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Synthesis and biological activity of 2-alkylbenzimidazoles bearing a *N*-phenylpyrrole moiety as novel angiotensin II AT_1 receptor antagonists

Jin Yi Xu,[a] Yi Zeng,[a] Qian Ran,[a] Zhen Wei,[a] Yi Bi,[a] Qian Hui He,[a] Qiu Juan Wang,[b] Song Hu,[b] Jing Zhang,[b] Ming Yue Tang,[b] Wei Yi Hua[a] and Xiao Ming Wu[a,*]

[a]*Department of Medicinal Chemistry, College of Pharmacy, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, China*
[b]*Department of Physiology, College of Pharmacy, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, China*

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Abstract—A series of 2-alkylbenzimidazoles bearing a *N*-phenylpyrrole moiety were synthesized and evaluated as a novel class of AT_1 receptor antagonists. Among them, compounds **10a** and **10g** inhibited [^{125}I] AngII-binding affinity to AT_1 receptor at nanomolar level and potently inhibited the Ang II-induced pressor response by oral administration. Moreover, evaluation in spontaneously hypertensive rats showed that **10a** is an orally active AT_1 receptor antagonist.

The renin–angiotensin system (RAS) is known to play a pivotal role in the regulation of fluid, electrolyte balance, and blood pressure, and is a modulator of cellular growth and proliferation.[1] Inhibitors of the RAS would be effective for the treatment of hypertension and congestive heart failure.[2] Among them, angiotensin-converting enzyme (ACE) inhibitors have been very successful in the treatment of hypertension and congestive heart failure during the last few decades. However, these inhibitors suffer from some side effects such as dry cough and angioedema caused by their nonspecific actions.[3] On the other hand, angiotensin II (AngII) receptor antagonists block the RAS at the AngII receptor level. This provides a more specific attempt to inhibit the activity of the RAS and has become the main pharmacological approach.[4]

The first non-peptide AngII receptor antagonists, *N*-benzylimidazole-5-acetic acid derivatives, were originally reported from Takeda laboratories.[5] Since then, this imidazole lead has been developed into a series of potent, selective, and orally active AT_1 receptor antagonists exemplified by losartan (DuP 753, **1**).[6]

The available data from the literature[7] indicated four key structural requirements for good binding affinity in the imidazole derivatives: a biphenyl tetrazole moiety linked to the imidazole nucleus; a short lipophilic alkyl chain at the 2-position of the heterocycle; a basic nitrogen acting as a hydrogen-bond acceptor in the 3-position of the heterocycle; polar substituents in the 5-position of imidazoles. These pharmacophore features can be best exemplified by the extremely potent benzimidazole antagonist CV-11194 (**2**)[8] and imidazo[4,5-*b*]pyridine antagonist L-158,809 (**3**).[9]

A large body of existing literature has described the extensive SAR work focusing on either the replacement of the imidazole with other heterocyclic and non-heterocyclic groups (e.g., valsartan[10]) or the modification of the acid functional group. We became interested in exploring new surrogates for the biphenyl tetrazole group because (1) there is a paucity of work studying the modification of biphenyl ring bearing an acid group, (2) it is extremely intriguing to us that compounds lost the AT_1 receptor affinity when a nitrogen atom was introduced in the distal phenyl ring, while little effects were observed if a nitrogen was placed in the proximal

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* Corresponding author. Tel.: +86 25 83242366; fax: +86 25 83302827; e-mail addresses: jinyixu@china.com; xmwu@cpu.edu.cn

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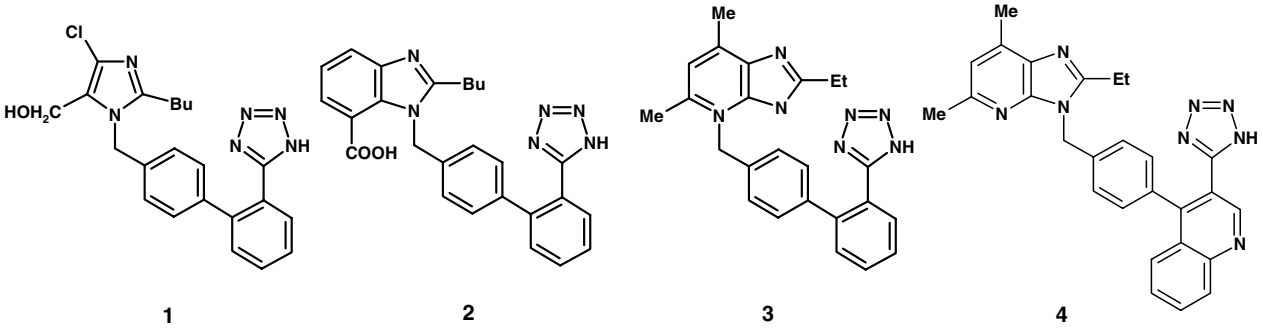
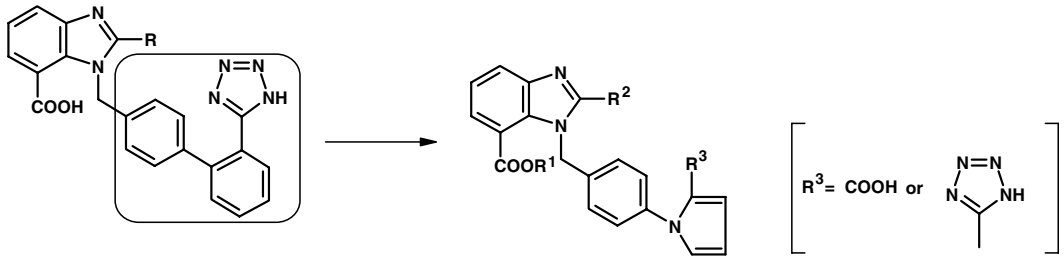
phenyl group.[11] Recently we have noticed a report of novel AT_1 receptor antagonists based on the 4-phenylquinoline such as compound **4** with moderate to good activity.[12]



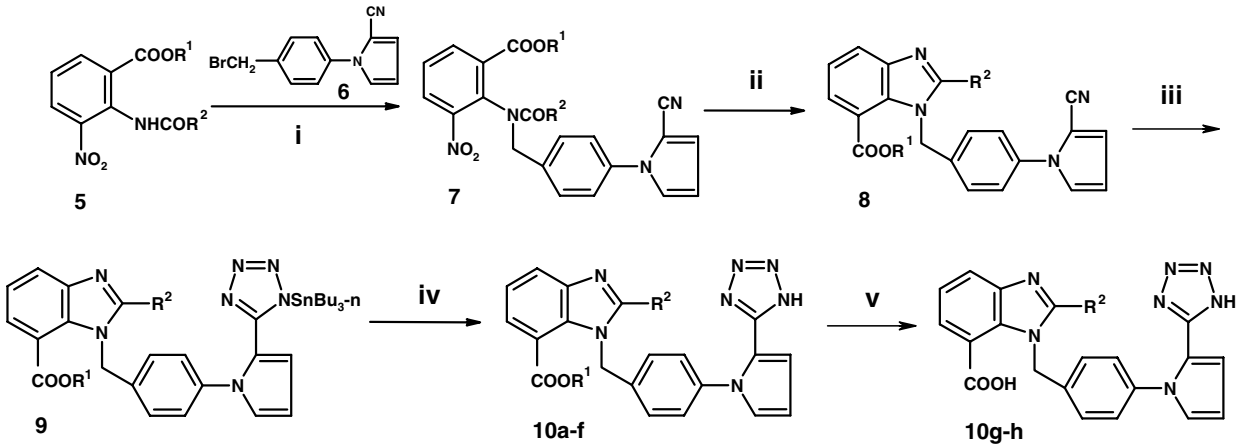
In order to search for a novel class of AT_1 receptor antagonists, our efforts were focused on the replacements of the biphenyl tetrazole moiety. Computer-assisted modeling techniques were used to evaluate structural parameters in comparison to the related biphenyl system of some potent compounds. Our previous QSAR analysis[13] of 42 AT_1 receptor antagonists suggested that the distance between the center of two phenyl rings of biphenyl fragment is optimal at about 0.40–0.65 nm, while the distance between the center of proximal ring and acidic group is at about 0.35–0.60 nm. According to our computational calculations, we found *N*-phenylpyrrole bearing an acidic group satisfies the above conditions, and could compare to the biphenyl bearing an acidic group spacers in terms of distances between comparable atoms. These results led us to propose novel 2-alkylbenzimidazole-based AT_1 receptor antagonists bearing a *N*-phenylpyrrole moiety. We wish to report herein our synthesis, and in vitro and in vivo biological evaluation of the designed compounds.



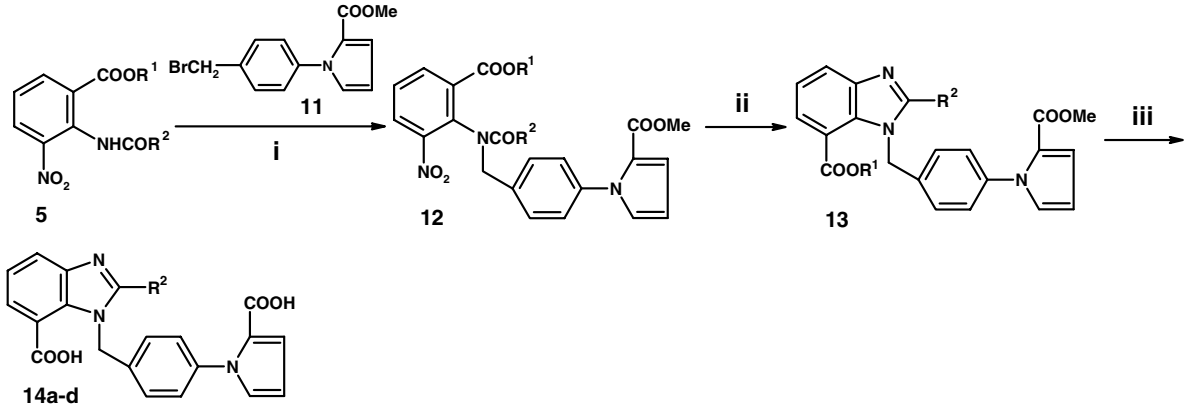
As shown in Schemes 1 and 2, 2-acylamino-3-nitrobenzoate **5** was reacted with 1-[4-(bromomethyl)-phenyl]-1*H*-pyrrole-2-carbonitrile **6** and methyl 1-[4-(bromomethyl)-phenyl] 1*H*-pyrrole-2-carboxylate **11** (**6** and **11** were prepared based on a described procedure in the literature[14]) using NaH in DMF to give the corresponding alkylated products **7** and **12**, respectively. Reductive cyclization of **7** and **12** was accomplished in good yields with iron powder and concentrated hydrochloric acid in boiling MeOH to provide **8** and **13**. The tetrazole derivatives **9** were obtained by reaction of **8** with tributyltin chloride and sodium azide through a 1.3-dipolar cycloaddition.[6] The *N*-(tributylstannyl) tetrazoles were converted to the free tetrazole by treatment with anhydrous hydrogen chloride in MeOH to give **10a–f** in 38–55% yields. Then saponification of **10a–b** with aqueous LiOH in THF produced **10g–h** in 40–42% yields. Saponification of **13** with NaOH in MeOH gave the products **14a–d** in 59–71% yields.

Angiotensin II receptor (AT_1)-binding assay. The prepared compounds were evaluated for their activity to competitively inhibit [^{125}I] AngII binding to the AT_1 receptor by a conventional ligand-binding assay using a bovine adrenal cortex as described previously.[15] The binding affinity is expressed as IC_{50} value (shown in Table 1), which is the concentration of compound which inhibits [^{125}I] AngII (0.1 nM) binding to AT_1 receptor by 50%. Initial analysis on the SAR demonstrated that benzimidazole, in agreement with the results of CV-11194 series described in the literature,[8,16] was an excellent replacement for the imidazole ring in our series. More interestingly, replacement of the biphenyl tetrazole by *N*-phenyl-1*H*-pyrrole-2-tetrazole appeared to improve in vitro potency by more than one order of magnitude, comparing **10g** to the parent structure CV-11149. The compound **10g** showed single-digit nanomole potency, with an increase of 17- and 79-fold over losartan and CV-11194, respectively. While the replacement of the tetrazole group with a carboxylic acid moiety produced a decrease in the binding affinity of these compounds (comparing **10g** with **14a**; **10h** with **14b**), this is similar to the results described for the biphenyl system (e.g., losartan).[6]

Angiotensin II receptor functional antagonism in rabbit aorta. The synthesized compounds were also evaluated

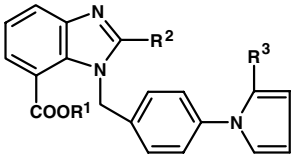


Scheme 1. Reagents and conditions: (i) NaH, DMF, rt (69–78%); (ii) Fe/HCl, MeOH, reflux (75–84%); (iii) *n*-Bu_3SnCl, NaN_3, toluene, reflux; (iv) HCl, MeOH, rt (38–55%); (v) LiOH, THF/H_2O, 80 °C, then HCl, rt (40–42%).



Scheme 2. Reagents and conditions: (i) NaH, DMF, rt (65–76%); (ii) Fe/HCl, MeOH, reflux (80–88%); (iii) NaOH, MeOH/H_2O, reflux; then HCl, rt (59–71%).

Table 1. Angiotensin II antagonistic activity of the target compounds**10a**–**h** and **14a**–**d**



10a-h, 14a-d

Compound	R^1	R^2	R^3	Binding IC_{50}(nM) ± SEM	pA_2[a]
10a	Me	Bu	CN_4H	9.8 ± 0.2	8.4
10b	Me	Pr	CN_4H	32 ± 1.5	7.9
10c	Me	Et	CN_4H	140 ± 8.6	7.5
10d	Me	Me	CN_4H	200 ± 14	7.0
10e	Et	Bu	CN_4H	19 ± 3.1	7.8
10f	Et	Pr	CN_4H	41 ± 5.2	7.1
10g	H	Bu	CN_4H	6.9 ± 0.1	8.5
10h	H	Pr	CN_4H	16 ± 1.8	8.2
14a	H	Bu	CO_2H	33 ± 2.4	8.0
14b	H	Pr	CO_2H	92 ± 4.6	7.0
14c	H	Et	CO_2H	160 ± 38	6.5
14d	H	Me	CO_2H	250 ± 47	5.9
1 (losartan)				120 ± 16 (150[b])	7.9
2 (CV-11194)				550[b]	

[a] Antagonism of AngII-induced contraction is expressed as pA_2, which was obtained as described in the Experimental Section (Supporting Information).

[b] Data taken from the literature (Ref. 19).

in a functional assay for their antagonism of AngII-induced contractions in the rabbit thoracic aortic rings.[17,18] Losartan was taken as a positive control drug in the assays. These compounds and losartan inhibited AngII (10 nM)-induced contraction in a concentration-related manner, as exemplified by compounds **10a** and **10g** in Figure 1. The antagonistic activity of the compounds was expressed as pA_2 and are listed in Table 1. The assay results showed that some of our compounds exhibited potent antagonistic activity of AT_1receptor in a functional assay, which correlated highly with our binding affinity results. Among them, compounds **10a** and **10g** had a pA_2 value of 8.4 and 8.5, respectively, and showed more potent activity than the positive drug losartan ($pA_2 = 7.9$) in the assay. Compounds **10a** and **10g** selectively inhibited AngII-induced contractions of rabbit aortic strips in a competitive manner and had no effect on the contraction induced by norepinephrine (10 nM), KCl (10 nM), and histamine (10 nM).

Antagonism of AngII-induced pressor response by oral administration and oral activity in the spontaneously hypertensive rats (SHR). Based on the results of in vitro AngII-binding assay and functional antagonism, **10a** and **10g** were selected for further evaluation in in vivo models. In assessing the inhibition of pressor response induced by AngII (100 ng/kg iv) in conscious normotensive rats, **10a** and **10g** were given by oral administration.[8,15] As shown in Figure 2, the inhibitory activity of **10a** was more potent and longer-acting than that of **10g** and losartan at a dose of 1 mg/kg po.

When evaluated orally in conscious SHR, compounds **10a** and **10g** at doses of 1–3 mg/kg significantly decreased blood pressure in a dose-dependent manner and were more efficacious than losartan. Compound **10a** at 1 mg/kg po reduced the mean arterial blood pressure by more than 40 mmHg with a duration of action exceeding 24 h (Figs. 3 and 4). Furthermore, it produced no observable alteration in the basal heart rate at these doses.

It should be pointed out here that compound **10g** showed less efficacy in vivo with respect to **10a**, although it had the higher binding affinity in vitro than **10a**. We believe that this might be attributed to its lower oral bioavailability due to the highly polar character of molecule with one tetrazole and one carboxylic acid group.

For the purpose of understanding the SAR of synthesized compounds from standpoint of computational chemistry, the MM_2 program calculation of these com-

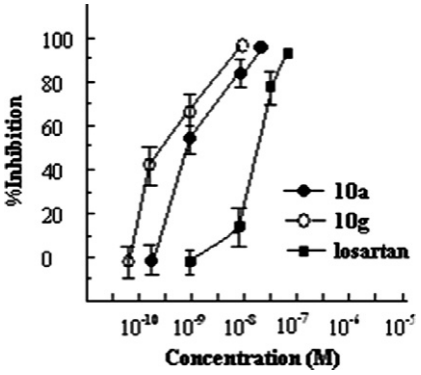


Figure 1. Concentration–inhibition curves of **10a**, **10g**, and losartan on the AngII (10 nM)-induced contraction in isolated rabbit aorta ($n = 5$–6).

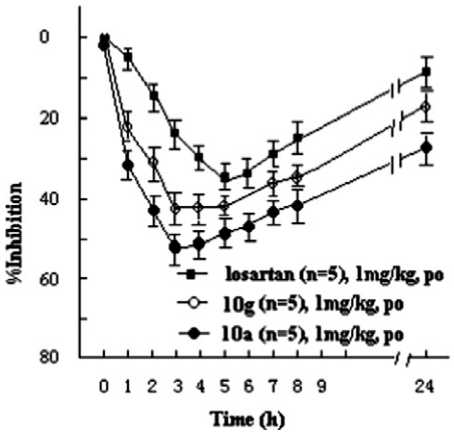


Figure 2. Inhibitory effects of **10a**,**10g**, and losartan (1 mg/kg po) on AngII (100 ng/kg iv)-induced pressor response in conscious normotensive rats.

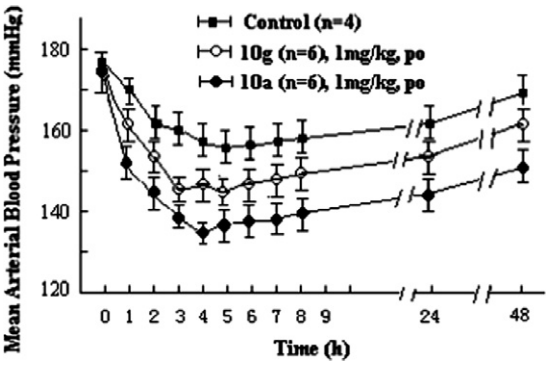


Figure 3. Effects of **10a** and **10g** at 1 mg/kg po on mean arterial pressure in conscious SHR. Values represent means ± SEM.

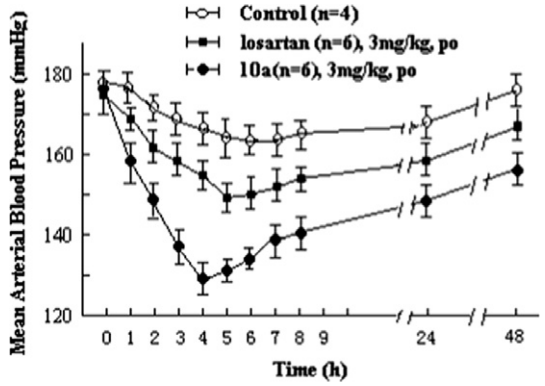


Figure 4. Effects of **10a** and losartan (3 mg/kg po) on mean arterial pressure in conscious SHR after oral administration. Values represent means ± SEM.

Table 2. The minimal energy conformational parameters for **10a** and losartan

Bond angle (deg)		Distance (nm)		Dihedral angle (deg)
Losartan				
C27–C22–N19	127.080	N19–N16	0.7599	174.895[a]
C22–N19–C18	130.202	N19–C2	0.5276	58.017[b]
N19–C18–C5	122.488	N17–C8	0.7416	45.340[c]
C8–C7–C2	122.100			
C7–C8–C13	121.547			
C8–C13–N14	126.504			
10a				
C27–C21–N18	127.125	N18–N15	0.7589	178.110[a]
C21–N18–C17	129.528	N18–C2	0.5173	57.786[b]
N18–C17–C5	118.787		0.7320	38.746[c]
C8–N7–C2	124.197			
N7–C8–C12	124.963			
C8–C12–N13	125.851			

[a] Expressed as the dihedral angle between imidazole (or benzimidazole) ring and the proximal phenyl ring.
[b] Expressed as the dihedral angle between the proximal phenyl ring and the distal phenyl (or pyrrole) ring.
[c] Expressed as the dihedral angle between the distal phenyl (or pyrrole) ring and tetrazole ring.

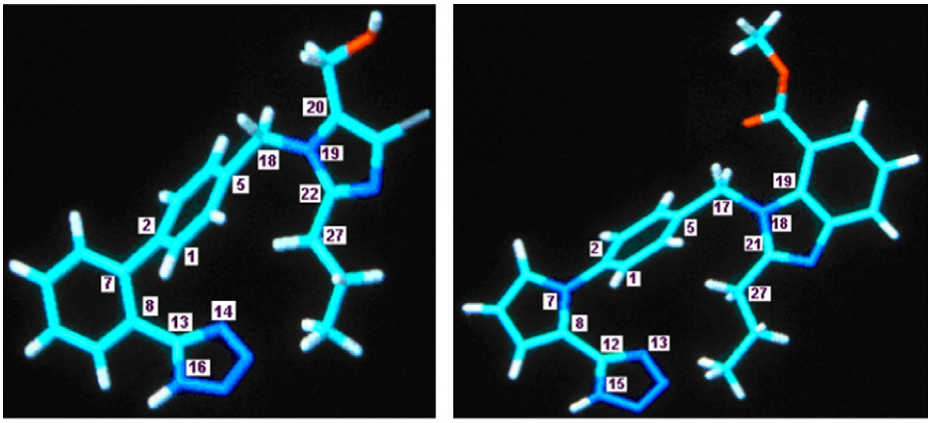


Figure 5. The dominant conformations of **10a** and losartan.

pounds was investigated on SGI Indigo R 40000 workstation as described previously.[13] In the computational studies on structural parameters, we found that the minimal energy conformations of the most active compound**10a** and losartan are similar and their structure parameters are relatively close, indicating that the two molecules have similar stereo electronic characteristics (Table 2). The dominant conformations of **10a** and losartan are shown as Figure 5. A more detailed study of the mode of action and their QSAR of this series of 2-alkylbenzimidazole derivatives is underway.

In conclusion, a series of 2-alkylbenzimidazole derivatives bearing a *N*-phenylpyrrole moiety were designed and synthesized as a novel class of non-peptide AT_1 receptor antagonists, and their biological activities were evaluated. The study results revealed that the bioisosteric replacement of biphenyl tetrazole with *N*-phenylpyrrole-2-tetrazole, and *N*-phenylpyrrole-2-carboxylic acid in this series, produced extremely potent novel analogues. As demonstrated with in vitro and in vivo results, compound **10a** is an orally active AT_1 receptor antagonist that is more potent and efficacious than losartan. We believe that **10a** has interesting pharmacological properties and this compound is currently under further investigation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.02.042.

References and notes

1. (a) Ferrario, C. M. *J. Cardiovasc. Pharmacol.* **1990**, *15*, S1; (b) Volpe, M.; Musumeci, B.; De Paolis, P.; Savoia, C.; Morganti, A. *J. Hypertens.* **2003**, *21*, 1429.

2. Unger, T. *Am. J. Cardiol.* **2002**, *89*, 3A.
3. (a) Chin, H. L.; Buchan, D. A. *Ann. Intern. Med.* **1990**, *112*, 312; (b) Wood, J. M.; Chin-Mah, S.; Schnell, C. *J. Cardiovasc. Pharmacol.* **1990**, *16*, S60.
4. Cockcroft, J. R.; Sciberras, D. G.; Goldberg, M. R.; Ritter, J. M. *J. Cardiovasc. Pharmacol.* **1993**, *22*, 584.
5. Matsumura, K.; Hashimoto, N.; Furukawa, Y.U.S. Patent 4207324, **1980**. Furukawa, Y.; Kishimoto, S.; Nishikawa, K.U.S. Patent 4340598, 4355040. **1982**.
6. Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S-E.; Timmermans, P. M. B. M. W. *J. Med. Chem.* **1991**, *34*, 2525.
7. Mederski, W. W. K. R.; Dorsch, D.; Bokel, H. H.; Beier, N.; Lues, I.; Schelling, P. *J. Med. Chem.* **1994**, *37*, 1632.
8. Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 1772.
9. Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T. B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919.
10. Bühlmayer, P.; Furet, P.; Criscione, L.; Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. V. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29.
11. Reitz, D. B.; Penick, M. A.; Reinhard, E. J.; Cheng, B. K.; Olins, G. M.; Corpus, V. M.; Palomo, M. A.; McGraw, D. E.; McMahon, E. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 99.
12. Cappelli, A.; Mohr, G. P.; Gallelli, A.; Rizzo, M.; Anzini, M.; Vomero, S.; Mennuni, L.; Ferrari, F.; Makovec, F.; Menziani, M. C.; Benedetti, P. G. D.; Giorgi, G. *J. Med. Chem.* **2004**, *47*, 2574.
13. Xu, J. Y.; Hua, W. Y.; Ji, N. N.; Wu, X. M. *J. Chin. Pharm. Univ.* **2005**, *36*, 99.
14. Artico, M.; Giuliano, R.; Porretta, G. C.; Scalzo, M. *Farmaco Ed. Sc.* **1972**, *27*, 60.
15. Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Shimoji, Y.; Fujimoto, K.; Kitahara, Y.; Sada, T.; Mizuno, M.; Ikeda, M.; Miyamoto, S.; Furukawa, Y.; Koike, H. *J. Med. Chem.* **1996**, *39*, . 323.
16. Kubo, K.; Kohara, Y.; Imamiya, E.; Sugiura, Y.; Inada, Y.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 2182.
17. Robertson, M. J.; Cunoosamy, M. P.; Clark, K. L. *Br. J. Pharmacol.* **1992**, *106*, 166.
18. Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; Arriba, A. F.; Rodriguez, R.; Carceller, E.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 2197.
19. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228.