Synthesis and Antihypertensive Activity of Some Aminoguanidine and Amidrazone Derivatives

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The synthesis of some benzylidenaminoguanidine, amidrazone and 1,2,4-triazole derivatives has been described. The antihypertensive activity of these compounds has been evaluated on spontaneously hypertensive rats. The activity of the aminoguanidine derivatives was somewhat less pronounced than that of the reference drug guanabenz. Amidrazone derivatives showed remarkable antihypertensive properties, whereas the activity of the correspondent 1,2,4-triazole derivatives was of minor interest.

Synthese und antihypertensive Aktivität von Aminoguanidin- und Amidrazon-Derivaten

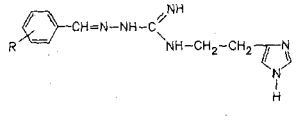
Es wird die Synthese einiger Benzylidenaminoguanidin-, Amidrazon- und 1,2,4-Triazol-Derivate beschrieben und deren antihypertensive Aktivität bei spontanhypertensiven Ratten (SHR) untersucht. Die Aktivität der Benzylidenaminoguanidin-Derivate war etwas geringer als jene der Referenzsubstanz Guanabenz. Die Amidrazone zeigten eine bemerkenswert antihypertensive Wirkung, während die Aktivität der entsprechenden 1,2,4-Triazolverbindungen weniger interessant war.

A series of arylidenaminoguanidine derivatives, structurally related to the clonidine-like antihypertensive drug guanabenz **1** have been described previously[1]. The chemical structure of these compounds **2** is characterized by a substituted benzylidenaminoguanidine moiety.

The guanidine molecule is further substituted in position 3 with a 4-ethylimidazole residue. Because some of these compounds explicated an interesting antihypertensive activity on the spontaneously hypertensive rats (SHR), we have tested two newly synthesized derivatives **2a, b** (Tab. 1) in order to verify whether the different substitution on the benzene ring produces an increased activity. Furthermore, in order to evaluate the significance of the 4-ethylimidazole moiety towards the activity, we introduced this residue as substituent in 2,6-dichlorophenylthiourea, which explicates antihypertensive activity in hypertensive rats[2]. The resulting compound **3** is devoid of activity.

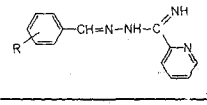
On the basis of these findings we synthesized and tested for antihypertensive activity some other compounds **4a, c** (Tab. 2) in which the aminoguanidine group has been substantially modified, to obtain an amidrazone structure.

The correspondent 1,2,4-triazole derivatives **5a, b** (Tab. 3) have been also synthesized and tested.



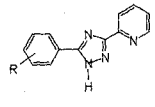
Tab. 1

Comp.	R	Yield (%)	M.p. (°C)	TLC
2a	2-Cl	80	195	n-PrOH/H_2O/AcOH (70:30:1)
2b	2,4 $(CH_3)_2$	72	190	n-BuOH/H_2O/AcOH (70:30:1)



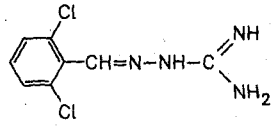
Tab. 2

Comp.	R	Yield (%)	M.p. (°C)	TLC
4a	2-Cl	67	116	EtOH/AcOEt (90:10)
4b	2-Br	76	127	EtOH/AcOEt (90:10)
4c[6]	2,6 $(Cl)_2$	84	125	EtOH/AcOEt (90:10)



Tab. 3

Comp.	R	Yield (%)	M.p. (°C)	TLC
5a	2-Cl	Method A: 33 Method B: 75	167	EtOH/AcOEt (70:30)
5b	2,6 $(Cl)_2$	Method A: 35 Method B: 81	255	EtOH/AcOEt (70:30)



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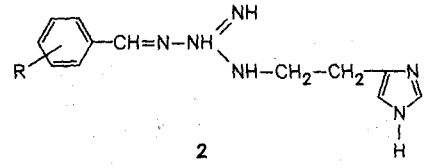

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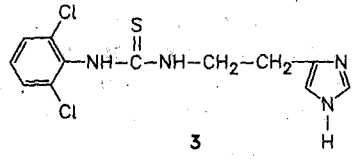

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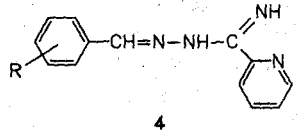

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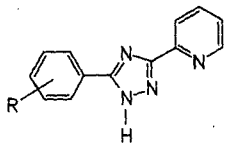

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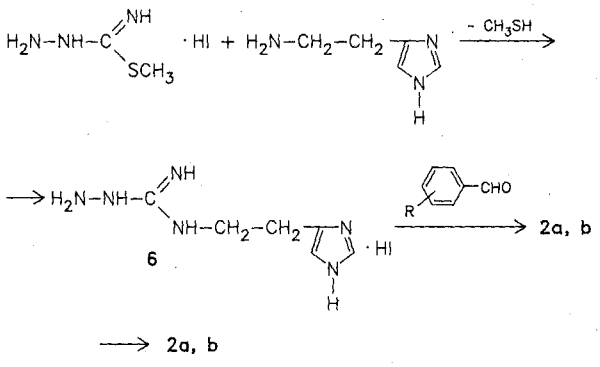
Chemistry

The synthesis of the arylidenaminoguanidine derivatives **2a, b** was carried out (Scheme 1) by aminolysis of S-methyl-isothiosemicarbazide hydroiodide with histamine, according to the general procedure described by *Kirsten* and *Smith*[3] followed by condensation of the aminoguanidine derivative **6**[4] with the appropriate aromatic aldehydes.

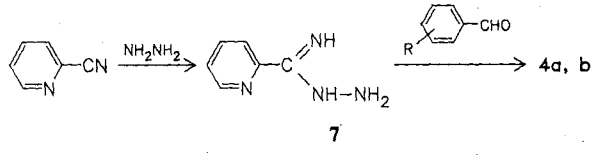
SCHEME 1



The thiourea derivative **3** has been synthesized by direct reaction between 2,6-dichlorophenylisothiocyanate and histamine.

The N^1-aryliden-2-pyridincarboxyamidrazone derivatives **4a–c** were prepared according to Scheme 2.

SCHEME 2



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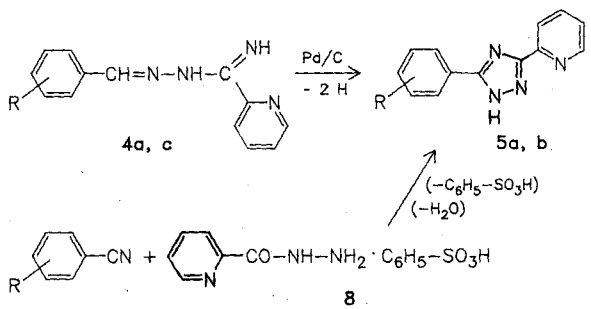
2-Pyridincarboxyamidrazone **7** was prepared by direct action of hydrazine on 2-cyanopyridine, according to *Case*[5]. The reaction of **7** with aromatic aldehydes yielded the derivatives **4a–c**. The azomethine structure was assigned to the compounds for which the ^{1}H-NMR spectra exhibited the typical low field –CH=N– signal in agreement with our previous work[6].

The 1,2,4-triazole derivatives **5a, b** were prepared by dehydrogenating[6, 7] the N^1-aryliden-2-pyridincarboxyamidrazone derivatives **4a, c** (Scheme 3).

The same compounds have been obtained (Scheme 3) through the reaction between 2-pyridincarboxyhydrazide benzenesulphonate **8** and the appropriate benzonitrile, according to *Pott's* method[6, 8]. Compounds **4c** and **5b** have been described by us[6]. The structures of the prepared compounds were confirmed by elemental analysis and IR- and NMR-spectra.

SCHEME 3



Results

The results, obtained examining the effects in SHR of the single i. p. administration of compounds **2a, b** in comparison with guanabenz, are illustrated in Fig. 1. The dosage of the tested compounds was 20 mg/Kg **(2a)** and 30 mg/Kg **(2b)**, on the basis of preliminary experiments.

Dosage levels greater than the employed dosage produced side effects such as sedation.

Guanabenz was used as a reference drug at the 0.2 mg/Kg dosage. After administration of compounds **2a** and **2b** a prolonged significant reduction of the blood pressure was observed. The activity of **2a** appears more pronounced at 30 min and decreases afterwards. Compound **2b** caused a reduction of blood pressure which reached its maximum at 30 min and retained its intensity during all the experiment. The activity of guanabenz is evident at low dosage but is more pronounced only at 90 min after the administration.

At comparable dosage compound **3** did not explicate any antihypertensive activity. Interestingly, the amidrazone derivatives **4a–c** showed a remarkable activity. These compounds and the 1,2,4-triazole derivatives **5a, b** have been administered intraperitoneally in SHR at the single dosage level of 27 μmol/Kg as a preliminary test.

The effects of **4a–c** on the blood pressure are shown in Fig. 2. The antihypertensive action of these compounds appears pronounced and long lasting.

On the other hand, compounds **5a** and **5b**, at the same dosage level, produced a reduction of blood pressure which reached its maximum at 30 min and which rapidly decreased afterwards.

Discussion and conclusions

From our results it appears that the two newly synthesized analogues of guanabenz, **2a, b** possess antihypertensive properties. The magnitude of their effects after acute i. p. administration of single doses is somewhat less pronounced than that of an optimal dosage of guanabenz in the same experimental conditions (Fig. 1). However, interesting differences are evident between the action of compounds **2a, b** and that of guanabenz. After administration of **2a, b**, the antihypertensive response is evident at 30 min, whereas guanabenz produces the greatest reduction of the blood pressure at 90 min after the treatment. Furthermore, compound **2b**

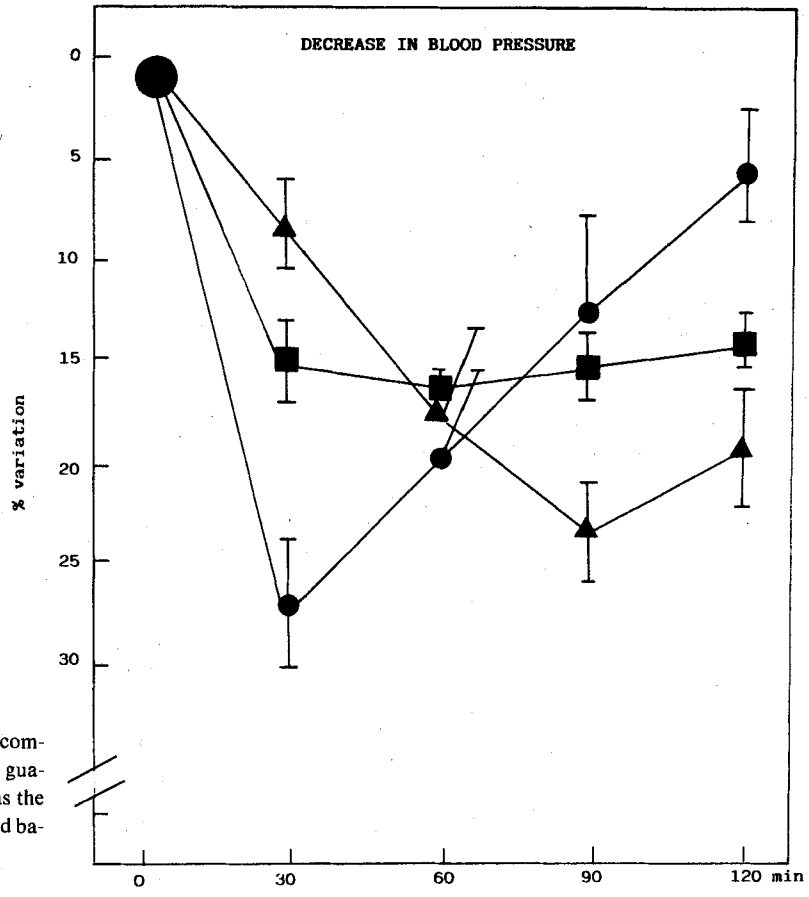


Fig. 1.
Time-dependency of the blood pressure lowering effects of compounds **2a** (20 mg/Kg; ●—●), **2b** (30 mg/Kg ■—■) and guanabenz (0.2 mg/kg ▲—▲) into groups of 4 rats expressed as the mean percent variation ± S. E. M. with respect to the stabilized basal value obtained before treatment.

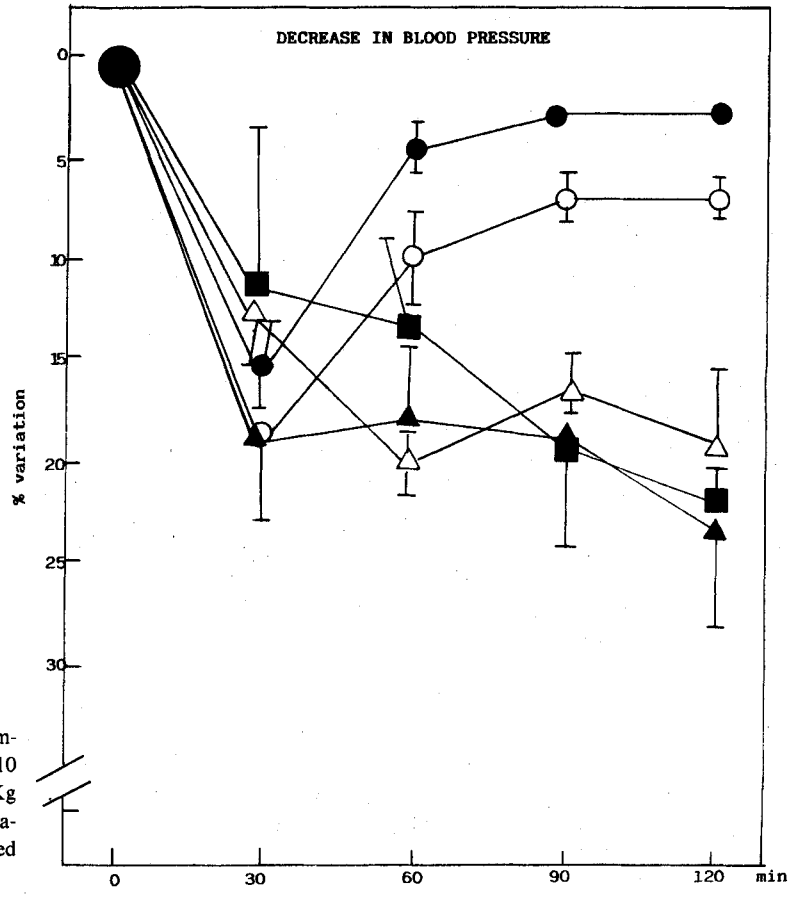


Fig. 2.
Time-dependency of the blood pressure lowering effects of compounds **4a** (6.98 mg/Kg ▲—▲), **4b** (8.18 mg/Kg △—△), **4c** (10 mg/Kg ■—■), **5a**, (6.93 mg/Kg ●—●) and **5b** (7.86 mg/Kg ○—○) into groups of 4 rats expressed as the mean percent variation ± S. E. M with respect to the stabilized basal value obtained before treatment.

shows a more prolonged activity since no variation of the initially observed maximum activity could be detected for 120 min after the treatment. The antihypertensive effects of **2a, b** and of guanabenz are associated with bradycardia, instead of being accompanied by reflex tachycardia. This finding suggests, among other possible mechanisms, a preferential action of compounds **2a, b** on the central nervous system. The 4-ethylimidazole moiety which characterizes the tested compounds produces a reduction of the potency in comparison with the parent drug guanabenz.

Interestingly, the presence of the 4-ethylimidazole moiety in compound **3** abolishes the antihypertensive activity of the parent compound 2,6-dichlorophenylthiourea.

In order to individuate other antihypertensive compounds structurally related to guanabenz we synthesized and tested the amidrazone derivatives **4a–c**. These compounds possess remarkable antihypertensive properties as regards both response intensity and duration (Fig. 2). These findings encourages further investigations on this class of compounds in order to find other active amidrazone derivatives. The antihypertensive activity of 1,2,4-triazoles **5a, b** appears of minor interest but proper substitutions at the triazole nucleous level may be attempted in order to improve at least the transport characteristics of these compounds.

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Experimental part

A) Chemistry

Melting points: Büchi apparatus, not corrected. – IR-Spectra: Perkin Elmer 399. – NMR-Spectra: FT on a 80 MHz Bruker WP 80 spectrometer, DMSO/DSS int.stand. – TLC: 0.25 mm precoated silica gel plates with GF 254 indicator, detection by UV. – The results for the elemental analysis of C,H,N were within ± 0.4 % of the calculated values.

1-(4-Imidazolylethyl)-3-[(2-chlorobenzyliden)amino]guanidine hydroiodide **(2a)**

A mixture of 1 g (3.3 mmol) of 1-(4-imidazolylethyl)-3-aminoguanidine hydroiodide[4] and 0.46 g (3.3 mmol) of 2-chlorobenzaldehyde was refluxed in EtOH (20 ml) for 2 h. The solvent was evaporated i. vac. and the residue was recrystallized from EtOH/Et_2O to give 1.1 g **2a**. – IR (nujol; cm^{-1}): 3350; 3300; 3220; 3180; 2720; 1660; 1640; 1600; 1585. – ^{1}H-NMR: δ (ppm) = 2.91 (broad t, $-CH_2$; J = 7 Hz), 3.63 (broad t, $-CH_2$; J = 7 Hz), 7.07 (d, H-5 imid.; J = 1.0), 7.40–7.65 (m, H-3, H-4, H-5 arom;). 7.81 (d, H-2 imid.; J = 1.0), 8.24–8.42 (m, H-6 arom.), 8.63 (–CH=N–). – ($C_{13}H_{15}ClN_6 \cdot HI$): C,H,N.

1-(4-Imidazolylethyl)-3-[(2,4-dimethylbenzyliden)amino]guanidine hydroiodide **(2b)**

0.8 g (2.7 mmol) of 1-(4-imidazolylethyl)-3-aminoguanidine hydroiodide[4] and 0.36 g (2.7 mmol) of 2,4-dimethylbenzaldehyde in 20 ml of EtOH were heated under reflux for 3 h. The solvent was evaporated i. vac. and the residue was recrystallized from absol. EtOH to obtain 0.8 g **2b**. – IR (nujol; cm^{-1}): 3330; 3290, 3240; 3140; 2720; 1660; 1640; 1600; 1585. – ^{1}H-NMR: δ (ppm): 2.35 (s, $-CH_3$), 2.44 (s, $-CH_3$), 2.90 (broad t, $-CH_2$; J = 6 Hz), 3.61 (broad t, $-CH_2$; J = 6 Hz), 7.05 (d, H-5 imid.; J = 1.1 Hz), 7.12 (pseudo s, H-3 arom. overlapping with H-5 arom.), 7.15 (pseudo d, partially hidden, H-5 arom.), 7.76 (d, H-2 imid.; J = 1.1 Hz), 8.01 (pseudo d, H-6 arom.; J = 8.5 Hz), 8.49 (–CH=N–). – ($C_{15}H_{20}N_6 \cdot HI$): C,H,N.

N-(2,6-dichlorophenyl)-N^1-(4-imidazolylethyl)-thiourea **(3)**

4.1 g (20 mmol) of 2,6-dichlorophenylisothiocyanate and 2.2 g (20 mmol) of histamine were refluxed in chloroform (50 ml) for 5 h. After cooling the precipitate was collected by filtration and recrystallized from EtOH to afford 4.2 g (67 %) of 3; m. p. 188 °C. – IR (nujol; cm^{-1}): 3200; 3040; 1585; 1130. – ^{1}H-NMR: δ (ppm) = 2.80 (broad t, $-CH_2$; J = 6 Hz), 3.65 (broad t, $-CH_2$; J = 6 Hz), 6.87 (pseudo s, H-4 imid.), 7.25–7.63 (m, H-3, H-4, H-5 arom.), 7.55 (d, H-2 imid.; J = 1.2 Hz), 7.98 (broad resonance –NH–). – ($C_{12}H_{12}Cl_2N_4S$): C,H,N.

N^1-(2-Chlorobenzyliden)-2-pyridincarboxyamidrazone **(4a)**

1.5 g (11 mmol) of 2-pyridincarboxyamidrazone[5] and 1.5 g (11 mmol) of 2-chlorobenzaldehyde in 30 ml of absol. EtOH were heated under reflux for 2 h. After cooling the precipitate was filtered and recrystallized from ethanol to afford 1.9 g **4a**. – IR (nujol cm^{-1}): 3510; 3395; 3050; 2720; 1630; 1580; 1560; 1520. – ^{1}H-NMR: δ (ppm) = 7.26 (broad, –NH–), 7.36–7.61 (m, H-3, H-4, H-5), 7.60 (partially hidden m, H-5 pyr; $J_{5,4}$ pyr = 7.2 Hz; $J_{5,6}$ pyr = 4.9 Hz; $J_{5,3}$ pyr 1.1 Hz), 7.99 (m, H-4 pyr; $J_{4,3} = J_{4,5}$ pyr = 7.6 Hz; $J_{4,6}$ pyr = 1.8 Hz), 8.25–8.49 (H-3 pyr, H-6 overlapping m), 8.72 (H-6 pyr; $J_{6,5}$ pyr = 4.9 Hz; $J_{6,4}$ pyr = 1.8 Hz; $J_{6,3}$ = 0.9 Hz), 8.84 (–CH=N). – ($C_{13}H_{11}ClN_4$): C,H,N.

N^1-(2-Bromobenzyliden)-2-pyridincarboxyamidrazone **(4b)**

1.1 g (8 mmol) of 2-pyridincarboxyamidrazone[5] and 1.5 g (8 mmol) of 2-bromobenzaldehyde in 30 ml of absol. EtOH were refluxed for 2 h. The precipitate was collected by filtration and recrystallized from ethanol to obtain 1.7 g **4b**. – IR (nujol; cm^{-1}): 3500, 3380; 3050; 2720; 1620; 1580; 1560; 1530. – ^{1}H-NMR: δ (ppm) = 7.28 (broad, –NH–), 7.37–7.81 (m, H-3, H-4, H-5), 7.60 (partially hidden m, H-5 pyr; $J_{5,3}$ pyr = 1.4 Hz), 7.99 (m, H-4 pyr $J_{4,3}$ pyr = $J_{4,5}$ pyr = 7.6 Hz; $J_{4,6}$ pyr = 1.7 Hz), 8.32 (m, partially hidden, H-3 pyr; $J_{3,4}$ pyr = 7.85 Hz; $J_{3,5}$ pyr = $J_{3,6}$ pyr = 1.2 Hz), 8.39 (m, partially hidden, H-6; $J_{6,5}$ = 7.1 Hz; J = 2.7 Hz) 8.73 (H-6 pyr; $J_{6,5}$ pyr = 4.8 Hz; $J_{6,4}$ pyr = 1.7 Hz; $J_{6,3}$ pyr = 1.0 Hz), 8.79 (–CH=N). – ($C_{13}H_{11}BrN_4$): C,H,N.

3-(2-Pyridyl)-5-(2-chlorophenyl)-1,2,4-triazole **(5a)**

a) A mixture of 1.8 g (7 mmol) of N^1-(2-chlorobenzyliden)-2-pyridincarboxamidrazone **(4a)**, 15 ml of decahydronaphthalene and 0.6 g of 10 % Pd/C was heated for 5 h at 210 °C. After cooling the mixture was filtered and the solvent was removed. The residue was recrystallized from dilute EtOH to obtain 0.6 g of **5a**.

b) A mixture of 1.5 g (11 mmol) of 2-chlorobenzonitrile and 3.7 g (12 mmol) of 2-picolinylhydrazide benzenesulphonate **(8)** was heated for 4 h at 220 °C. After cooling the melt was extracted with NaOH (10 %). On neutralization of the extract with conc. HCl a precipitate was obtained, which was recrystallized from dilute EtOH yielding 2.1 g of **5a**. – IR (nujol; cm^{-1}): 3180; 3050; 2720; 1600. – ^{1}H-NMR: δ (ppm) = 7.44–7.76 (overlapping m, H-3, H-4, H-5, H-5 pyr.), 7.82–8.32 (overlapping m, H-6, H-3 pyr, H-4 pyr.), 8.79 (mc, H-6 pyr; the splitting suggest the presence of isomers). – ($C_{13}H_9ClN_4$): C,H,N.

B) Pharmacology

Spontaneously hypertensive rats (SHR) obtained from Charles-River (Italia) have been used. All tested animals were males, 180–250 g in body weight, with systolic blood pressure 175 mm Hg.

The blood pressure and heart rate effects were evaluated by the indirect tail-cuff method. Animals were acclimated to the blood pressure measuring protocol by daily measurements. The rats were placed in individual cages to restrict excess movement.

Before compound administration the animals were left undisturbed for at least 1 h in a thermostated room (32 °C). – After the initial blood pressure was obtained animals were injected intraperitoneally with the compounds.

Compounds **2a, b** were dissolved in bidistilled water, whereas compounds **3, 4a–c** and **5a, b** were suspended in carboxymethylcellulose. Changes in arterial blood pressure and heart rate were registered at 30, 60, 90 and 120 min after the treatment. – Each compound was administered to groups of 4 rats and the mean effect for each group was determined. – Control groups were included in the examination and showed no variation in the considered parameters. Guanabenz was used as a reference drug.

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