 137.42, 136.46, 136.06, 135.79, 135.57, 134.63, 134.18, 133.90, 132.79, 130.58, 130.55, 130.50, 129.38, 129.33, 129.21, 128.69, 128.06, 127.71, 127.50, 127.22, 126.87, 126.78, 126.42, 123.33, 122.70, 122.43, 122.30, 121.39, 119.60, 116.00, 111.15, 109.52, 82.70, 66.69, 46.76, 46.24, 31.40, 29.01, 20.15, 18.56, 14.30, 13.53. MS (ESI) *m/z* calcd for: $C_{58}H_{51}N_{10}O_5$ $[M + H]^+$: 967.4; found: 967.3.

((2-Acetoxybenzoyl) oxy) methyl 1-((2′-(1H-tetrazol-5-yl) -[1,1′-biphenyl] -4-yl) methyl)-2-ethoxy-1H-benzo[d] imidazole-7-carboxylate ($\mathbf{III_2}$)

Compound $\mathbf{III_2}$ was prepared as the mentioned general procedure above. Yield: 86.4%.^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.97 (dd, $J = 7.5$, 2.0 Hz, 1H, PhH), 7.72 (m, $J = 7.5$, 1.5 Hz, 2H, PhH), 7.61 (m, 2H, PhH), 7.52 (td, $J = 7.6$, 2.0 Hz, 2H, PhH), 7.38 (t, $J = 7.5$ Hz, 2H, PhH), 7.24 (m, 2H, PhH), 6.86 (d, 4H, PhH), 6.15 (s, 2H, −CH_2-Ph), 5.52 (s, 2H, −O-CH_2-O), 4.6 (q, $J = 8.0$ Hz, 2H, −CH_2CH_3), 2.24 (s, 3H, −$COOCH_3$), 1.39 (t, $J = 8.0$ Hz, 3H, −CH_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.09, 167.34, 167.25, 158.36, 154.61, 150.94, 140.38, 138.26, 136.06, 135.79, 134.34, 134.18, 131.83, 130.55, 130.50, 129.33, 129.21, 127.71, 127.50, 126.98, 126.42, 124.22, 122.64, 122.43, 121.39, 116.00, 82.70, 66.69, 46.24, 20.92, 14.30. MS (ESI) *m/z* calcd for: $C_{34}H_{29}N_6O_7$ $[M + H]^+$: 633.2; found: 633.1.

Biological activity detection

In vivo antihypertension assays

The antihypertension activities of new compounds were tested on SBP and DBP of SHRs (250 ± 20 g, Beijing Vital River Lab Animal Co., Ltd., China). Eighteen Male SHRs were divided randomly into test compound groups, positive control group, and negative control group. Every compound was suspended in 0.5% sodium carboxymethylcellulose solution and orally administered (5 and 10 mg/kg, respectively). Positive groups, Losartan and Telmisartan (10 mg/kg), were given the same volume as compound groups. The negative control groups were supplied with the same volume of sodium carboxymethylcellulose solution. BP and heart rates were detected 24 h by MPA-2000 biological signal analysis system (Alcott Biotech, China). Six detections were operated in each part of BP measurement. The means of the six values were taken as the SBP level and DBP level separately. The MBP (mean arterial pressure) was calculated with the formula: MBP = (SBP − DBP)/3 + DBP. All compounds' data were presented as mean ± SD [19].

Pharmacokinetics detection

LC-MS method was used to monitor the concentration of compound $\mathbf{I_1}$ in plasma. LC-MS-ESI mass spectrometer (Agilent) was used with a C18 column (2.1 mm × 150 mm, 3 mm) with mobile phases: (A) Sodium dihydrogen phosphate and (B) acetonitrile. The flow rate was 1 ml/min, and the injection volume was 20 µl. The gradient elution program of mobile phase A:B (v/v) were 25:75, 30:70, 50:50. LC-MS spectral data of every sample were collected. The pharmacokinetic parameters were calculated with the Microsoft-excel program (DAS 2.0). Six Male Wistar rats (200–250 g, Shanghai Slac Lab Animal Company) were administrated with $\mathbf{I_1}$ (10 mg/kg).

Blood samples were collected from each rat with a retro-orbital puncture at pre-setting time intervals [0.5, 1, 2, 4, 6, 8, 12, 24, 48, 78 h] into microfuge tubes containing heparin. The plasma samples were separated by centrifugation of the blood samples (4000 × *g*) at 4 °C for 10 min. Plasma

samples (200 µl) were collected, internal standard (100 µl) and acetonitrile (200 µl) were added. The mixture was vortexed for 1 min to remove proteins. The supernatant was filtered by filter (0.22 µm), and the obtained filtrate (20 µl) was tested in LC-MS. Linearity 3 was detected by extracting plasma standards at nominal concentrations (2.0, 5.0, 10.0, 50.0, 100.0, 500.0 ng/ml). The calibration line was generated by least-squares linear regression of PHR (the peak height ratio) of analyte/internal standard vs. nominal concentration with weighted concentration [20, 21].

Statistics

The data were analyzed with a one-way analysis of variance, and the results were expressed as means ± standard error. When all statistical significance was provided ($p < 0.05$), a nova one-way and *t*-test were used to compare with the control, and the probability value <0.05 was considered significant. Pharmacokinetic parameters were acquired by software DAS.2.0. The animal research was accorded with the "Principles of Laboratory Animal Care" and permitted by IACUC.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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