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Original article

Nonpeptidic angiotensin II AT_1 receptor antagonists derived from 6-substituted aminocarbonyl and acylamino benzimidazoles

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ABSTRACT

Both 6-substituted aminocarbonyl and acylamino benzimidazole derivatives were designed and synthesized as nonpeptidic angiotensin II AT_1 receptor antagonists. Compounds **6f**, **6g**, **11e**, **11f**, **11g**, and **12** showed nanomolar AT_1 receptor binding affinity and high AT_1 receptor selectivity over AT_2 receptor in a preliminary pharmacological evaluation. Among them, the two most active compounds **6f** (AT_1 IC_{50} = 3 nM, AT_2 IC_{50} > 10,000 nM, PA_2 = 8.51) and **11g** (AT_1 IC_{50} = 0.1 nM, AT_2 IC_{50} = 149 nM, PA_2 = 8.43) exhibited good antagonistic activity in isolated rabbit aortic strip functional assay. In addition, they were orally active AT_1 receptor antagonists in spontaneous hypertensive rats.

1. Introduction

The renin–angiotensin aldostenone system (RAAS) is a highly complex system that is essential in fluid/electrolyte homeostasis and blood pressure regulation [1,2]. Angiotensin II (Ang II) is an active octapeptide and a potent vasoconstrictor in the RAAS, which is produced in vivo from angiotensin I by the angiotensin-converting enzyme. In humans, Ang II interacts with two main receptor subtypes, namely, AT_1 and AT_2. The AT_1 receptor subtype mediates virtually all the known physiological actions of Ang II in cardiovascular, neuronal, endocrine, and hepatic cells, among others [3]. AT_1 receptor antagonists are clinically used as therapy for hypertension and heart failure [4], moreover, they show potentials for the prevention of target-organ damage and anti-tumor effects [5]. Seven of these drugs, including one recently listed drug azilsartan [6], have already been licensed for the treatment of high blood pressure (Fig. 1). All these drugs contain common structural features represented by a biphenyl fragment bearing an acidic moiety (i.e., tetrazole, carboxylic group) that is linked to heterocycles by means of a methylene group. Among the large variety of heterocyclic systems developed, the ortho-fused bicyclic moiety benzimidazole appears to be a particularly effective heterocyclic system considering its interaction with the AT_1 receptor [7]. Such effectiveness is exemplified by the commercially available candesartan [8], the most potent AT_1 antagonist to date. It's demonstrated that substitutions at the benzimidazole ring [8–12], such as a nitro group at the 5-position, an acylureas lipophilic group at the 6-position, and a carboxylic group at the 7-position, can promote selective AT_1 antagonism. Notably, 6-carbamoyl benzimidazole has been rarely used to evaluate the corresponding effect for AT_1 antagonism. Bansal's proposal [11] of the presence of L3 lipophilic pockets at the AT_1 receptor encouraged us to postulate that a carbamoyl group at the 6-position of benzimidazole with an alkyl-chain-bearing phenyl group may provide additional interactions (e.g., π–π interaction) that consequently enhance the overall interaction between the antagonist and the receptor. The literature shows [13] that the phenylethylamino fragment possesses a biological effect that lowers hypertensive pressure. Furthermore, Rapposell [14] reported that the simple reversion of the amido-function of the model compound induces a dramatic change of affinity toward the AT_1 receptor. Thus, new 6-aminocarbonyl benzimidazoles **A**, which are expected to have higher activity than losartan, were designed. For comparison, the

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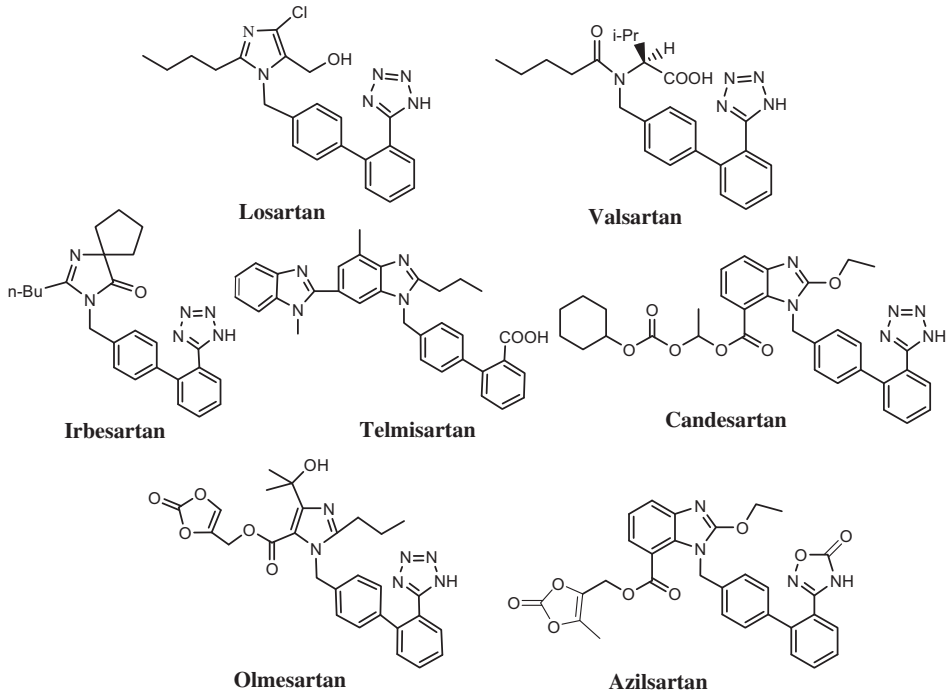


Fig. 1. Representive AT_1 receptor antagonists.

congeners 6-acylamino benzimidazoles **B** were also designed and synthesized to examine their effect as nonpeptidic selective AT_1 receptor antagonists (Fig. 2).

2. Results and discussion

2.1. Chemistry

The target compounds were prepared following the route in Schemes 1 and 2. The starting material 4-methyl-2-*n*-propyl-1*H*-benzimidazole-6-carboxylic acid (**1**) was prepared from 3-methyl-4-nitrobenzoic acid following the previously reported method [15]. This compound was transformed to acyl chloride and then coupled with various amines to give acylamide compounds **3a**–**3i** with yield ranging from 72% to 85%. The acylamides were then alkylated with methyl 4′-(bromomethyl)biphenyl-2-carboxylate (**4**) using potassium *tert*-butoxide in DMF to furnish the corresponding products in yields of 57% to 72%. Finally, compounds **5a**–**5i** were hydrolyzed using aqueous sodium hydroxide in boiling methanol with a yield of over 70%. In Scheme 2, compound **2** was coupled with ammonium carbonate to give 4-methyl-2-*n*-propyl-1*H*-benzimidazole-6-carboxamide (**7**). This compound was alkylated with compound **4** first, and then was converted to the corresponding carbamate (**9**) by a refined Hofmann rearrangement [16]. Compound **9** was refluxed with sodium hydroxide in dioxane to give 4′-[(6-amino-4-methyl-2-*n*-propyl-1*H*-benzimidazol-1-yl) methyl]biphenyl-2-carboxylic acid (**10**). This compound was coupled with different acyl chlorides to give the target compounds **11a**–**11g**. The target compound **12** was obtained by direct hydrolysis of compound **9** using aqueous sodium hydroxide in boiling methanol.

All target compounds were identified by IR, ^{1}H NMR, ^{13}C NMR and HRMS. As confirmatory evidence of the regiochemistry of the final products, a Nuclear Overhauser Effect (NOE) experiment was conducted on one of the alkylated products, namely, compound **5h** (Fig. 3). In DMSO-d_6, **5h** showed an NOE between the hydrogen of the methyl at C-4 (δ 2.59) and the proton at C-5 (δ 7.60), an NOE between the protons on the methylene adjacent to N-1 (δ 5.60) and the proton at C-7 (δ 7.95), as well as an NOE between the protons on the methylene adjacent to N-1 (δ 5.60) and the proton at the methylene adjacent to C-2. Furthermore, the structures of compounds **5a**, **5f**, and **6a** were confirmed by X-ray crystallography [17] (Figs. 4–6). Taken together, these structures indicate that N_1 alkylation and not N_3 alkylation occurred.

2.2. Biological evaluation

The prepared compounds were evaluated for their in vitro Ang II receptor binding affinity in the competitive inhibition of [^{125}I] Ang II binding to the AT_1 and AT_2 receptors by a conventional ligand-

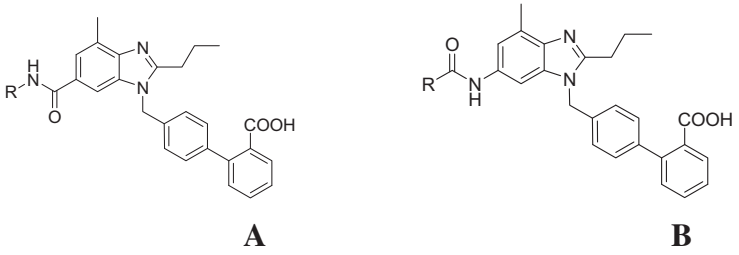
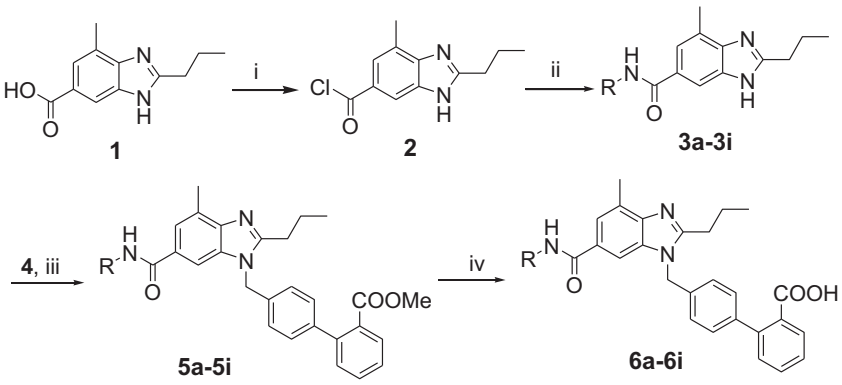


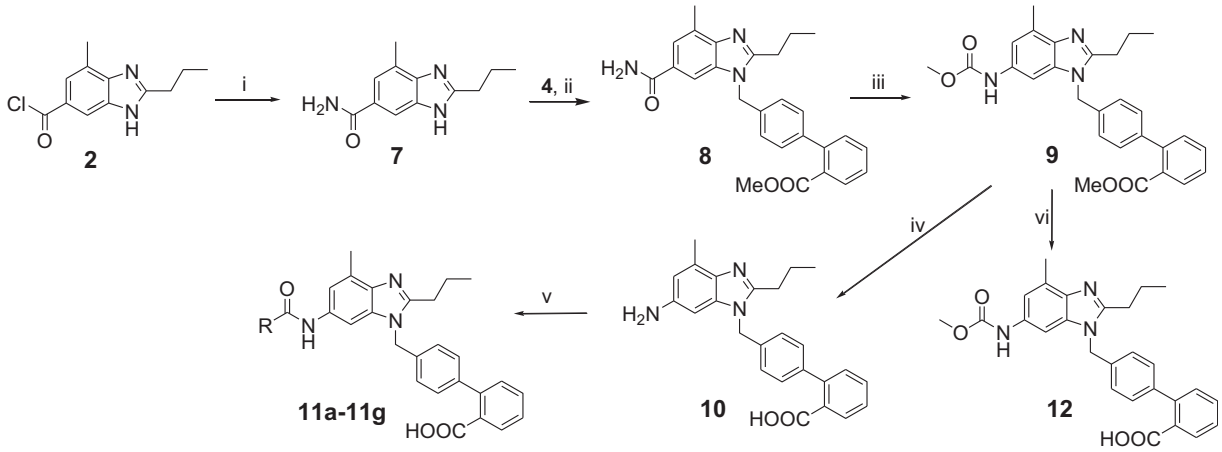
Fig. 2. The structure of the designed compounds.



a: R= n-propyl; b: R= n-butyl; c: R= 4-morpholinyl; d: R= 1-piperidinyl;
e: R= 4-methylphenyl; f: R= n-propyl; g: R= 4-morpholinyl;
h: R= phenyl; i: R= 4-morpholinyl.

Reagents and conditions: (i) $SOCl_2$, refluxed; (ii) RNH_2, DCM, Et_3N; (iii) KOtBu, DMF; (iv) NaOH, MeOH, reflux, then HCl, 0°C.

Scheme 1. Synthesis of compounds **6a**–**6i**.



a: R= methyl; b: R= ethyl; c: R= n-propyl; d: R= phenyl;
e: R= 4-methylphenyl;f: R= phenyl; g: R= phenyl.

Reagents and conditions: (i) $(NH_4)_2CO_3$, DCM, Et_3N; (ii) KOtBu, DMF; (iii) NaOCl, KF/Al_2O_3, MeOH, refluxed; (iv) NaOH, Dioxane, reflux; (v) RCOCl, DCM, Et_3N; (vi) NaOH, MeOH, refluxed, then HCl, 0°C.

Scheme 2. Synthesis of compounds **11a**–**11g** and **12**.

binding assay as described previously [18]. The results are expressed as IC_{50} values, which are the concentrations of a compound that inhibit [^{125}I] Ang II binding to the receptor by 50%. The antagonistic activity of the more potent compounds (**6f**, **6g**, **11e**, **11f**, **11g**, and **12**) was also investigated in vitro using the contractile response of isolated rabbit aortic strips in a functional assay.

Losartan was taken as a positive control drug in the assays. Finally, the most potent compounds **6f** and **11g** were evaluated in an in vivo model [19]. As a rational design for this work, pharmacophore hypothesis generation was performed using the HipHop module of the Discovery Studio software [20] using the training set consisting of six clinical sartans [21,22]. The fit values of the synthesized compounds were determined on the selected hypothesis of the AT_1 receptor antagonist using the best fit algorithm as described in the literature [23].

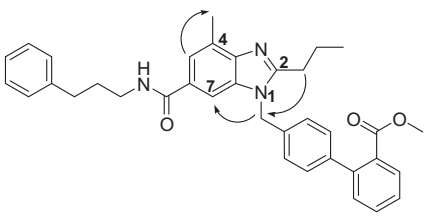


Fig. 3. NOESY of compound **5h**.

As summarized in Table 1, the binding assay and the antagonistic activity results showed that as expected, all compounds displayed a certain degree of inhibition activity. Several compounds showed high selectivity for the AT_1 receptor over the AT_2 receptor, given that the binding affinities were in the submicromolar range for the AT_1 receptor and in the micromolar range for the AT_2 receptor. Of all the synthesized compounds, compounds **6f** and **11g** were the most potent (**6f**: AT_1 IC_{50} = 3 nM, PA_2 = 8.51; **11g**: AT_1 IC_{50} = 0.1 nM, PA_2 = 8.43), exhibiting almost the same binding affinity as the marketed AT_1 receptor antagonist telmisartan (IC_{50} = 1.0 nM, 0.33 nM [24]) and approximately 10 times the

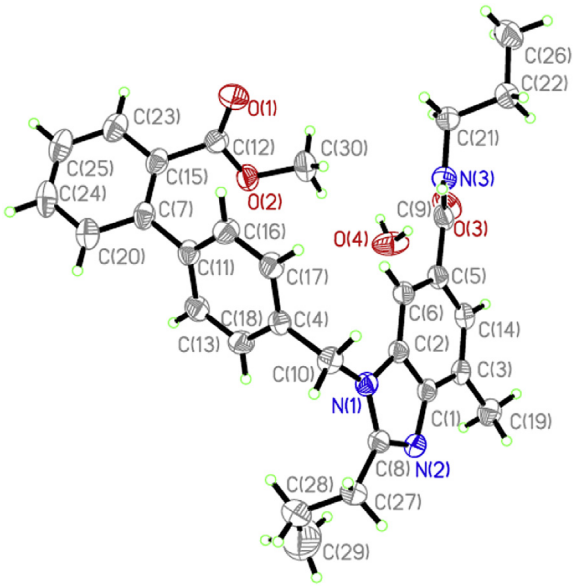


Fig. 4. Crystal structure of compound **5a**.

affinity of losartan (IC_{50} = 16.2 nM, 150 nM [25], 6.7 nM [26]). Compounds **6g**, **11e**, **11f**, and **12** were also much more active than losartan. The pA_2 of these compounds were 8.20, 8.25, 8.21, and 8.15, respectively, which are higher than that of losartan (pA_2 = 7.92). In addition, compounds **6b**, **6i**, **11b**, **11c**, **11d**, and **11e** showed the same activity level as losartan (10 nM < AT_1 IC_{50} < 100 nM). These results suggest that both 6-substituted aminocarbonyl benzimidazole and acylamino benzimidazoles are good angiotensin II AT_1 receptor antagonists.

Based on the results of in vitro Ang II-binding assay and functional antagonism, **6f** and **11g** were selected for further evaluation of in vivo models. When evaluated orally in conscious spontaneously hypertensive rats (SHR), both compounds at doses of 10 mg/kg significantly decreased blood pressure by more than 30 mmHg (Fig. 7), which is more efficacious than losartan.

In the molecular modeling simulation section, fit value indicates how well the features in the pharmacophore map the chemical features in the molecule [27]. The higher the fit value, the more active the compound. In this study, five features were included in the selected pharmacophore hypothesis; the highest fit value was 5. Accordingly, the estimated activity could be classified according to the fit value as highly active (fit value > 4, +++), moderately active (2 < fit value < 4, ++), and with low activity (fit value < 4, +). All synthesized compounds of this study were also classified according to the literature [28] by their activity as highly active (<100 nM, +++), moderately active (100 nm to 10,000 nM, ++) and low activity (>10,000 nM, +). All but two highly active compounds were predicted correctly, and only seven moderately active compounds were predicted to be highly active. Despite these disparities, the pharmacophore hypothesis could still be considered relatively reasonable. Furthermore, the molecular modeling simulation performed above reflected the interaction of ligands with the AT_1 receptor. Unexpectedly, the benzene ring in the phenylethyl, and not the propyl at the 2-position of the benzimidazole ring, mapped onto the hydrophobic aliphatic feature (Fig. 8). The same binding modality was also observed in the mapping of our previously published analogues [21,22] with the pharmacophore, in which the methyl in the second benzimidazole ring, and not the propyl, mapped onto the hydrophobic aliphatic feature. Notably, the different interaction modalities of telmisartan and losartan have been reported in the literature [29] and were obtained through the docking of ligands with the homology-modeled AT_1 receptor.

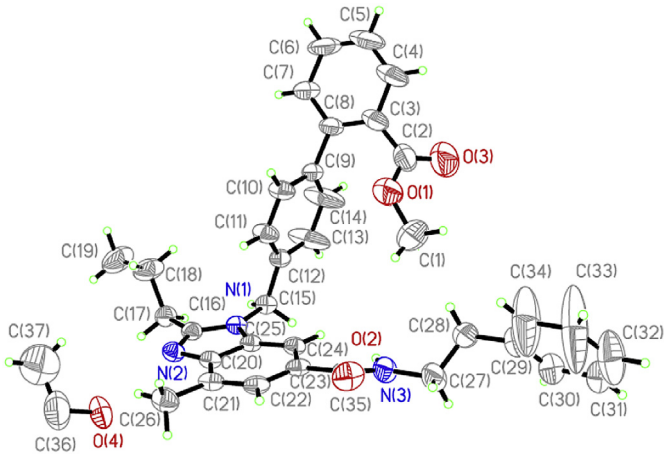


Fig. 5. Crystal structure of compound **5f**.

3. Conclusions

Two families of 6-substituted aminocarbonyl and acylamino benzimidazole derivatives were designed and synthesized as nonpeptidic Ang II AT_1 receptor antagonists. Compounds **6f** and **11g** were found to be the two most potent AT_1-selective Ang II receptor antagonists. These compounds would be valuable as lead compounds for further rational design of more potent Ang II AT_1 receptor antagonists.

4. Experimental section

4.1. Chemistry

The melting points were determined on an XT − 4A melting point apparatus and are uncorrected. All the target compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. Infrared (IR) spectra were recorded on a Bruker Alpha Spectrometer, Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded

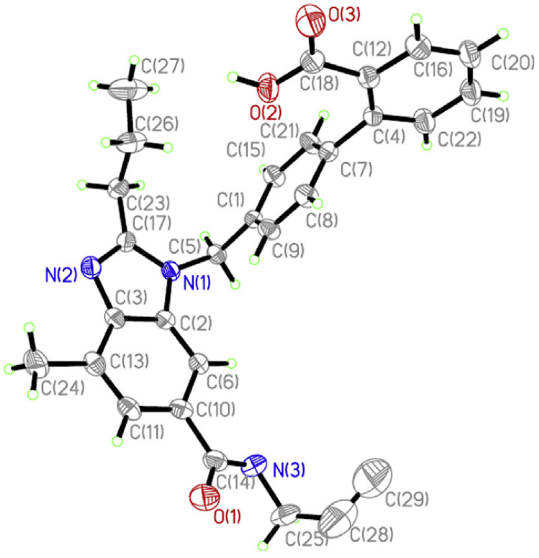
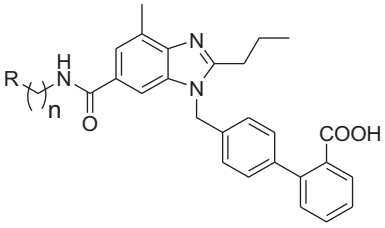
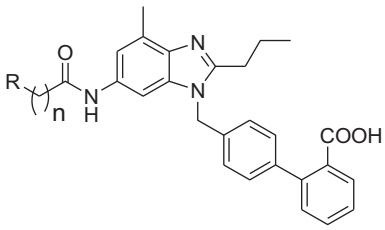


Fig. 6. Crystal structure of compound **6a**.

Table 1
Fit values on the selected pharmacophore and experimental data of the target compounds.



6a-6i



11a-11g,12

No.	*n*	R	Fit value	IC_{50} (nM)		Est. act. scale[a]	Act. (**AT_1R**) scale[b]	pA_2
				AT_1	AT_2			
6a	0	*n*-Propyl	4.78	1345	–	+++	++	
6b	0	*n*-Butyl	4.70	13	164	+++	+++	
6c	0	4-Morpholinyl	4.77	1008	–	+++	++	
6d	0	1-Piperidinyl	4.87	20	42	+++	+++	
6e	0	4-Methylphenyl	4.90	39	61	+++	+++	
6f	2	Phenyl	4.84	3	>10,000	+++	+++	8.51
6g	2	4-Morpholinyl	3.14	11	>10,000	++	+++	8.20
6h	3	Phenyl	4.93	115	–	+++	++	
6i	3	4-Morpholinyl	3.24	10	718	++	+++	
11a	0	Methyl	4.84	1430	–	+++	++	
11b	0	Ethyl	4.88	0.4	78	+++	+++	
11c	0	*n*-Propyl	4.48	0.3	53	+++	+++	
11d	0	Phenyl	4.40	3.9	6	+++	+++	
11e	0	4-Methylphenyl	4.44	4.9	>10,000	+++	+++	8.25
11f	1	Phenyl	4.36	1.2	77	+++	+++	8.21
11g	2	Phenyl	4.79	0.1	149	+++	+++	8.43
12	0	Methoxy	4.49	0.7	4366	+++	+++	8.15
		Losartan	4.76	16.2	>10,000	+++	+++	7.92
		Telmisartan	4.91	1.0		+++	+++	

[a] Estimated activity scale: highly active (fit value > 4, +++), moderately active (2 < fit value < 4, ++), and with low activity (fit value < 4, +).
[b] Activity scale: highly active (<100 nM, +++), moderately active (100 nM to 10,000 nM, ++), and with low activity (>10,000 nM, +) [22].

on a Bruker NMR spectrometer using TMS as internal standard (chemical shift in ppm). High-resolution mass spectra were recorded on a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Silica gel column chromatography was performed with silica gel (200–300 mesh) and F_{254} pre-coated silica gel TLC plate.

*4.1.1. 4-Methyl-2-n-propyl-1H-benzimidazole-6-carboxylic chloride **(2)***

A mixture of 4-methyl-2-*n*-propyl-1*H*-benzimidazole-6-carboxylic (**1**, 2.18 g, 10 mmol) and thionyl chloride (20 mL, 280 mmol) was refluxed for 3 h, then the excess thionyl chloride was removed under reduced pressure to obtain the crude acyl chloride (**2**) as an off-white solid. It was used for the next step directly.

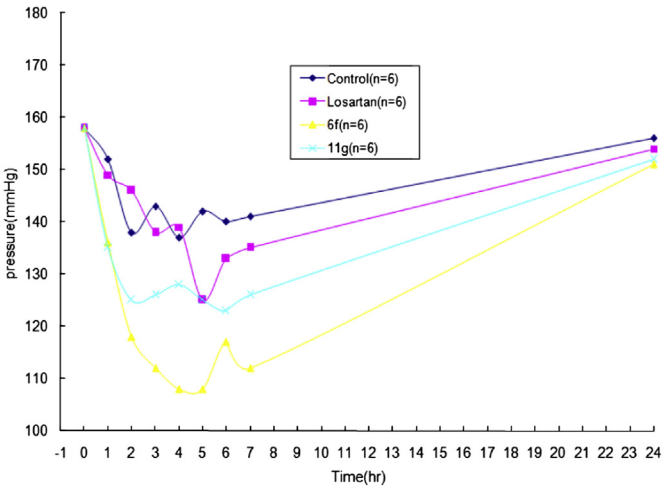


Fig. 7. Effects of **6f**, **11g** and losartan (10 mg/kg po) on mean arterial pressure in conscious SHR after oral administration.

*4.1.2. General synthetic procedure for **3a–3i***

To a stirred suspension of acyl chloride (**2**) in 60 mL of dichloromethane at 0 °C was added dropwise triethylamine (1.52 g, 15 mmol), followed by a solution of one of the selected amines (10 mmol) in 10 mL of dichloromethane. The resulting mixture was stirred at room temperature for 8 h. The reaction mixture was filtered, and the filtrate was washed with 1*N* hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous sodium sulphate, filtered, and concentrated under vacuum. The residue was purified by recrystallization in ethanol to provide pure **3a–3i** as white solids in yield of 72–85%.

*4.1.2.1. N-n-Propyl-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3a**).* White solid, yield 83%. m.p.:124–125 °C. IR (ATR, cm^{-1}): 3290 (NH), 1605 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, $J = 7.3$ Hz, 3H, 3″-Me), 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.59 (m, 2H, 2′-CH_2), 1.76 (m, 2H, 2″-CH_2), 2.55 (s, 3H, 4-Me), 2.78 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.21 (m, 2H, 1″-CH_2), 7.47 (s, 1H, 5-H), 7.81 (s, 1H, 7-H); ESIMS (*m*/*z*): 260.3 $[M + H]^+$.

*4.1.2.2. N-n-Butyl-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3b**).* White solid, yield 80%. m.p.:119–121 °C. IR (ATR, cm^{-1}): 3123 (NH), 1624 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, $J = 7.3$ Hz, 3H, 4″-Me), 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.32 (m, 2H, 3″-CH_2), 1.59 (m, 2H, 2″-CH_2), 1.79 (m, 2H, 2′-CH_2), 2.55 (s, 3H,

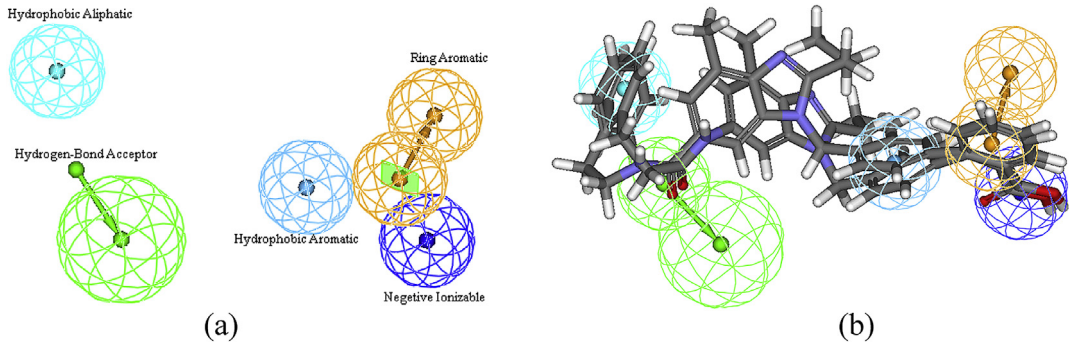


Fig. 8. (a) The selected pharmacophore hypothesis; (b) mapping of **6f** and **11g** with the selected hypothesis.

4-Me), 2.81 (t, J = 7.3 Hz, 2H, 1′-CH_2), 3.53 (m, 2H, 1″-CH_2), 7.49 (s, 1H, 5-H), 7.85 (s, 1H, 7-H); ESIMS (m/z): 274.3 $[M + H]^+$.

*4.1.2.3. N-(4-Morpholinyl)-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3c**).* White solid, yield 78%. m.p.:179–181 °C. IR (ATR, cm^{-1}): 3107 (NH), 1629 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, J = 7.2 Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.37 (s, 3H, 4-Me), 2.56 (t, J = 7.2 Hz,2H, 1′-CH_2), 3.46 (t, J = 7.2 Hz, 4H, 1″-CH_2), 3.72 (t, J = 7.2 Hz, 4H, 2″-CH_2), 7.52 (s, 1H, 5-H), 7.86 (s, 1H, 7-H); ESIMS (m/z): 288.3 $[M + H]^+$.

*4.1.2.4. N-(1-Piperidinyl)-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3d**).* White solid, yield 72%. m.p.:174–176 °C. IR (ATR, cm^{-1}): 3119 (NH), 1590 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, J = 7.2 Hz, 3H, 3′-Me), 1.54 (m, 2H, 3″-CH_2), 1.62 (m, 4H, 2″-CH_2),1.74 (m, 2H, 2′-CH_2), 2.31 (s, 3H, 4-Me), 2.57 (t, J = 7.2 Hz, 2H, 1′-CH_2), 3.46 (m, 4H, 1″-CH_2), 7.49 (s, 1H, 5-H), 7.94 (s, 1H, 7-H); ESIMS (m/z): 286.3 $[M + H]^+$.

*4.1.2.5. N-(4-Methylphenyl)-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3e**).* White solid, yield 73%. m.p.:215–217 °C. IR (ATR, cm^{-1}): 3212 (NH), 1642(C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, J = 7.2 Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.31 (s, 3H, 4″-Me), 2.36 (s, 3H, 4-Me), 2.57 (t, J = 7.2 Hz, 2H, 1′-CH_2), 7.15–8.18 (m, 6H, Ar-H); ESIMS (m/z): 308.3 $[M + H]^+$.

*4.1.2.6. N-(2-Phenylethyl)-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3f**).* White solid, yield 85%. m.p.:152–154 °C. IR (ATR, cm^{-1}): 3193 (NH), 1631 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, J = 7.3 Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.55 (s, 3H, 4-Me), 2.78 (t, J = 7.2 Hz, 2H, 1′-CH_2), 2.95 (t, J = 7.2 Hz, 2H, 2″-CH_2), 3.82 (t, J = 7.2 Hz, 2H, 1″-CH_2), 7.06–7.18(m, 5H, Ar-H), 7.47 (s, 1H, 5-H), 7.84 (s, 1H, 7-H); ESIMS (m/z): 322.2 $[M + H]^+$.

*4.1.2.7. N-[2-(4-Morpholinyl)ethyl]-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3g**).* Light yellow solid, yield 76%. m.p.:149–151 °C. IR (ATR, cm^{-1}): 3188 (NH), 1635 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, J = 7.3 Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.37 (t, J = 7.2 Hz, 4H, 3″-CH_2), 2.52 (s, 3H, 4-Me), 2.78 (t, J = 7.2 Hz, 2H, 1′-CH_2), 2.83 (t, J = 7.2 Hz, 2H, 2″-CH_2), 3.62 (m, 2H,1″-CH_2), 3.82 (t, J = 7.2 Hz, 4H,4″-CH_2), 7.47 (s, 1H, 5-H), 7.84 (s, 1H, 7-H); ESIMS (m/z): 331.3 $[M + H]^+$.

*4.1.2.8. N-(3-Phenylpropyl)-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3h**).* White solid, yield 79%. m.p.:189–191 °C. IR (ATR, cm^{-1}): 3181 (NH), 1633 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95(t, J = 7.2 Hz, 3H, 3′-Me), 1.77(m, 2H, 2′-CH_2), 2.08(m, 2H, 2″-CH_2), 2.49(s, 3H, 4-Me), 2.58(t, J = 6.0 Hz, 2H, 3″-CH_2), 2.76(t, J = 7.2 Hz, 2H, 1′-CH_2), 3.45(t, J = 6.0 Hz, 2H, 1″-CH_2), 7.07–7.88(m, 7H, Ar-H), 8.41(s, 1H, CONH); ESIMS (m/z): 336.4 $[M + H]^+$.

*4.1.2.9. N-[3-(4-Morpholinyl)propyl]-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**3i**).* Light yellow solid, yield 82%. m.p.:99–101 °C. IR (ATR, cm^{-1}): 3177 (NH), 1633 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, J = 7.3 Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.12 (m, 2H, 2″-CH_2), 2.37 (t, J = 7.2 Hz, 4H, 3″-CH_2), 2.52 (s, 3H, 4-Me), 2.78 (t, J = 7.2 Hz, 2H, 4″-CH_2), 2.83 (t, J = 7.2 Hz, 2H, 1′-CH_2), 3.62 (m, 2H, 1″-CH_2), 3.82 (t, J = 7.2 Hz, 4H, 5″-CH_2), 7.47 (s, 1H, 5-H), 7.84 (s, 1H, 7-H); ESIMS (m/z): 345.4 $[M + H]^+$.

*4.1.3. General synthetic procedure for **5a–5i***

To a stirred solution of compound **3** (2 mmol) in 15 mL of dimethylformamide at 0 °C, potassium *tret*-butoxide (2.2 mmol) was added. The mixture was stirred for 30 min at 0 °C, and then methyl 4′-bromomethylbiphenyl-2-carboxylate (**4**, 2.1 mmol) was added. After stirring at room temperature for 12 h, the mixture was poured into ice water (80 mL) and extracted with ethyl acetate (40 mL × 3). The combined ethyl acetate layers were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to provide an off-white solid. The solid was purified by column chromatography [elution: petroleum ether/ethyl acetate (1:1, v/v)] to provide the pure product as white solids in yield of 57–72%.

*4.1.3.1. Methyl 4′-[(6-n-propylaminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl) methyl]biphenyl-2-carboxy-late (**5a**).* White solid, yield 57%. m.p.: 175–177 °C. IR (ATR, cm^{-1}): 1720 (C=O), 1627 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, J = 7.23 Hz, 3H, 3″-Me), 0.96 (t, J = 7.23 Hz, 3H, 3′-Me), 1.58 (m, 2H, 2″-CH_2), 1.75 (m, 2H, 2′-CH_2), 2.55 (s, 3H, 4-Me), 2.77 (t, J = 7.16 Hz, 2H, 1′-CH_2), 3.20 (t, J = 7.24 Hz, 2H, 1″-CH_2), 3.63 (s, 3H, COOMe), 5.56 (s, 2H, N-CH_2-Ar), 7.07–7.89 (m, 10H, Ar-H), 8.45 (s, 1H, CONH); ESIMS (m/z): 484.0 $[M + H]^+$.

*4.1.3.2. Methyl 4′-[(6-n-butylaminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylate (**5b**).* White solid, yield 64%. m.p.: 196–198 °C. IR (ATR, cm^{-1}): 1721 (C=O), 1629 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, J = 7.24 Hz, 3H, 4″-Me), 0.95 (t, J = 7.25 Hz, 3H, 3′-Me), 1.32 (m, 2H, 3″-CH_2), 1.59 (m, 2H, 2″-CH_2), 1.75 (m, 2H, 2′-CH_2), 2.56 (s, 3H, 4-Me), 2.81 (t, J = 7.16 Hz, 2H, 1′-CH_2), 3.53 (m, 2H, 1″-CH_2), 3.60 (s, 3H, COOMe), 5.56 (s, 2H, N-CH_2-Ar), 7.11–7.92 (m, 10H, Ar-H), 8.45 (s, 1H, CONH); ESIMS (m/z): 498.1 $[M + H]^+$.

*4.1.3.3. Methyl 4′-[[6-(4-morpholinyl)carbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carbo-xylate (**5c**).* White solid, yield 61%. m.p.: 124–126 °C. IR (ATR, cm^{-1}): 1725 (C=O), 1627 (C=O);^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, J = 7.2 Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.58 (s, 3H, 4-Me), 2.81 (t, J = 7.6 Hz, 2H, 1′-CH_2), 3.52 (m, 4H, 1″-CH_2), 3.61 (s, 3H, COOMe),

3.74 (m, 4H, 2″-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 10H, Ar-H); ESIMS (*m*/*z*): 512.5 $[M + H]^+$.

*4.1.3.4. Methyl 4′-[[6-(1-piperidinyl)carbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxy-late (**5d**).* White solid, yield 68%. m.p.: 159–161 °C. IR (ATR, cm^{-1}): 1718 (C=O), 1618 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.96 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.53 (m, 2H, 3″-CH_2), 1.62 (m, 4H, 2″-CH_2),1.76 (m, 2H, 2′-CH_2), 2.55 (s, 3H, 4-Me), 2.75 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.48 (m, 4H, 1″-CH_2), 3.63 (s, 3H, COOMe), 5.55 (s, 2H, N-CH_2-Ar), 7.09–7.86(m, 10H, Ar-H); ESIMS (*m*/*z*): 510.4 $[M + H]^+$.

*4.1.3.5. Methyl 4′-[[6-(4-methylphenyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate (**5e**).* White solid, yield 65%. m.p.: 177–179 °C. IR (ATR, cm^{-1}): 1723 (C==O), 1641 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.75 (m, 2H, 2′-CH_2), 2.38 (s, 3H, 4″-Me), 2.56 (s, 3H, 4-Me), 2.71 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.76 (s, 3H, COOMe), 5.59 (s, 2H, N-CH_2-Ar), 7.12–7.88 (m, 14H, Ar-H), 8.42 (d, $J = 8.0$ Hz, 1H, CONH); ESIMS (*m*/*z*): 532.4 $[M + H]^+$.

*4.1.3.6. Methyl 4′-[[6-(2-phenylethyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl] methyl]biphenyl-2-carboxylate (**5f**).* White solid, yield 72%. m.p.: 191–193 °C. IR (ATR, cm^{-1}): 1731 (C=O), 1629 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.57 (s, 3H, 4-Me), 2.71 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 2.92 (t, $J = 7.2$ Hz, 2H, 2″-CH_2), 3.81 (t, $J = 7.2$ Hz, 2H, 1″-CH_2), 3.78 (s, 3H, COOMe), 5.58 (s, 2H, N-CH_2-Ar), 7.14–7.85 (m, 14H, Ar-H), 8.45 (d, $J = 8.0$ Hz, 1H, CONH); ESIMS (*m*/*z*): 546.6 $[M + H]^+$.

*4.1.3.7. Methyl 4′-[[6-[2-(4-morpholinyl)ethyl]aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]bi-phenyl-2-carboxylate (**5g**).* White solid, yield 63%. m.p.: 67–68 °C. IR (ATR, cm^{-1}): 1720 (C=O), 1635 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.18$ Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.39 (m, 4H, 3″-CH_2), 2.55 (s, 3H, 4-Me), 2.79 (t, $J = 7.22$ Hz, 2H, 1′-CH_2), 2.88 (m, 2H, 2″-CH_2), 3.49 (m, 4H, 1″-CH_2), 3.62 (s, 3H, COOMe), 3.72 (m, 4H, 4″-CH_2), 5.55 (s, 2H, N-CH_2-Ar), 7.09–7.93 (m, 10H, Ar-H); ESIMS (*m*/*z*): 555.5 $[M + H]^+$.

*4.1.3.8. Methyl 4′-[[6-(3-phenylpropyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl] methyl]biphenyl-2-carboxylate (**5h**).* White solid, yield 66%. m.p.: 137–139 °C. IR (ATR, cm^{-1}): 1730 (C=O), 1624 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94(t, $J = 7.2$ Hz, 3H, 3′-Me), 1.75(m, 2H, 2′-CH_2), 2.12(m, 2H, 2″-CH_2), 2.55(s, 3H, 4-Me), 2.62(t, $J = 6.0$ Hz, 2H, 3″-CH_2), 2.81(t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.48(t, $J = 6.0$ Hz, 2H, 1″-CH_2), 3.65(s, 3H, COOMe), 5.57(s, 2H, N-CH_2-Ar), 7.09–7.89(m, 15H, Ar-H), 8.42(s, 1H, CONH); ESIMS (*m*/*z*): 560.6 $[M + H]^+$.

*4.1.3.9. Methyl 4′-[[6-[3-(4-morpholinyl)propyl]aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl] methyl]biphenyl-2-carboxylate (**5i**).* White solid, yield 69%. m.p.: 58–60 °C. IR (ATR, cm^{-1}): 1720 (C=O), 1635 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.3$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 1.82 (m, 2H, 2″-CH_2), 2.39 (t, $J = 7.2$ Hz, 4H, 4″-CH_2), 2.48 (m, 2H, 3″-CH_2), 2.52 (s, 3H, 4-Me), 2.78 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.42 (m, 2H, 1″-CH_2), 3.67 (s, 3H, COOMe), 3.81 (m, 4H, 5″-CH_2), 5.59 (s, 1H, N-CH_2-Ar),7.09–7.96 (m, 10H, ArH), 8.52 (s, 1H, CONH); ESIMS (*m*/*z*): 569.5 $[M + H]^+$.

*4.1.4. General synthetic procedure for compounds **6a**–**6i***

A mixture of compound **5** (0.4 mmol), methanol (10 mL) and 2*N* aqueous sodium hydroxide (5 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under vacuum to remove methanol. The residue was adjusted to pH 6.5 with 3*N* aqueous hydrochloric acid. The resulting precipitate was filtered, dried, and then recrystallized in methanol–chloroform (1:1) to provide pure **6a**–**6i** as white solids in yield of 71–83%.

*4.1.4.1. 4′-[(6-n-Propylaminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**6a**).* White solid, yield 75%. m.p.: 285–286 °C. IR (ATR, cm^{-1}): 3340 (OH), 1710 (C=O), 1644 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, $J = 7.2$ Hz, 3H, 3″-Me), 0.96 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.59 (m, 2H, 2″-CH_2), 1.74 (m, 2H, 2′-CH_2), 2.56 (s, 3H, 4-Me), 2.78 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.21 (t, $J = 7.2$ Hz, 2H, 1″-CH_2), 5.55 (s, 2H, N-CH_2-Ar), 7.07–7.89 (m, 10H, Ar-H), 8.45 (s, 1H, CONH), 12.72 (br, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.88, 14.20, 16.86, 20.89, 22.86, 29.06, 41.41, 46.15, 99.86, 107.59, 121.33, 126.33, 127.67, 128.66, 129.08, 129.44, 130.80, 131.22, 132.52, 134.99, 136.29, 140.37, 140.75, 143.99, 156.84, 166.85, 169.85; HRMS (ESI) Calcd for $C_{29}H_{32}N_3O_3$ $[M + H]^+$: 470.2444, Found 470.2435.

*4.1.4.2. 4′-[(6-n-Butylaminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**6b**).* White solid, yield 79%. m.p.: 253–254 °C. IR (ATR, cm^{-1}): 3360 (OH), 1705 (C=O), 1638 (C=O);^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, $J = 7.2$ Hz, 3H, 4″-Me), 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.34 (m, 2H, 3″-CH_2), 1.59 (m, 2H, 2″-CH_2), 1.78 (m, 2H, 2′-CH_2), 2.58 (s, 3H, 4-Me), 2.82 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.56 (m, 2H, 1″-CH_2), 5.55 (s, 2H, N-CH_2-Ar), 7.09–7.92 (m, 10H, Ar-H), 8.44 (s, 1H, CONH), 12.71 (br, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.70, 13.78, 16.44, 19.64, 20.47, 28.64, 31.32, 40.06, 45.73, 107.17, 120.90, 125.91, 127.24, 128.66, 129.02, 130.38, 130.79, 134.57, 135.87, 139.96, 140.33, 143.56, 156.42, 166.39, 169.43; HRMS (ESI) Calcd for $C_{30}H_{34}N_3O_3$ $[M + H]^+$: 484.2600, Found 484.2594.

*4.1.4.3. 6-(4-Morpholinyl)carbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**6c**).* White solid, yield 83%. m.p.: 159–161 °C. IR (ATR, cm^{-1}): 3375 (OH), 1708 (C=O), 1597 (C=O); ^1H NMR (400MHz, DMSO-d_6) δ: 0.96 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.53 (s, 3H, 4-Me), 2.71 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 3.52 (m, 4H, 1″-CH_2), 3.77 (m, 4H, 2″-CH_2), 5.55 (s, 2H, N-CH_2-Ar), 7.07–7.89 (m, 10H, Ar-H), 12.72 (br, 1H, COOH);; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.87, 16.42, 20.75, 28.67, 46.01, 54.97, 66.13, 107.39, 109.32, 121.22, 126.29, 127.37, 128.04, 128.73, 129.16, 130.46, 130.92, 131.57, 132.21, 134.17, 135.96, 140.08, 140.44, 156.12, 169.54, 169.90; HRMS (ESI) Calcd for $C_{30}H_{32}N_3O_4$ $[M + H]^+$: 498.2393, Found 498.2387.

*4.1.4.4. 4′-[[6-(1-Piperidinyl)carbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**6d**).* White solid, yield 82%. m.p.: 199–201 °C. IR (ATR, cm^{-1}): 3370 (OH), 1709 (C=O), 1594 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.54(m, 2H, 3″-CH_2), 1.63(m, 4H, 2″-CH_2), 1.76 (m, 2H, 2′-CH_2), 2.63 (s, 3H, 4-Me), 2.89 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.48(m, 4H, 1″-CH_2), 5.75 (s, 2H, 2H, N-CH_2-Ar), 7.20–8.62 (m, 10H, Ar-H), 12.70 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.78, 16.32, 20.63, 24.04, 25.49, 28.61, 45.83, 106.68, 120.64, 126.14, 127.25, 128.59, 129.62, 130.34, 130.77, 132.15, 134.16, 135.93, 139.93, 140.32, 142.17, 155.78, 169.43, 169.59; HRMS (ESI) Calcd for $C_{31}H_{34}N_3O_3$ $[M + H]^+$: 496.2600, Found 496.2589.

*4.1.4.5. 4′-[[6-(4-Methylphenyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carbo-xylic acid (**6e**).* White solid, yield 75%. m.p.: 292–294 °C. IR (ATR, cm^{-1}): 3360 (OH), 1718 (C=O), 1654 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.45 (s, 3H, 4″-

Me), 2.63 (s, 3H, 4-Me),3.09 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.75 (s, 2H, N-CH_2-Ar), 7.06 ~ 8.62 (m, 15H, Ar-H), 12.70 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.78, 16.46, 20.43, 20.46, 28.68, 45.78, 107.72, 120.36, 121.33, 125.96, 127.26, 127.49, 128.68, 128.87, 130.40, 130.80, 132.10, 132.26, 134.64, 135.85, 136.76, 139.99, 140.35, 143.95, 156.82, 165.62, 169.42; HRMS (ESI) Calcd for $C_{33}H_{32}N_3O_3$ $[M + H]^+$: 518.2444, Found 518.2428.

*4.1.4.6. 4′-[[6-(2-Phenylethyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxy-lic acid (**6f**).* White solid, yield 79%. m.p.: 284–286 °C. IR (ATR, cm^{-1}): 3288 (OH), 1739 (C═O), 1631 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.3$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.56 (s, 3H, 4-Me), 2.78 ~ 2.84 (m, 4H, 1′-CH_2, 2″-CH_2), 3.47 (t, $J = 6.5$ Hz, 2H, 1″-CH_2), 5.56 (s, 2H, N-CH_2-Ar), 7.09–7.88 (m, 15H, Ar-H), 8.48 (d, $J = 5.6$ Hz, 1H, CONH), 12.70 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.93, 16.58, 20.64, 28.80, 35.34, 41.06, 45.90, 107.36, 109.36, 121.10, 126.11, 127.41, 128.39, 128.73, 128.80, 129.18, 130.52, 130.93, 132.44, 134.67, 135.87, 13970, 140.10, 140.45, 156.64, 166.64, 169.53; HRMS (ESI) Calcd for $C_{34}H_{33}N_3O_3$ $[M + H]^+$: 532.2600, Found 532.2589.

*4.1.4.7. 4′-[[6-[2-(4-Morpholinyl)ethyl]aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**6g**).* White solid, yield 71%. m.p.: 165–167 °C. IR (ATR, cm^{-1}): 3370 (OH), 1691 (C═O), 1598 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.42 (m, 4H, 3″-CH_2), 2.67 (s, 3H, 4-Me), 2.76 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 2.93 (m, 2H, 2″-CH_2), 3.45 (m, 4H, 1″-CH_2), 3.77 (m, 4H, 4″-CH_2), 5.82 (s, 2H, N-CH_2-Ar), 7.29–8.22 (m, 10H, Ar-H), 8.78 (s, 1H, CONH), 12.65 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.51, 17.16, 21.19, 29.37, 37.25, 37.25, 46.52, 53.98, 58.17, 66.83, 107.91, 121.69, 126.19, 127.10, 127.23, 128.00, 128.07, 129.38, 135.23, 135.39, 137.60, 142.10, 144.35, 157.18, 167.21, 173.51; HRMS (ESI) Calcd for $C_{32}H_{37}N_4O_4$ $[M+H]^+$: 541.2815, Found 541.2801.

*4.1.4.8. 4′-[[6-(3-Phenylpropyl)aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxy-lic acid (**6h**).* White solid, yield 76%. m.p.: 239–241 °C. IR (ATR, cm^{-1}): 3380 (OH), 1693 (C═O), 1598 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 1.96 (m, 2H, 2″-CH_2), 2.58 (s, 3H, 4-Me), 2.68 (t, $J = 7.6$ Hz, 2H, 3″-CH_2), 2.82 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.51 (m, 2H, 1″-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 15H, Ar-H), 8.45 (s, 1H, CONH), 12.66(s, 1H, COOH); ^{13}C NMR (100MHz, DMSO-d_6) δ: 14.31, 16.99, 19.04, 21.03, 29.19, 31.46, 33.17, 46.29, 107.77, 121.51, 126.18, 126.47, 127.79, 127.83, 128.74, 128.78, 129.21, 129.58, 130.92, 131.32, 132.70, 135.18, 136.39, 140.53, 140.87, 142.26, 144.14, 157.01, 167.09, 170.01; HRMS (ESI) Calcd for $C_{35}H_{36}N_3O_3$ $[M + H]^+$: 546.2757, Found 546.2745.

*4.1.4.9. 4′-[[6-[3-(4-Morpholinyl)propyl]aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**6i**).* White solid, yield 72%. m.p.: 205–206 °C. IR (ATR, cm^{-1}): 3370 (OH), 1690 (C═O), 1628 (C═O);^{1}H NMR (400MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 1.85 (m, 2H, 2″-CH_2), 2.38 (m, 4H, 4″-CH_2), 2.46 (m, 2H, 3″-CH_2), 2.57 (s, 3H, 4-Me), 2.62 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.27 (m, 2H, 1″-CH_2), 3.77 (m, 4H, 5″-CH_2),5.57 (s, 2H, N-CH_2-Ar), 7.12–8.22 (m, 10H, Ar-H), 8.31 (s, 1H, CONH), 12.72(s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.93, 16.59, 20.62, 26.09, 28.77, 30.82, 37.92, 45.91, 53.39, 56.21, 66.24, 107.37, 1210.7, 125.66, 126.59, 127.01, 127.38, 127.62, 128.26, 128.79, 129.28, 134.67, 134.94, 137.29, 141.38, 143.74, 156.56, 162.39, 166.58, 172.86; HRMS (ESI) Calcd for $C_{33}H_{39}N_4O_4$ $[M + H]^+$: 555.2971, Found 555.2966.

*4.1.5. 4-Methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (**7**)*

To a stirred suspension of acyl chloride (**2**) in 60 mL of dichloromethane at 0 °C was added dropwise triethylamine (1.52 g, 15 mmol), followed by ammonium carbonate (0.96 g, 10 mmol). The resulting mixture was stirred at room temperature for 8 h and then was filtered, the filtrate was washed with 1*N* hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The residue was purified by recrystallization in ethanol to provide pure product as a white solid, yield 86%. m.p.: 284–286 °C. IR (ATR, cm^{-1}): 3161 (NH), 1657 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.35 (s, 3H, 4-Me), 2.55 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 7.49 (s, 1H, 5-H), 7.88 (s, 1H, 7-H); ESIMS (*m*/*z*): 218.2 $[M + H]^+$.

*4.1.6. Methyl 4′-[(6-aminocarbonyl-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylate (**8**)*

To a stirred solution of compound **7** (2 mmol) in 15 mL of dimethylformamide at 0 °C, potassium *tert*-butoxide (2.2 mmol) was added. The mixture was stirred for 30 min at 0 °C, and then 4′-bromomethylbiphenyl-2-carboxylate (**4**, 2.1 mmol) was added. After stirring at room temperature for 12 h, the mixture was poured into water (80 mL) and extracted with ethyl acetate (40 mL × 3). The combined ethyl acetate layers were washed with brine (50 mL × 3), dried over anhydrous magnesium sulphate, and concentrated under a reduced pressure to provide an off-white solid. The solid was purified by column chromatography (elution: 1:1 petroleum ether/ethyl acetate) to provide a white crystalline solid, yield 74%. m.p.: 162–164 °C. IR (ATR, cm^{-1}): 1732 (C═O), 1620 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, $J = 7.18$ Hz, 3H, 3′-Me), 1.74 (m, 2H, 2′-CH_2), 2.55 (s, 3H, 4-Me), 2.79 (t, $J = 7.22$ Hz, 2H, 1′-CH_2), 3.65 (s, 3H, COOMe), 5.55 (s, 2H, N-CH_2-Ar), 7.09–7.93 (m, 10H, Ar-H); ESIMS (*m*/*z*): 442.3 $[M + H]^+$.

*4.1.7. Methyl 4′-[(6-methoxycarbonylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylate (**9**)*

To a stirred mixture of compound **8** (1.32 g, 3 mmol) and KF/Al_2O_3 (6 g) was added 10% sodium hypochlorite solution, the reaction mixture was refluxed for 30 min and then cooled, filtered, the filtrate was concentrated and the residue was purified by column chromatography, 0.82 g white solid was obtained. Yield 79%. m.p.: 154–156 °C. IR (ATR, cm^{-1}): 1730 (C═O), 1632 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.01 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.82 (m, 2H, 2′-CH_2), 2.65 (s, 3H, 4-Me), 2.87 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.64 (s, 3H, NHCOOMe), 3.76 (s, 3H,COOMe),5.36 (s, 2H, N-CH_2-Ar), 6.79–7.85 (m, 10H, Ar-H), 8.42 (s, 1H, CONH); ESIMS (*m*/*z*): 472.2 $[M + H]^+$.

*4.1.8. 4′-[(6-Amino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl) methyl]biphenyl-2-carboxylic acid (**10**)*

The mixture of compound **9** (0.7 g, 2.1 mmol), sodium hydroxide (0.4 g, 10 mmol) and dioxane (20 mL) was heated at 100 °C for 3 h, then was concentrated, ethanol was added and the solution was acidified with conc. hydrochloride acid to pH = 6, the mixture was filtered and the filtrate was concentrated to obtain 0.44 g light brown solid, yield 53%. m.p.: 195–197 °C. IR (ATR, cm^{-1}): 3300 (OH), 1710 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.58 (s, 3H, 4-Me), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 10H, Ar-H); HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_2$ $[M + H]^+$: 400.2025, Found 400.2033.

*4.1.9. General procedure for compounds **11a–11g***

To a stirred mixture of compound **10** (0.40 g, 1 mmol) in 20 mL of dichloromethane at 0 °C was added triethylamine (1.5 mmol), and then added dropwise different acyl chloride (1 mmol) in 5 mL of dichloromethane. The resulting mixture was stirred at room

temperature for 5 h, then 10 mL of water was added. The organic phase was separated, washed with diluted hydrochloride acid and water, dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized in ethanol to provide pure **11a**–**11g** as light yellow or white solids in yield of 68–80%.

*4.1.9.1. 4′-[(6-Acetylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**11a**).* Light yellow solid, yield 68%, m.p.: 215–217 °C. IR (ATR, cm^{-1}): 3420 (OH), 1716 (C=O), 1682 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.12 (s, 3H, 1″-Me), 2.58 (s, 3H, 4-Me), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.42, 16.99, 21.16, 24.44, 29.48, 46.19, 98.69, 115.06, 126.33, 127.59, 128.17, 129.13, 129.21, 129.33, 130.72, 132.00, 134.59, 135.14, 136.22, 138.31, 140.32, 140.74, 154.43, 168.43, 171.42; HRMS (ESI) Calcd for $C_{27}H_{28}N_3O_3$ $[M + H]^+$: 442.2131, Found 442.2128.

*4.1.9.2. 4′-[(6-n-Propionylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**11b**).* White solid, yield 78%, m.p.: 165–167 °C. IR (ATR, cm^{-1}): 3340 (OH), 1717 (C=O), 1658 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.25 (t, $J = 7.2$ Hz, 3H, 2″-Me), 1.76 (m, 2H, 2′-CH_2), 2.26 (m, 2H, 1″-CH_2), 2.58 (s, 3H, 4-Me), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 10.23, 14.34, 16.99, 21.16, 29.10, 29.93, 46.16, 98.70, 115.09, 126.34, 127.71, 128.22, 129.17, 129.45, 130.84, 131.03, 134.55, 135.18, 136.40, 138.30, 140.53, 140.64, 154.45, 170.46, 172.08; HRMS (ESI) Calcd for $C_{28}H_{30}N_3O_3$ $[M + H]^+$: 456.2287, Found 456.2276.

*4.1.9.3. 4′-[(6-n-Butyrylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**11c**).* White solid, yield 81%, m.p.: 178–180 °C. IR (ATR, cm^{-1}): 3336 (OH), 1717 (C=O), 1653 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.92 (t, $J = 7.2$ Hz, 3H, 3′-Me), 0.98 (t, $J = 7.2$ Hz, 3H, 3″-Me), 1.78 (m, 2H, 2′-CH_2), 1.86 (m, 2H, 2″-CH_2), 2.53 (s, 3H, 4-Me), 2.62 (t, $J = 7.2$ Hz, 2H, 1″-CH_2), 2.82 (t, $J = 7.2$ Hz, 2H, 1′-CH_2), 5.45 (s, 2H, N-CH_2-Ar), 7.06–7.96 (m, 10H, Ar-H), 12.45 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.15, 14.33, 16.99, 19.08, 21.15, 29.10, 38.77, 46.15, 98.72, 115.14, 126.33, 127.71, 128.21, 129.19, 129.46, 130.85, 131.03, 134.54, 135.18, 136.41, 138.33, 140.53, 140.66, 154.45, 170.48, 171.24; HRMS (ESI) Calcd for $C_{29}H_{32}N_3O_3$ $[M + H]^+$: 470.2444, Found 470.2437.

*4.1.9.4. 4′-[(6-Benzoylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**11d**).* White solid, yield 79%, m.p.: 195–197 °C. IR (ATR, cm^{-1}): 3270 (OH), 1699 (C=O), 1653 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.93 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.78 (m, 2H, 2′-CH_2), 2.68 (s, 3H, 4-Me), 2.85 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.67 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 15H, Ar-H), 12.45 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.34, 17.03, 21.15, 29.13, 46.22, 100.23, 116.49, 126.42, 127.76, 128.02, 128.15, 128.79, 129.03, 129.19, 129.75, 130.90, 131.24, 131.83, 132.00, 133.28, 134.17, 135.15, 135.56, 136.48, 138.90, 140.47, 154.80, 165.66, 170.13; HRMS (ESI) Calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$: 504.2287, Found 504.2279.

*4.1.9.5. 4′-[[6-(4-Methylbenzoyl)amino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**11e**).* White solid, yield 75%, m.p.: 175–177 °C. IR (ATR, cm^{-1}): 3300 (OH), 1699 (C=O), 1653 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.38 (s, 3H, 4″-Me), 2.58 (s, 3H, 4-Me),2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 14H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.37, 17.05, 21.16, 21.45, 29.15, 46.31, 100.41, 116.62, 126.00, 126.68, 126.85, 127.70, 128.00, 128.11, 129.18, 129.28, 129.45, 132.01, 132.68, 134.21, 135.11, 135.26, 137.13, 138.86, 141.71, 141.99, 144.07, 154.70, 165.49, 173.43; HRMS (ESI) Calcd for $C_{33}H_{32}N_3O_3$ $[M + H]^+$: 518.2444, Found 518.2442.

*4.1.9.6. 4′-[(6-Phenylacetylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**11f**).* White solid, yield 78%, m.p.: 186–188 °C. IR (ATR, cm^{-1}): 3280 (OH), 1717 (C=O), 1653 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.58 (s, 3H, 4-Me), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.56 (s, 2H, 1″-CH_2), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 15H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.34, 17.00, 21.14, 29.12, 29.49, 43.75, 46.32, 98.95, 115.14, 126.20, 126.88, 127.19, 128.21, 128.46, 128.68, 129.18, 129.61, 130.00, 134.36, 135.13, 135.60, 136.73, 138.50, 141.41, 154.57, 169.22, 172.26; HRMS (ESI) Calcd for $C_{33}H_{32}N_3O_3$ $[M + H]^+$: 518.2444, Found 518.2441.

*4.1.9.7. 4′-[[6-(3-Phenylpropionyl)amino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid (**11g**).* White solid, yield 74%, m.p.: 168–170 °C. IR (ATR, cm^{-1}): 3420 (OH), 1683 (C=O), 1650 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.81 (m, 2H, 2′-CH_2), 2.62 (s, 3H, 4-Me), 2.77 (m, 2H, 1″-CH_2), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 2.96 (m, 2H, 2″-CH_2), 5.67 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 15H, Ar-H), 12.56 (s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.24, 17.02, 21.17, 29.12, 31.39, 38.38, 46.29, 98.88, 115.15, 126.17, 126.35, 127.19, 128.17, 128.44, 128.70, 128.76, 129.17, 130.01, 134.39, 135.13, 135.66, 138.43, 141.36, 141.76, 154.48, 170.48, 172.25; HRMS (ESI) Calcd for $C_{34}H_{34}N_3O_3$ $[M + H]^+$: 532.2600, Found 532.2594.

*4.1.10. 4′-[(6-Methoxycarbonylamino-4-methyl-2-n-propyl-1H-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid (**12**)*

The mixture of compound **9** (0.5 g, 1.1 mmol), 1*N* aqueous sodium (5.5 mL, 5.5 mmol) and methanol (20 mL) was heated at 60 °C for 3 h, then was concentrated, 10 mL water was added, cooled, and the solution was acidified with 1*N* hydrochloride acid to pH = 6, the precipitate formed was filtered to obtain 0.39 g white solid, yield 77%. m.p. 198–200 °C; IR (ATR, cm^{-1}): 3331 (OH), 1717 (C=O), 1610 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, $J = 7.2$ Hz, 3H, 3′-Me), 1.76 (m, 2H, 2′-CH_2), 2.58 (s, 3H, 4-Me), 2.81 (t, $J = 7.6$ Hz, 2H, 1′-CH_2), 3.76 (s, 3H, COOMe), 5.57 (s, 2H, N-CH_2-Ar), 7.19–7.92 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.33, 16.99, 21.18, 29.10, 46.20, 51.93, 97.81, 114.56, 126.44, 127.74, 128.35, 129.17, 129.50, 130.87, 131.17, 133.03, 134.24, 135.36, 136.44, 138.07, 140.47, 140.75, 154.31, 154.61, 170.14; HRMS (ESI) Calcd for $C_{27}H_{28}N_3O_4$ $[M + H]^+$: 458.2080, Found 458.2082.

4.2. Biological evaluation

4.2.1. Procedure for receptor binding assay

The AT_1 receptor binding assay was carried out by the competitive displacement of the binding of [^{125}I] Sar^1 Ile^8-Ang II with angiotensin AT_1 receptor as described previously [18]. Each 180-μL incubate contained the following: [^{125}I] Sar^1 Ile^8-Ang II (25 pM), AT_1(AT_2) receptor (25 μg), and standard (losartan) or test compounds (**6a**∼**6i**, **11a**∼**11g**, **12**). The binding was performed at 37 °C for 180 min in 96-well filtration plates (Costar, USA) and was terminated by rapid vacuum filtration using a vacuum device; dried filter disks were punched out and counted in a gamma counter. IC_{50} values were estimated from the linear portion of the competition curves.

4.2.2. Procedure for Angiotensin II receptor functional antagonism in rabbit aorta strips

Japanese white rabbits (2 kg to 3 kg body weight, Vitalriver Company, China) were killed by cervical dislocation after slight

anesthesia with 20% urethane solution. The thoracic aorta was carefully dissected out and placed in ice-cold Krebs–Henseleit solution of the following composition (mM): NaCl 118; KCl 4.7; KH_2PO_4 1.2; $MgSO_4 \cdot 7H_2O$ 1.17; $CaCl_2 \cdot 2\ H_2O$ 2.5; $NaHCO_3$ 25; glucose 11.1 [30]. It was cut into helical strips 3 mm to 4 mm wide and 15 mm to 20 mm long. These strips were mounted in 10-mL tissue baths kept at 37 °C and aerated with 95% O_2 and 5% CO_2. Each strip was connected to a force transducer; the changes in isometric tension were recorded by a four-channel recorder (Medlab-U/4c501, China). The tissues were allowed to equilibrate for 1 h and were washed every 15 min. At the beginning of the experiment, a 67-mM KCl solution was administered to check the sensitivity of the preparations and to determine their maximal contractile response. After a 30 min washout, the test substances or their respective vehicles were added. After 60 min, cumulative concentration–response curves of Ang II were obtained. Only one curve was obtained from each strip, and the contractile response was expressed as a percentage (%) of the maximal contraction achieved with KCl. The pA_2 values were calculated using Schild's plot [31]. Antagonist potency was evaluated by the estimation of pA_2 values.

4.2.3. Procedure for oral activity in the spontaneously hypertensive rats (SHR)

Male SHR, 19–21 weeks old. Six animals served as controls. They received a vehicle (water, 10 mL/kg). The hypertensive animals were divided into three groups ($n = 6$). Group 1 received losartan (standard drug: 10 mg/kg); groups 2 and 3 were given the same doses of the tested compounds **6f** and **11g**, respectively. Both the vehicle and the test compound were orally administered [32]. Blood pressure and heart rate were measured by tail plethysmography (BP-98A, Softron, Japan) after a warming period in unanesthetized rats. The BP measurements required only a few minutes per individual rat. All data were expressed as means ±SEM [11].

4.3. Molecular modeling experiments

Molecular modeling studies were performed using a Silicon Graphics desktop (SGI) Fuel work station. The training set was selected as described above, and the pharmacophore model for AT_1 receptor antagonists was generated using the HipHop module in Discovery Studio, version 2.0, from Accelrys, Inc. Molecules were built in a 3D window, and conformational models for each molecule were generated using the diverse conformation module. Then, the resulting sd files were used for common features hypothesis generation using the HipHop module by default. Through these experiments, we specified the features that are crucial for binding with Ang II receptor, which are in agreement with the literature [21,22].

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.08.014. These data include MOL files of the most important compounds described in this article.

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