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Synthesis and Angiotensin II Antagonist Activity of Novel 2-Arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylic Acids

A. SHAFIEE, F. HADIZADEH, L. KARIMI, M. MAHMOUDIAN* AND N. RAZZAGHI*

*Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, PO Box 14155-6451, Tehran and *Department of Pharmacology, Iran University of Medical Sciences, PO Box 14155-6183, Tehran, Iran*

Abstract

A series of 2-arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylic acids were synthesized and evaluated as angiotensin II antagonists on guinea-pig ileal smooth muscle.

2-Phenylthio-3-(2-*n*-butyl-1-(4-carboxybenzyl)imidazolyl) acrylic acid was found to be the most active compound (pIC50 $7{\cdot}62 \pm 0{\cdot}23$), being almost as active as the reference losartan (pIC50 7·85).

The renin angiotensin system has a key role in regulation of cardiovascular homoeostasis and blood pressure in mammals (Yanagisawa et al 1996; Almansa et al 1997). Angiotensin-converting enzyme inhibitors have side effects such as dry cough and angioedema, caused by potentiation of bradykinin, substance P and other active peptides. Nonpeptide angiotensin II receptor antagonists are therefore of interest (Carini et al 1990; Duncia et al 1990; Keenan et al 1993).

Angiotensin II antagonist activity of 2-arylmethyl-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl) acrylic acids has been reported (Keenan et al 1993). Here, we report synthesis and angiotensin antagonist activity of novel 2-arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylic acids.

Materials and Methods

Chemical procedures

2-Arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylates, as sodium salts **7a–e** and **8a–e**, were synthesized according to Figure 1. The *N*-alkylation of 2-alkyl-4-formylimidazole (**1**) (Paul & Menschik 1979) with 4-carbomethoxybenzyl bromide (**2**), gave a 70 : 30 mixture of 2-alkyl-1-(4-carbomethoxybenzyl)-4-formylimidazole (**3**) and 2-alkyl-1-(4-carbomethoxybenzyl)-5-formylimidazole (**4**), respectively (Shafiee et al 1997). Condensation of **3** and **4** (Gairns et al 1986) with ethyl arylthioacetates (Lefeuvre 1966; Maxwell et al 1984) gave imidazole acrylates **5** and **6**. These were hydrolyzed by refluxing in ethanol–water with equimolar sodium hydroxide to give the title compounds **7a–e** and **8a–e**.

The compounds were characterized by ^{1}H NMR, infrared and microanalysis. The purity of all products was determined by thin-layer chromatography using several solvent systems of different polarity.

Evaluation of pharmacological activity

Male pirbright white guinea-pigs (300–450 g) were killed by a blow to the head. Samples of ileum (1–2 cm) were excised and mounted in a 15-mL organ bath containing modified tyrode solution (mM: NaCl 137, KCl 2·7, $CaCl_2$ 0·9, NaH_2PO_4 0·4, $MgCl_2$ 1·5, $NaHCO_3$ 11·9 and glucose 5), maintained at 37°C and oxygenated with a 95% O_2 and 5% CO_2 mixture throughout the experiment. A resting tension of 0·5–1 g was applied to the ileal segments and they were left to equilibrate for 60 min. The solution was changed every 15 min. Isotonic contraction of the muscle was recorded using a Bio-science isotonic transducer and Washinton Oscillograph (model 400 MD2R) (Milanian et al 1990). Control contractile response to angiotensin II ($2{\cdot}26 \times 10^{-9}$ M) was recorded.

Correspondence: A. Shafiee, Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

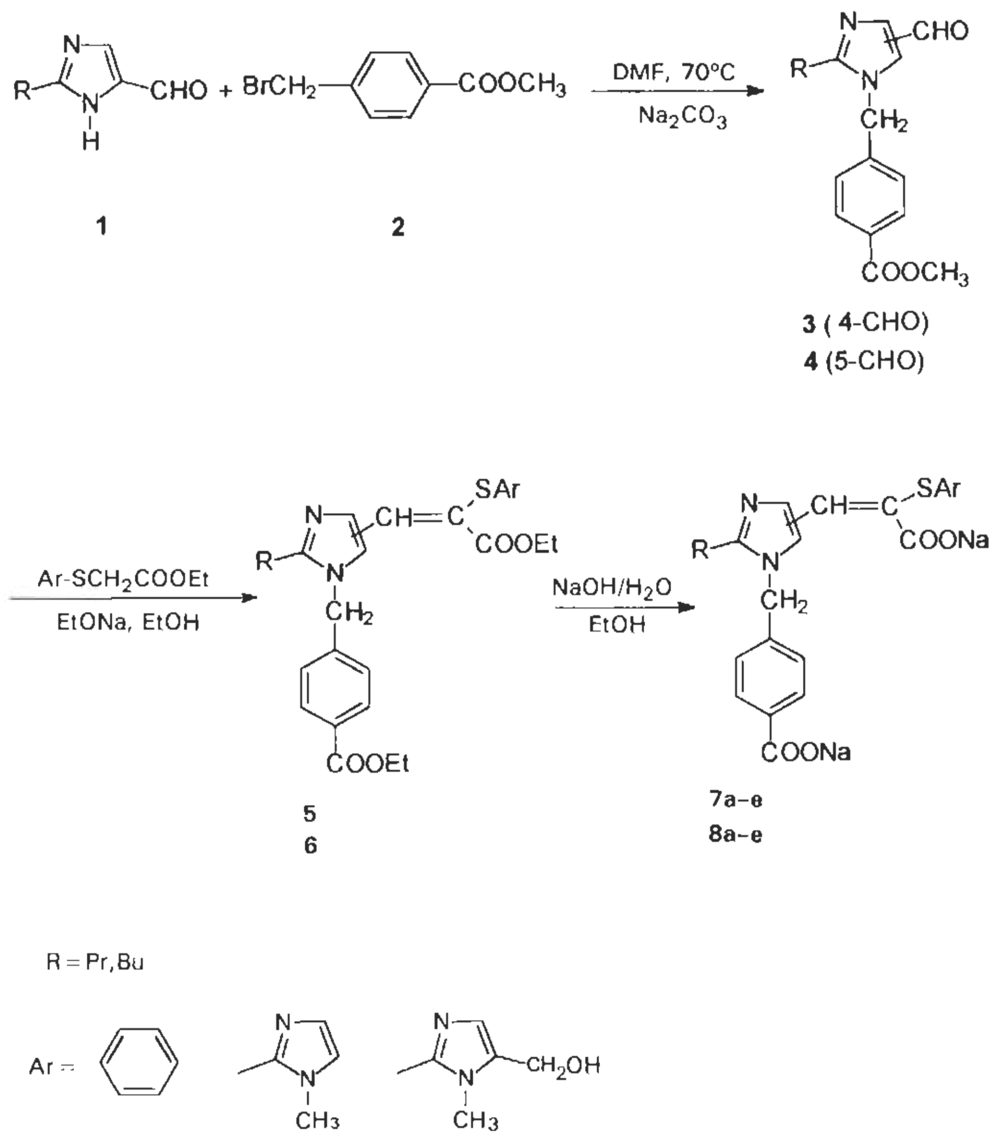


Figure 1. Synthesis of sodium 2-arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylates.

The tissue was washed and then incubated with test compounds 15 min before addition of angiotensin II. The procedure was repeated with increasing concentration of test compounds (10^{-10}–10^{-5} M) (Wong et al 1990).

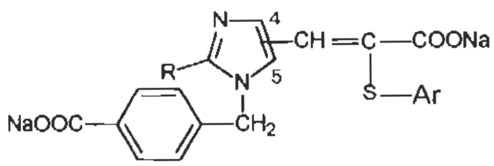
Alternatively, acetylcholine (10^{-7} M) was used as contractile agent and the procedure was repeated as described.

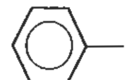
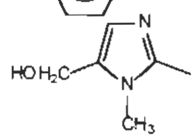
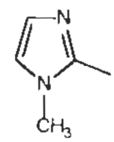
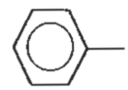
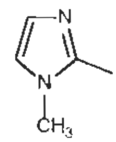
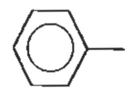
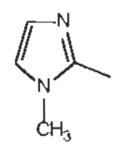
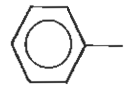
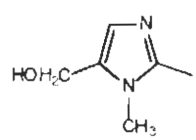
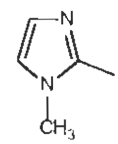
Results and Discussion

The angiotensin II antagonist activity (pIC50) of **7a–e** and **8a–e** was determined as the concentration needed to produce 50% inhibition of contractile response of guinea-pig ileal smooth muscle to angiotensin II ($2{\cdot}26 \times 10^{-9}$ M) (Wong et al 1990). The results are given in Table 1. The selectivity of test compounds for antagonizing the effect of angiotensin II was determined by their inability to antagonize the effect of acetylcholine at 10^{-7} M.

2-Arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazol-4-yl)acrylates **7a–e** did not have significant antagonistic activity (pIC50 < 5). This was in agreement with a similar study carried out on 2-arylmethyl-3-(2-alkyl-1-(4-carboxylbenzyl)-imidazol-4-yl)acrylates (Keenan et al 1993). For the imidazole-5-ylacrylates **8a–e**, comparison of the activity of the 2-substituent of imidazole indicated

Table 1. Angiotensin II antagonist activity of 2-arylthio-3-(2-alkyl-1-(4-carboxybenzyl)imidazolyl)acrylic acids.



Compound	Substitution	R	Ar	pIC50
7a	4	$n-C_3H_7$		< 5
7b	4	$n-C_3H_7$		< 5
7c	4	$n-C_3H_7$		< 5
7d	4	$n-C_4H_9$		< 5
7e	4	$n-C_4H_9$		< 5
8a	5	$n-C_3H_7$		6.53 ± 0.17
8b	5	$n-C_3H_7$		6.69 ± 0.12
8c	5	$n-C_4H_9$		7.62 ± 0.23
8d	5	$n-C_4H_9$		7.15 ± 0.09
8e	5	$n-C_4H_9$		6.69 ± 0.11
Losartan				7.85[a]

[a]From Wong et al (1990). Angiotensin II antagonist activity (pIC50) was determined as the concentration needed to produce 50% inhibition of contractile response of guinea-pig ileal smooth muscle to angiotensin II (2.26×10^{-9} M). Values are ± s.e.m., n = 3 or 4.

that an increase in the length from propyl to butyl increases activity (**8c** > **8a**, **8e** > **8b**).

It was found that when R = Bu, the phenyl substituent is more active than imidazolyl (**8c** > **8e**). Introduction of a hydroxymethyl substituent on the imidazolyl moiety increased activity relative to imidazolyl itself (**8d** > **8e**). The most active compound in this series was **8c** (pIC50 7.62). Its potency was comparable with that of losartan, a commercially available angiotensin II antagonist (pIC50 7·85, Wong et al 1990).

Acknowledgement

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References

Almansa, C., Gomez, L. A., Cavalcanti, F. L., Arriba, A. F., Rafanell, J. G., Forn, J. (1997) Synthesis and structure activity relationship of a new series of potent AT1 selective angiotensin II receptor antagonists: 5-(biphenyl-4-ylmethyl)pyrazoles. J. Med. Chem. 40: 547–558

Carini, D. J., Duncia, J. V., Johnson, A. L., Chiu, A. T., Price, W. A., Wong, P. C., Timmermans, P. B. M. W. M. (1990) Nonpeptide angiotensin II receptor antagonists: N-[(benzyloxy)benzyl]imidazoles and related compounds as potent antihypertensives. J. Med. Chem. 33: 1330–1336

Duncia, J. V., Chiu, A. T., Carini, D. J., Gregory, G. B., Johnson, A. L., Price, W. A., Wells, G. J., Wong, P. C., Calabrese, J. C., Timmermans, P. B. M. W. M. (1990) The discovery of potent nonpeptide angiotensin II receptor antagonist: a new class of potent antihypertensives. J. Med. Chem. 33: 1312–1329

Gairns, R. S., Grant, R. D., Moody, C. J., Rees, C. W., Tsoi, S. C. (1986) Synthesis of fused $1\lambda^4$,2-thiazines (2-azathiabenzenes). J. Chem. Soc. Perkin Trans. 13: 483–489

Keenan, R. M., Weinstock, J., Finkelstein, J. A., Franz, R. G., Gaitanopoulos, D. E., Girard, G. R., Hill, D. T., Morgan, T. M., Samanen, J. M., Peishoff, C. E., Tucker, L. M., Aiyar, N., Griffin, E. Ohlstein, E. H., Stack, E. J., Weidley, E. F., Edwards, R. M. (1993) Potent nonpeptide angiotensin II receptor antagonists. 2. 1-(Carboxybenzyl)imidazole-5-acrylic acids. J. Med. Chem. 36: 1880–1892

Lefeuvre, A. (1966) Application of diethyl (phenylthio) malonate in the synthesis of heterocycles. Chem. Abstr. 69: 35898a

Maxwell, J. R., Wasdahl, D. A., Wolfson, A. C., Stenberg, V. I. (1984) Synthesis of 5-aryl-2H-tetrazoles, 5-aryl-2H-tetrazole-2-acetic acids, and [(4-phenyl-5-aryl-4H-1,2,4-triazol-3-yl)thio] acetic acids as possible superoxide scavengers and antiinflammatory agents. J. Med. Chem. 27: 1565–1570

Milanian, I., Mahmoudian, M., Pousti, Z. (1990) Effect of imipramine on ganglionic transmission in guinea-pig ileum in vitro. Asia Pac. J. Pharmacol. 5: 127–130

Paul, R. Menschik, J. (1979) Synthesis of two novel bicyclic systems, imidazo[1,5-d]-as-triazine and imidazo[1,2-d]-as-triazine. J. Heterocycl. Chem. 16: 277–282

Shafiee, A., Hadizadeh, F., Foroumadi, A. (1997) Synthesis of subsitituted-pyrrolo-[2,3-d]imidazoles and substituted-pyrrolo-[3,2-d]imidazoles. Indian J. Chem. 36B: 813–815

Yanagisawa, H., Amemiya, Y., Kanazaki, T., Shimoji, Y., Fujimoto, K., Kitahara, Y., Sada, T., Mizuno, M., Ikeda, M., Miyamoto, S., Furukawa, Y., Koike, H. (1996) Nonpeptide angiotensin II receptor antagonists: synthesis, biological activities, and structure-activity relationships of imidazole-5-carboxylic acids bearing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position and their related compounds. J. Med. Chem. 39: 323–338

Wong, P. C., Price., W. A., Chiu, A. T., Carini, D. J., Duncia, J. V., Johnson, A. L., Wexler, R. R., Timmermans, P. B. M. W. M. (1990) Nonpeptide angiotensin II receptor antagonists studies with EXP9270 and DuP 753. Hypertension 15: 823–834