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Synthesis and antagonistic activity of four new 2-alkyl-*N*-biphenyl fused imidazoles on angiotensin II receptors

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Abstract

In the current study, four new 2-alkyl-*N*-biphenyl fused imidazoles were synthesized and the pharmacological properties of these compounds as angiotensin II antagonists were studied. First, the potency of the synthesized compounds on guinea-pig ileum was evaluated and the vasopressor effect of the most potent compound **6a** was compared with losartan on isolated perfused rat kidney. The antagonistic activity of compound **6a** (sodium 2-propyl-5-carbomethoxy-1-[(biphenyl-4-yl)methyl]pyrrolo[3,2-d]imidazole-2′-carboxylate) on angiotensin II receptors was greater than the other synthesized compounds and in isolated perfused rat kidney was similar to losartan.

1. Introduction

The most important effector component of the rennin–angiotensin system, angiotensin II [1], is synthesized by a cascade of reactions in response to fall in blood pressure and loss of fluids and salt from the body [2]. This vasopressor octapeptide plays an important role in the homeostatic regulation of water balance [2]. Despite the clinical efficacy of the angiotensin converting enzyme (ACE) inhibitors, these compounds induce side effects such as dry cough and angioedema, caused by potentiation of bradykinin, substance P and other active peptides, therefore nonpeptide angiotensin II receptor antagonists are of interest [3,4]. As the angiotensin II receptors are the final site of action in the system [5], a receptor antagonist would provide a direct approach to blocking the system [6]. Because angiotensin II can be formed through alternative pathways such as via angiotensin I chymases, which are not affected by ACE inhibiton [7], the selective blockade of angiotensin II receptors theoretically may inhibit the actions of angiotensin II more completely than ACE inhibition. The antihypertensive activity of 2-alkyl-*N*-biphenyl fused imidazoles as angiotensin II receptor antagonists has already been established [8,9]. In the current study, the angiotensin II antagonistic activity of four new 2-alkyl-*N*-biphenyl fused imidazoles were studied on guinea pig ileum and compared to losartan. Consequently, the antagonistic effect of the most potent compound **6a** was compared with losartan on isolated perfused rat kidney. When the isolated rat kidney is perfused at constant flow, changes in the perfusion pressure reflect the vascular resistance of the kidney vasculature without activation of homeostatic compensatory mechanisms.

2. Chemistry

The starting compounds, **1** and **4** were synthesized as reported previously [10]. Compounds **2** and **5** were synthesized through the hydrolysis of compounds **1** and **4**, respectively. The sodium salts of the acids **2** and **5** namely compounds **3** and **6** were prepared by neutralization of the corresponding acids with sodium hydrox-

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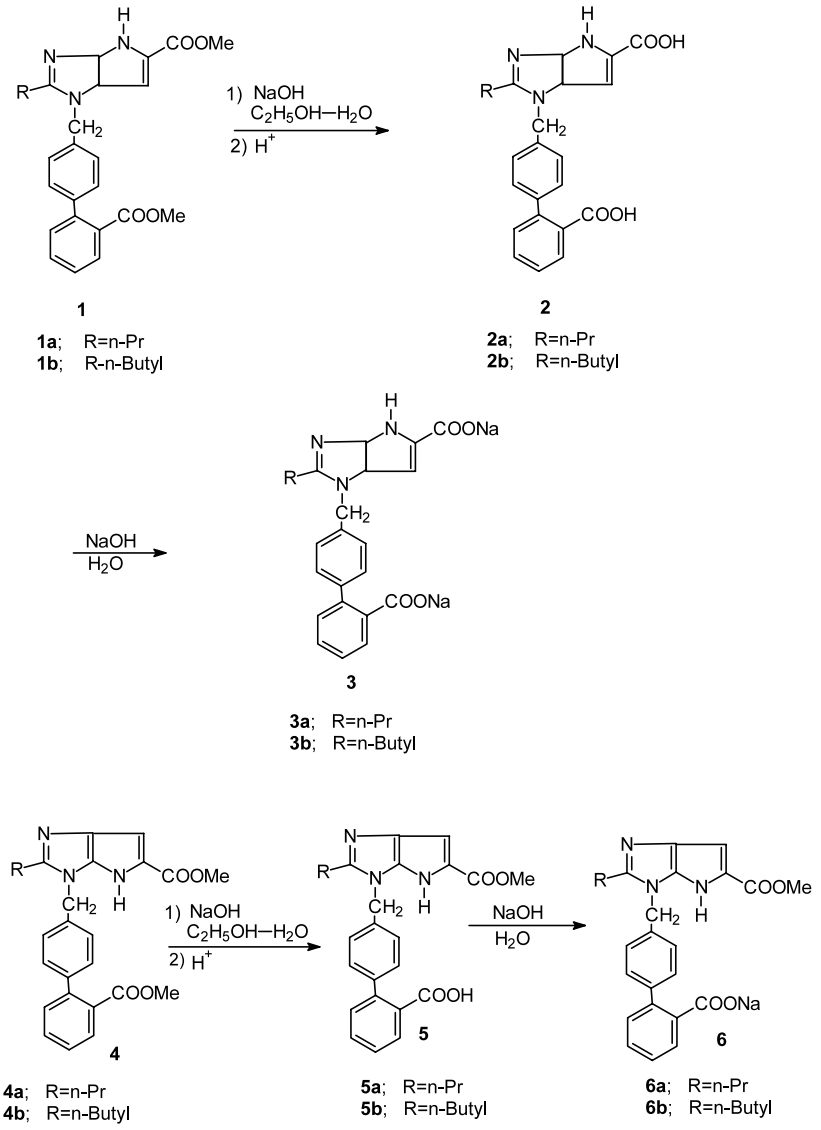

Fig. 1.

ide (Fig. 1). The structures of compounds **2a**, **2b**, **5a**, **5b** were confirmed by elemental analysis, IR, NMR and mass spectroscopy.

The ^{1}H-NMR of compounds **5** were in agreement with the suggested structures. In compounds **4b** the methyl esters at position 5 and 2′ appeared at 3.75 and 3.65 ppm, respectively. In compound **5b** the methyl ester appeared at 3.76 ppm, indicating that the ester at position 2′ is hydrolyzed to acid.

In addition, the mass spectrum fragmentation pattern of compound **5** (see Fig. 2) is also in agreement with the suggested structure.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin–Elmer Model 781 spectrograph. The ^{1}H-NMR spectra were obtained on a Varian 400 Unity Plus and chemical shifts (δ) were determined in ppm relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV.

3. Experimental procedures

3.1. Pharmacology

3.1.1. Guinea-pig ileum

Male guinea-pigs weighed (350–450 g) were killed by stunning and cutting the carotid artery. Segments of ileum 2 cm in length were removed and mounted in a 50 ml tissue bath containing oxygenated (95% O_2, 5% CO_2) Krebs bicarbonate solution kept at 37 °C. The isotonic contractions were recorded (NARCO physiograph model MK-III-s) with a resting tension of 0.5 g.The segments were allowed to equilibrate and were washed every 15 min. After a 60 min stabilization period, the

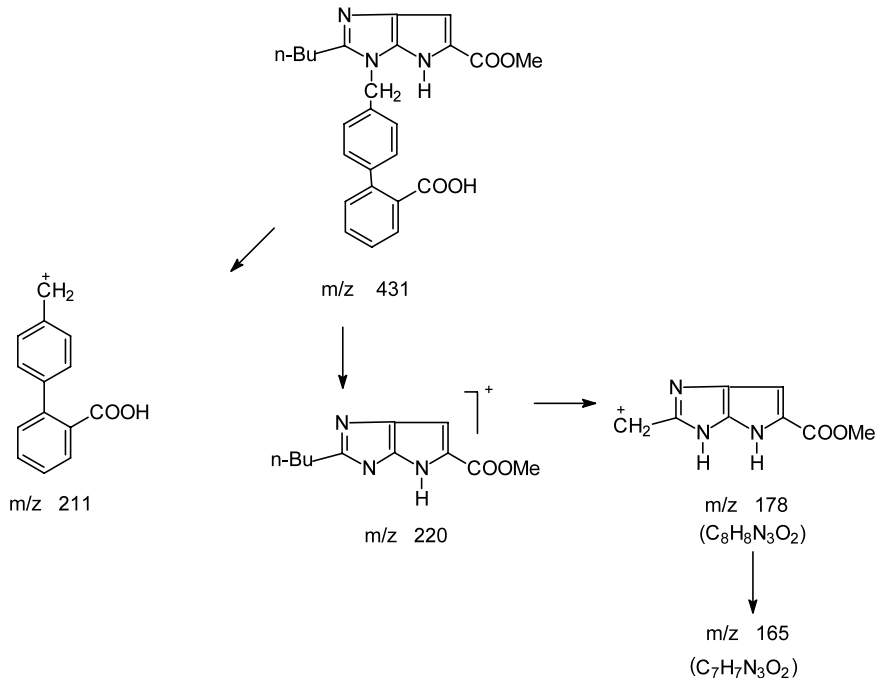

Fig. 2. Mass spectrum fragmentation pattern of compound **5b**.

response to angiotensin II was recorded cumulatively before and 13 min after adding each compound.

3.1.2. Isolated perfused rat kidney

Male Wistar rats (300–350 g) having free access to commercial pellet chow and tap water were anaesthetized with pentobarbital (50 mg kg^{-1}). The abdominal cavity was exposed by a ventricular incision, heparin was injected into the vena cava (500 U kg^{-1}) and renal artery was cannulated using a number 20 hypodermic needle with a polished tip via the superior mesenteric artery without disruption of flow. Perfusion was initiated in situ and continued with Tyrode's solution and equilibrated with 95% O_2 and 5% CO_2. Perfusion medium was fed to the kidney by means of a peristaltic pump (LKB, Varioperpex II) through PTFE tubings (Pharmacia Biotech, 18-8207-01) with a constant flow at 85–95 mmHg. The ligatures around the cannula were tied and kidney was removed and placed in a thermostated glass chamber.

Alterations in perfusion pressure, arising from changes in renal vascular resistance, were recorded on a Beckman polygraph (R-612) by means of a pressure transducer (Beckman, 4-327) situated parallel to perfusion cannula.

In order to observe antagonistic responses, the renal vasculature was perfused (30 min) by addition of different concentrations of antagonist to the perfusion medium reservoir. Subsequently, dose response curves were obtained by injection of increasing bolus doses of angiotensin II into the perfusion line. The injection of bolus doses of angiotensin was performed as described by Ebrahimi and Rouzrokh [11]. In brief, the injecting mechanism is known as six-way injection valve, a precisely machined manual or motorized valve located just before the kidney (Valco C22). The valve, which is mounted in the path of the perfusate, provides two flow paths. In the load position, the valve connects the pump directly to the kidney. Using a syringe, the sample contained the perfusion medium is injected into a loop which has a small defined volume. In the inject position, the sample which is in the loop at atmospheric pressure, is directly inserted into the flow path of the perfusate. Highly reproducible injections are achieved when the loop is completely filled with the sample.

Vasoconstriction was measured as the mean peak increase in perfusion pressure at each dose of angiotensin II measured as elevation from baseline. To avoid damage to renal vasculature throughout the study, doses of angiotensin II were used which kept the maximum perfusion pressure under 190 mmHg.

3.2. Synthesis

3.2.1. 2-Propyl-1-([(2′-carboxybiphenyl-4-yl)methyl]pyrrolo[2,3-d]imidazole-5-carboxylic acid (**2a**)

To a stirring solution of methyl 2-propyl-1-[(2′-carbomethoxybiphenyl-4-yl) methyl]pyrrolo [2,3-d]imidazole-5-carboxylate (**1a**) [10] (0.4 g, 0.93 mmol) in 4 ml methanol at room temperature sodium hydroxide (66 ml, 5% in ethanol–water 50:50) was added. The stirring was continued for 12 h. The pH of the solution was adjusted to 7–8 by the addition of hydrochloric acid

(3%).The solvent was evaporated; the residue was dissolved in water (33 ml) and filtered. The pH of the filtrate was adjusted to 4–5 with hydrochloric acid (3%). The precipitate was filtered and washed with ethanol (1 ml) to give 0.3 g (80%) of compound **2a**; M.p. 201–203 °C; IR (KBr) 1695 (C=O), 1680 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ: 12.43 (brs, 1H, N–H), 7.71 (dd, 1H, $J=8$, 1.5 Hz, aromatic), 7.55–7.25 (m, 7H, aromatic), 6.48 (s, 1H, CH pyrrole), 5.31 (s, 2H, N–CH_2), 2.78 (t, 2H, CH_2), 1.79 (m, 2H, CH_2), 0.94 (t, 3H,CH_3). *Anal*. Calc. for $C_{23}H_{21}N_3O_4$: C, 68.48; H, 5.21; N, 10.42. Found: C, 68.67; H, 5.01; N, 10.65%.

*3.2.1.1. Disodium 2-propyl-1-[(biphenyl-4-yl)methyl]pyrrolo[2,3-d]imidazole 2′,5-dicarboxylates (**3a**)*. Compound **2a** (0.2 g, 0.5 mmol) was dissolved in 0.1 normal sodium hydroxide solution (10 ml). The solvent was evaporated to give compound **3a**.

*3.2.2. 2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]pyrrolo[2,3-d]imidazole-5-carboxylic acid (**2b**)*

This compound was prepared from compound **1b** [10] using the procedure as described for compound **2a** in 76% yield. M.p. 160–162 °C; IR (KBr): 1695 (C=O), 1680 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ: 11.38 (brs, 1H, NH), 7.70 (d, 1H, aromatic), 7.41 (m, 7H, aromatic), 6.45 (s, 1H, CH pyrrole), 5.28 (s, 2H, CH_2N), 2.76 (t, 2H, CH_2), 1.50 (m, 4H, CH_2), 0.95 (t, 3H, CH_3); Mass: *m/z* (%) 373 ($M^+ - CO_2$, 15), 211(100), 162 (63), 120 (88). *Anal*. Calc. for $C_{24}H_{23}N_3O_4$: C, 69.06; H, 5.51; N, 10.07. Found: C, 69.28; H, 5.74; N, 10.21%.

*3.2.2.1. Disodium 2-butyl-1-[(biphenyl-4-yl)methyl]pyrrolo[2,3-d]imidazole 2′,5-dicarboxylates (**3b**)*. This compound was prepared using the procedure as described for compound **3a**.

*3.2.3. Methyl 2-propyl-1[(2′-carboxylbiphenyl-4-yl)methyl]pyrrolo[3,2-d]imidazole-5-carboxylate (**5a**)*

This compound was prepared from compound **4a** [10] using the procedure as described for compound **2a** in 90% yield. M.p. 274–275 °C; IR (KBr): 1700 (C=O), 1650 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ: 11.68 (brs, 1H, NH), 7.70 (d, 1H, aromatic), 7.50–7.05 (m, 7H, aromatic), 6.74 (s, 1H, CH pyrrole), 5.39 (s, 2H, CH_2N), 3.77 (s, 3H, OCH_3), 2.70 (t, 2H, CH_2), 1.95 (m, 2H, CH_2); 0.91 (t, 3H, CH_3); Mass: *m/z* (%): 417 (M^+, 7), 211 (100), 163 (42), 97 (9). *Anal*. Calc. for $C_{24}H_{23}N_3O_4$: C, 69.06; H, 5.51; N, 10.07. Found: C, 69.18; H, 5.72; N, 10.29%.

*3.2.3.1. Sodium 2-propyl-5-carbomethoxy-1-[(biphenyl-4-yl)methyl]pyrrolo[3,2-d]imidazole-2′-carboxylate (**6a**)*. Compound **5a** (0.17 g) was dissolved in 0.1 normal sodium hydroxide (4.1 ml). The solvent was evaporated to give compound **6a**.

*3.2.4. Methyl 2-butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]pyrrolo[3,2-d]imidazole-5-carboxylate (**5b**)*

This compound was prepared from compound **4b** [10] using the procedure as described for compound **5a** in 90% yield. M.p. 272–274 °C; IR (KBr): 1695 (C=O), 1660 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ: 11.94 (brs, 1H, NH), 7.71 (d, 1H, aromatic), 7.49 (m, 7H, aromatic), 6.74 (s, 1H, CH pyrrole), 5.38 (s, 2H, CH_2N), 3.76 (s, 3H, OCH_3), 2.65 (t, 2H, CH_2), 1.44 (m, 4H, CH_2); 0.83 (t, 3H, CH_3); Mass: *m/z* (%): 431 (M^+, 5), 220 (6), 211 (98), 178 (100), 165 (58), 152 (12). *Anal*. Calc. for $C_{25}H_{25}N_3O_4$: C, 69.60; H, 5.80; N, 9.74. Found: C, 69.51; H, 5.85; N, 9.81%.

*3.2.4.1. Sodium 2-butyl-5-carbomethoxy -1-[(biphenyl-4-yl)methyl]pyrrolo[3,2-d]imidazole-2′-carboxylate (**6b**)*. This compound was prepared from compound **5b** using the procedure as described for compound **6a**.

3.3. Solutions and drugs

All solutions were prepared freshly on the day of the experiment. Angiotensin II and losartan were purchased from Sigma, St. Louis, USA. All salts were of analytic grade and were obtained from Merck.

Tyrode solution (mM): KCl, 2.68; NaCl, 136.9; $MgCl_2$, 1.05; $NaHCO_3$, 11.9; NaH_2PO_4, 0.42; $CaCl_2$, 1.8; and glucose, 5.55.

Krebs bicarbonate solution (mM): NaCl, 118.4; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25; and dextrose 10.1.

3.4. Quantification and data analysis

The contractile responses to angiotensin II in the absence or presence of antagonists were expressed as the percentages of maximum contractile response to angiotensin II in the absence of antagonists. The antagonistic activity of the synthesized compounds was quantified by determination of pA_2 values in the guinea-pig ileum and

Table 1
pA_2 values for the antagonism of angiotensin II induced constriction of guinea-pig ileum by 2-alkyl-*N*-biphenyl fused imidazoles and losartan

Antagonist	pA_2
Compound **6a**	8.8 ± 0.3*
Compound **3a**	7.35 ± 0.1*
Compound **6b**	7.44 ± 0.1*
Compound **3b**	6.69 ± 0.3**
Losartan	9.93

*$P < 0.05$, **$P < 0.01$, compared to losartan.

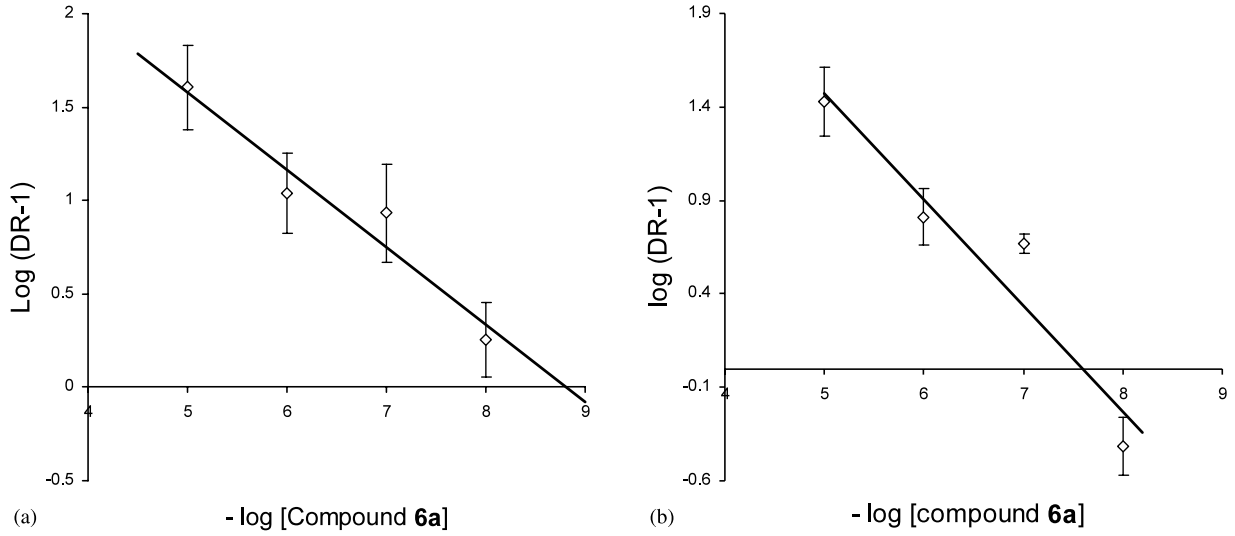

Fig. 3. Schild plots for the antagonism of vasoconstrictor effects of angiotensin II in the guinea-pig ileum (a) and isolated perfused rat kidney (b) by compound **6a**. Points are mean ± s.e. ($n = 3$). pA_2 value for compound **6a** in the ileum and perfused kidney were 8.8 ± 0.3 and 7.6 ± 0.2, respectively.

rat perfused kidney [12]. In brief, ED_{50} determined as dose producing 50% of the maximum response. Dose ratios were calculated by division of individual ED_{50} values obtained in the presence of antagonist. Values for pA_2 were obtained by plotting log (dose ratio-1) on the ordinate scale against log antagonist concentration on the abscissa scale; the intercept of the regression line on the abscissa scale giving the pA_2 value. pA_2 values for antagonists were compared using one-way ANOVA as presented in Table 1. Comparison of responses in the

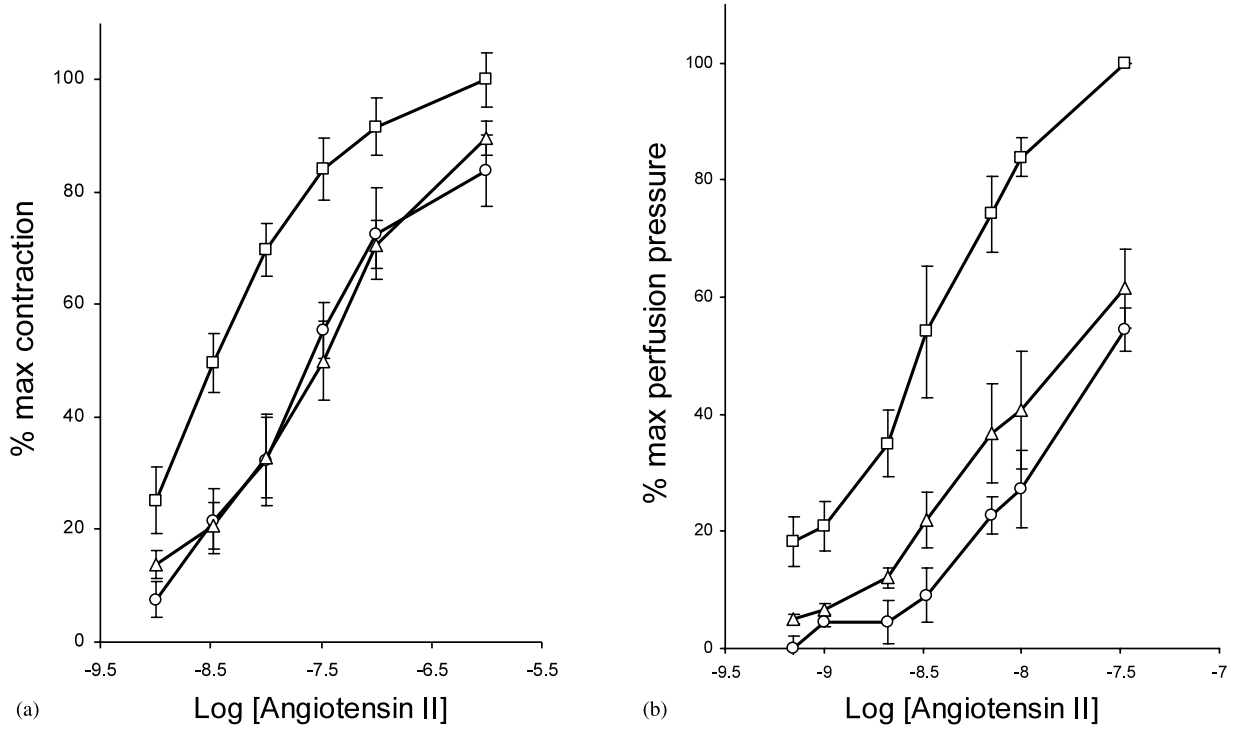

Fig. 4. Dose–response curves for vasoconstrictor responses to angiotensin II constructed in the absence of antagonist (□) and in presence of compound **6a** (○) (10^{-7} M) and losartan (△) (10^{-7} M) in guinea-pig ileum (a) and isolated perfused rat kidney (b). Points are mean responses expressed as a percentage of the maximum response (± s.e. $n = 3$). ED_{50} of angiotensin II (3.3×10^{-9} M), in presence of compound **6a** and losartan was 1.5×10^{-8} and 1.9×10^{-8} M, respectively ($P < 0.05$). In guinea-pig ileum, ED_{50} of angiotensin II (3.3×10^{-9} M), in presence of compound **6a** and losartan was 2.6×10^{-8} and 3.3×10^{-8} M, respectively ($P < 0.05$). Comparison of compound **6a** and losartan yielded no significant difference in guinea-pig ileum and rat isolated kidney ($P > 0.05$).

presence of antagonists was performed by means of independent sample t-test. Differences between groups were considered to be significant at $P < 0.05$.

4. Results and discussion

The antagonistic activity of compounds **3a**, **3b**, **6a**, **6b** and losartan in guinea-pig ileum are presented as pA_2 values in Table 1. The pA_2 values for compound **6a** and losartan in isolated perfused rat kidney were 7.6 ± 0.2 and 7.8 ± 0.3, respectively.

Fig. 3 shows the Schild plot of the angiotensin II antagonistic activity of compound **6a** on guinea-pig ileum and isolated perfused rat kidney. Fig. 4 shows the dose–response curves for vasopressor responses to angiotensin II in presence of compound **6a** (10^{-7} M) and losartan (10^{-7} M) in guinea-pig ileum and isolated perfused rat kidney revealing a right shift.

As it is clear from Table 1, compound **6a** has more potent antagonistic activity than compounds **6b**, **3a**, **3b** and less than losartan in the guinea-pig ileum. It seems that the antagonistic activities of both compound **6a** and losartan in isolated perfused rat kidney were less than their activities in guinea-pig ileum. Other authors have reported such tissue–specific and species–specific differences of antagonistic activity of nonpeptide angiotensin II antagonists [13] and even indicating possible involvement of tissue-dependent noncompetitive factor(s) [14]. Different theories have been proposed for this variation such as different subtypes of AT1 receptor [15] or diverse post receptor mechanisms [16]. Thus, although the major pharmacological actions of angiotensin II such as contraction of kidney vasculature [17] and guinea pig ileum are mediated by angiotensin AT1 receptors [18–21], it appears that cellular mechanisms responsible for angiotensin II induced contraction of smooth muscles differ from one tissue to another counting at least partially for different potency of antagonists in different tissues.

It is also observed that in guinea-pig ileum the compounds with a propyl side chain (**6a** and **3a**) had more antagonistic activity as angiotensin II antagonists than the compounds, with a butyl group side chain (**6b** and **3b**, respectively).

In conclusion, the antagonistic activity of compound **6a** on angiotensin II receptors was greater than other synthesized compounds and in isolated perfused rat kidney was similar to losartan.

Acknowledgements

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