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Antihypertensive Effect of some Oxazolo[3,2-*a*]pyridines, Thiazolo[3,2-*a*]pyridines and Pyrido[2,1-*b*]oxazines in Conscious Spontaneously Hypertensive Rats

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Abstract

The antihypertensive activity of eighteen oxazolo[3,2-*a*]pyridine, thiazolo[3,2-*a*]pyridine and pyrido[2,1-*b*]oxazine derivatives has been evaluated in conscious spontaneously hypertensive rats (SHRs), and compared with that of nifedipine, used as reference.

At a dose of 50 mg kg^{-1} (i.p.) eleven compounds resulted in a significant reduction in mean arterial blood pressure; four of the eleven were particularly effective, resulting in significant hypotension more than 6 h after administration and an effect that was still apparent after 24 h. The hypotension induced by nifedipine gradually decreased, disappearing 6–8 h after administration. The long-lasting activity shown by these compounds is, in general, not accompanied by reflex tachycardia. Intraperitoneal administration of two oxazolo[3,2-*a*]pyridine derivatives and two pyrido[2,1-*b*]oxazine derivatives resulted in potent and long-lasting antihypertensive action in SHRs.

Further studies on the mechanism of action of these derivatives might help the determination of better structure–activity correlations and the design, synthesis and evaluation of better antihypertensive agents.

An increase in vascular resistance constitutes a primary haemodynamic disorder leading to arterial hypertension (Freis 1960). Reduction of blood pressure by reduction of total peripheral resistance is a priority objective in the treatment of this pathology. This reduction can be achieved with drugs belonging to several families of therapeutic agents: calcium antagonists, ACE inhibitors, α-adrenergic blockers and K^+-channel openers (Klaus 1992; Stumpe 1992; Guidelines Subcommittee 1993).

The 1,4-dihydropyridine calcium antagonists are widely accepted as first-line antihypertensive agents. Nifedipine is the prototype of this class and its efficacy and safety in hypertension have long been recognized (Cauvin et al 1983; Sorkim et al 1985). In recent years, however, the reflex tachycardia and the short-acting effect of nifedipine have prompted the development of new dihydropyridine derivatives with the aim of increasing vascular selectivity (Ohtsuka et al 1989; Takada et al 1991; Kanda et al 1992) and consequently of removing the negative inotropic effect on cardiac muscle (Klaus 1992) and of obtaining effective long-lasting antihypertensive derivatives with more prolonged plasma half-life (Julius 1988; Rafterty et al 1991). In the same way, the formulation of nifedipine sustained-release preparations has been developed to overcome its relatively short duration of action and to offer the additional advantage of better patient acceptability (Unidipin Co-operative Study group 1992).

In our search for new antihypertensive agents we have prepared and tested several oxazolo[3,2-*a*]pyridines (San Feliciano et al 1991; Caballero et al 1993, 1996), thiazolo[3,2-*a*]pyridines and pyrido[2,1-*b*]oxazines (San Feliciano et al 1992) to determine the main structural requirements of antihypertensive agents and to discover the most active members of these new families.

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Some time ago we communicated the results of preliminary studies on the antihypertensive and bradycardic activity observed until 5 h after administration of some pyrido[2,1-*b*]oxazines (San Feliciano et al 1992). In this paper we report results obtained from in-vivo evaluation of the antihypertensive activity of eighteen new compounds. The structures of the compounds investigated are listed in Table 1.

Materials and Methods

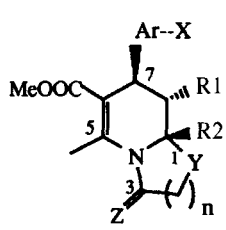
Antihypertensive activity in conscious animals

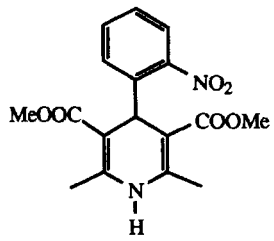
Experiments were performed with male adult spontaneously hypertensive rats (SHR; 20–30 weeks) from the Animal Department, Faculty of Pharmacy, University of Salamanca.

Two days before the experiment a polyethylene (PE-50) cannula was implanted in the left carotid artery under anaesthesia with sodium pentobarbital (40 mg kg^{-1}, i.p.). The cannula was exited subcutaneously at the back of the neck. After cannulation animals were housed separately with food and water freely available. This procedure enabled serial measurement of arterial blood pressure and heart rate in conscious, unrestrained rats.

After 48 h the arterial blood pressure was measured with a Letica pressure transducer connected to a PRS 205 amplifier of a Letica Polygraph series 4000. Heart rate was measured by means of a CAR 1000 cardiotachometer triggered by the arterial pressure pulse. After a period of 15 min, in which blood pressure and heart rate reached equilibrium, each compound was injected intraperitoneally as a single dose. The mean blood pressure and heart rate were monitored at 15 and

Table 1. The structures of compounds P2–P19 and nifedipine.





Nifedipine

Compound	X	Y	Z	R1	R2	Ar	n
P2	Cl	O	H_2	COOMe	Me	Phenyl	1
P3	Cl	O	H_2	COOEt	Me	Phenyl	1
P4	NO_2	O	H_2	COOMe	Me	Phenyl	1
P5	NO_2	O	H_2	COOEt	Me	Phenyl	1
P6	Cl	O	H_2	CH_2OH	Me	Phenyl	1
P7	NO_2	O	H_2	CH_2OH	Me	Phenyl	1
P8	H	O	H_2	COOMe	Me	2-Pyrroyl	1
P9	H	O	H_2	COOMe	Me	2-Thienyl	1
P10	H	O	H_2	COOMe	Me	2-Furyl	1
P11	H	O	H_2	COOMe	Me	2-Pyridyl	1
P12	H	O	H_2	H	H	Phenyl	1
P13	Cl	O	H_2	COOMe	Me	Phenyl	2
P14	NO_2	O	H_2	COOMe	Me	Phenyl	2
P15	NO_2	O	H_2	COOEt	Me	Phenyl	2
P16	Cl	O	O	COOMe	Me	Phenyl	1
P17	NO_2	O	O	COO*t*-Bu	Me	Phenyl	1
P18	NO_2	O	O	COOMe	Me	Phenyl	1
P19	Cl	S	H_2	COOMe	Me	Phenyl	1

30 min and 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after administration. Each animal was used for one experiment only. The figures depict only values measured up to 12 h.

An initial evaluation was performed by comparing the effects of 5-mg-kg^{-1} doses of nifedipine with those of 50-mg-kg^{-1} doses of the compounds to be tested. The most active compounds (P4, P5, P13 and P15; Table 1) were then assayed at three lower doses.

Drug administration

Intraperitoneal administration was chosen as a rapid means of administration and because of the limited amount of samples. The compounds were dissolved in an aqueous solution of carmellose and Tween 80, both at 0·1%, and administered at doses between 10 and 50 mg kg^{-1}. The vehicle (5 mL kg^{-1}) was administered to the control group. Nifedipine (Andreu) was used as the reference drug.

Expression and analysis of results

Modifications were expressed as mean values of arterial blood pressure (MAP, mmHg) or heart rate (beats min^{-1}). All data were expressed as the mean ± s.e.m. of at least six experiments. Statistical evaluation was performed by use of Student's *t*-test for unpaired values. The values displayed in figures as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ were significantly different from the control group.

ED40 (i.e. the dose of product required to reduce the initial blood pressure by 40 mmHg) was calculated from the dose–response–time curves of nifedipine and compounds P4, P5, P13 and P15; the potency of the compounds relative to nifedipine was determined by use of a computerized pharmacological calculation program (Tallarida & Murray 1984).

Results

Before drug administration the MAP and heart rate in the SHR were 154·4 ± 2·8 mmHg and 355·5 ± 7·6 beats min^{-1}, respectively (n = 160). The vehicle used in our experiments (carmellose and Tween 80, both at 0·1%) did not cause significant changes in MAP or heart rate (control group in corresponding figures and tables).

Changes in MAP and heart rate after intraperitoneal administration of nifedipine or compounds P2 to P19, are shown in Figs 1–5 and Tables 2 and 3 (data corresponding to 24 h post-administration are not included).

At a dose of 50 mg kg^{-1} (i.p.) compounds P2, P3, P4, P5, P7, P10, P13, P14, P15, P16 and P18 produced a significant reduction in MAP; compounds P6, P8, P9, P11, P12, P17 and P19 were inactive (results not shown). The greatest degree of hypotension was observed with P4, P5, P13 and P15; this led us to evaluate these products at smaller doses also.

Comparison of the results obtained at doses of 50 mg kg^{-1} active product and 5 mg kg^{-1} nifedipine showed there to be two main groups of compound. The first, including P7, P14 and P16 (Table 3). They resulted in maximum reduction of MAP in 15–30 min, and the effect disappeared 4–6 h after adminis-

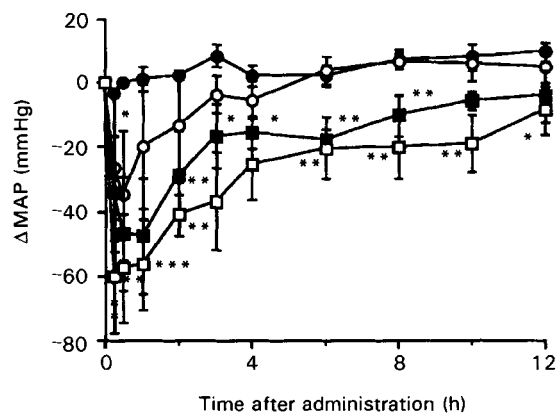


FIG. 1. Effect of intraperitoneal administration of vehicle (●) 4 mL kg^{-1} or nifedipine (○) 1 mg kg^{-1}, (■) 2·5 mg kg^{-1} or (□) 5 mg kg^{-1} on mean arterial blood pressure (MAP) in conscious SHRs. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with control group.

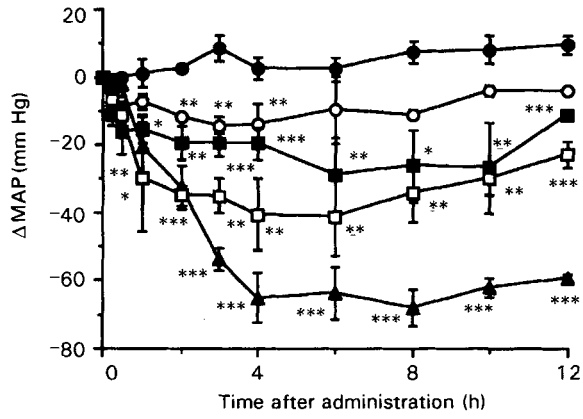


FIG. 2. Effect of intraperitoneal administration of vehicle (●) 4 mL kg^{-1} or P4 (○) 10 mg kg^{-1}, (■) 25 mg kg^{-1}, (□) 35 mg kg^{-1} or (▲) 40 mg kg^{-1} on mean arterial blood pressure (MAP) in conscious SHRs. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with control group.

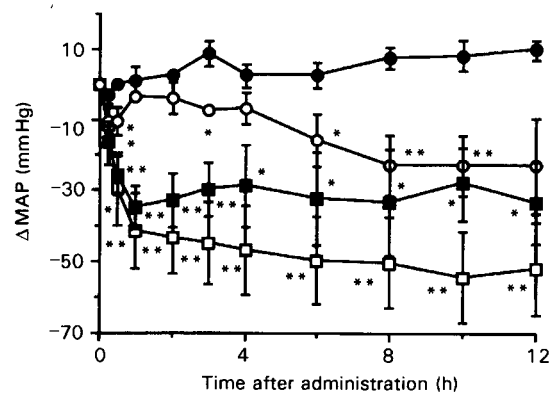


FIG. 3. Effect of intraperitoneal administration of vehicle (●) 4 mL kg^{-1} or P5 (○) 10 mg kg^{-1}, (■) 25 mg kg^{-1} or (□) 50 mg kg^{-1} on mean arterial blood pressure (MAP) and heart rate (HR) in conscious SHRs. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control group.

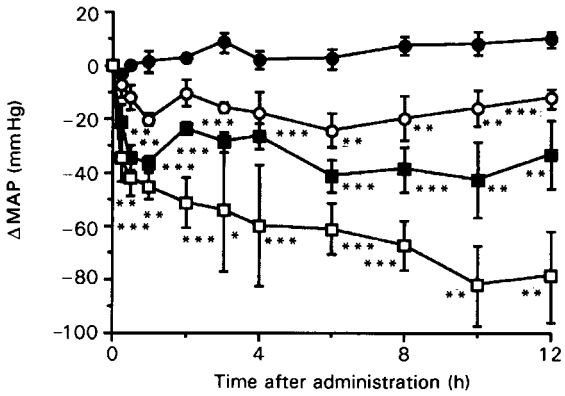


FIG. 4. Effect of intraperitoneal administration of vehicle (●) 4 mL kg^{-1} or P13 (○) 5 mg kg^{-1}, (■) 25 mg kg^{-1} or (□) 40 mg kg^{-1} on mean arterial blood pressure (MAP) in conscious SHRs. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with control group.

tration. The most active compound in this group, P14, resulted in less tachycardia than nifedipine (results not included).

The second group contained the remaining active compounds: P2, P3 (Table 3), P4 (Fig. 2), P5 (Fig. 3), P10 (Table 3), P13 (Fig. 4), P15 (Fig. 5) and P18 (Table 3); these led to a gradual and maintained reduction of MAP, maximum hypotension being reached in 3–6 h. The hypotension observed for compounds P3 (Table 3), P15 (Fig. 5) and P18 (Table 3) was characterized by an initial decrease followed by a slight

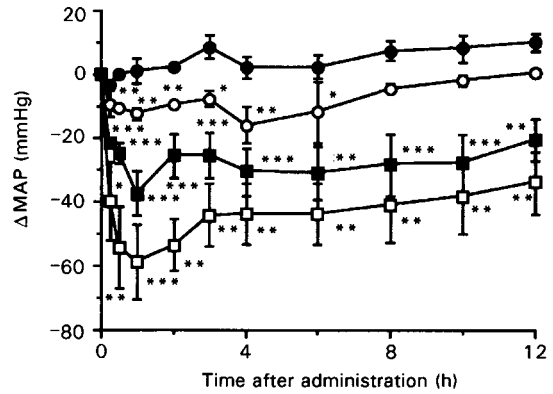


FIG. 5. Effect of intraperitoneal administration of vehicle (●) 4 mL kg^{-1} or P15 (○) 10 mg kg^{-1}, (■) 25 mg kg^{-1} or (□) 50 mg kg^{-1} on mean arterial blood pressure (MAP) in conscious SHRs. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with control group.

recovery of blood-pressure levels and finally a later and maintained decrease of MAP. The hypotension induced by P2 only was accompanied by a small, non-significant tachycardia (results not included). This product, the most toxic of all the compounds assayed, resulted in 50% lethality at 50 mg kg^{-1}.

The dose–response curves were constructed for the most potent and long-acting compounds (P4, P5, P13 and P15) and nifedipine. The course of MAP and heart rate after intraperitoneal administration of these compounds to SHRs is shown in Figs 1–5 and Table 2. These compounds resulted in significant hypotension for more than 6 h after administration. In contrast, the hypotension induced by nifedipine gradually decreased, and disappeared 6–8 h after administration. A significant decrease of MAP still remained, furthermore, 24 h after administration of 50 mg kg^{-1} P4 (-50 ± 15 mmHg), 25 and 50 mg kg^{-1} P5 (-19.9 ± 1.8 and -31.5 ± 12.2 mmHg, respectively), 40 mg kg^{-1} P13 (-45 ± 11.5 mmHg) and 50 mg kg^{-1} P15 (-26.7 ± 10.6 mmHg) (results not included in the figures).

In contrast with nifedipine, hypotension levels induced by the new compounds increased with time after administration and became significantly greater at 8, 12 and 24 h, as indicated by the relative potency values of P5 and P13 (Table 4) which demonstrate that the assayed compounds have longer-lasting hypotensive effects than nifedipine.

On comparing ED40 (12 h) values the hypotensive activity of products P5 and P13 was, furthermore, calculated to be 12·5 and 4·4 times greater than that of nifedipine (Table 5).

Table 2. Representative modification of heart rate (beats min^{-1}) obtained in conscious SHRs after intraperitoneal administration of vehicle (control group), nifedipine (5 mg kg^{-1}), P4 (50 mg kg^{-1}), P5 (50 mg kg^{-1}), P13 (40 mg kg^{-1}) or P15 (50 mg kg^{-1}).

Time (h)	Control	Nifedipine	P4	P5	P13	P15
0·25	+3·8 ± 5·5	+73 ± 35‡	−66 ± 13	−8·0 ± 14	−11·3 ± 17	+13 ± 10
0·50	−3·8 ± 3·8	+80 ± 13‡	−51 ± 23	−3·0 ± 18	+6·3 ± 13	+7·1 ± 11
1	−21 ± 14	+68 ± 8·8†	−17 ± 3·3*	+14 ± 8·0	−1·3 ± 12	−7·1 ± 16
2	−3·8 ± 8·5	+88 ± 20†	+25 ± 13	+17 ± 11	−6·3 ± 13	−7·9 ± 18
3	+19 ± 20	+87 ± 14†	+23 ± 24	+26 ± 13	+14 ± 9·8	+15 ± 16
4	+19 ± 11	+66 ± 35	−18 ± 3·2	+21 ± 13	+16 ± 19	+21 ± 23
6	+19 ± 20	+56 ± 27	−15 ± 16	+39 ± 16	+45 ± 10	+16 ± 17
8	+23 ± 12	+56 ± 27	−15 ± 16	+39 ± 16	+36 ± 15	+12 ± 18
10	+16 ± 8·9	+20 ± 15	−20 ± 10	+23 ± 12	+36 ± 12	+1·4 ± 18
12	+5·0 ± 7·4	+38 ± 25	−10 ± 10	+10 ± 11	+25 ± 20	+26 ± 15

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, significantly different from control group.

Table 3. Modification of mean arterial blood pressure (mmHg) obtained in conscious SHRs after intraperitoneal administration of vehicle (control), P2, P3, P7, P10, P14, P16 or P18.

Time (h)	Control	Compound (mg kg^{-1})						
		P2 (50)	P3 (50)	P7 (50)	P10 (50)	P14 (50)	P16 (50)	P18 (25)
0·25	−3·1 ± 1·0	1·5 ± 1·5	−10·2 ± 1·5*	−11·0 ± 1	0·7 ± 0·6	−20·2 ± 8·2*	−9·1 ± 8·2	−3·8 ± 5·6
0·50	−0·1 ± 0·9	0·7 ± 6·8	−17·7 ± 1·5*	−23·0 ± 8·5*	−6·7 ± 1·6	−35·2 ± 3·2‡	−16·1 ± 8·4	−16·8 ± 3·8
1	1·1 ± 3·9	3·3 ± 6·8	−6·6 ± 6·7	−25·0 ± 7·5*	−15·0 ± 1·5	−29·2 ± 4·2‡	−11·9 ± 3·1	−14·0 ± 3·2
2	2·5 ± 0·9	−5·5 ± 12	−9·7 ± 8·4	3·5 ± 3·5	−19·0 ± 1·0	−21·0 ± 4·0†	−6·9 ± 8·9	−8·3 ± 3·8
3	8·5 ± 3·6	−12·5 ± 7·5*	−10·0 ± 11	3·5 ± 3·5	−22·0 ± 1·0	−15·7 ± 2·7†	2·5 ± 5·8	−9·0 ± 9·2
4	2·3 ± 3·3	−14·0 ± 6·0*	−10·0 ± 13	2·5 ± 7·5	−21·0 ± 2·0	−18·7 ± 0·3†	1·8 ± 2·0	−18·3 ± 8·3
6	2·4 ± 3·5	−21·5 ± 8·5*	−9·3 ± 9·5	0·0 ± 0·0	−13·4 ± 1·4*	−14·7 ± 11*	−1·3 ± 8·9	−30·0 ± 9·5
8	7·4 ± 3·1	−26·5 ± 8·5†	−8·3 ± 9·5	−1·5 ± 8·5	−8·7 ± 2·9*	−10·7 ± 7·3*	5·1 ± 7·3	−25·7 ± 0·9
10	8·2 ± 4·2	−29·0 ± 11*	−4·3 ± 1·3*	1·5 ± 12	−5·3 ± 1·2*	−10·5 ± 5·5	5·2 ± 4·5	−21·3 ± 2·3
12	9·8 ± 2·8	−26·5 ± 8·5†	−1·0 ± 1·3*	7·0 ± 3·0	−3·0 ± 2·8*	−5·0 ± 0·0	3·5 ± 4·3	−17·0 ± 4·8

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, significantly different from control group.

Table 4. Time-evolution of antihypertensive potencies relative to nifedipine of compounds P4, P5, P13 and P15 in conscious SHRs.

Compound	Time after intraperitoneal administration (h)				
	1	4	8	12	24
Nifedipine	1	1	1	1	1
P4	0·036 (0·0013–0·08)*	0·239 (0·02–0·43)	0·286 (0·22–0·39)	0·371 (0·12–0·50)	0·213 (0·19–0·24)
P5	0·054 (0·013–0·12)	0·181 (0·06–0·23)	0·529 (0·28–1·68)	4·417 (0·69–9·54)	1·265 (1·12–2·45)
P13	0·075 (0·019–0·19)	0·657 (0·54–0·69)	1·042 (0·22–1·55)	13·45 (12·1–20·4)	12·48 (10·1–20·5)
P15	0·084 (0·056–0·12)	0·269 (0·22–0·33)	0·255 (0·18–0·41)	0·272 (0·22–0·36)	0·583 (0·45–0·75)

*Lower and upper confidence limits.

Within this group of the most active compounds, only P15 at a dose of 25 mg kg^{-1} (results not shown) caused slight tachycardia whereas some doses of P4 (35 and 40 mg kg^{-1}) and P5 (10 and 25 mg kg^{-1}) caused non-significant bradycardia. Table 2 lists the results obtained from a comparative study of modification of the heart rate by doses of nifedipine or these compounds.

Discussion

In SHRs the calcium permeability of smooth-muscle cell membranes is known to be abnormally high (Mulvany & Nyborg 1982; Sugiyama et al 1990; Kanda et al 1992). Vascular tone is believed to depend greatly on calcium influx in animal models of hypertension. 1,4-Dihydropyridines are clearly selective for vascular smooth muscle whereas other, non-1,4-dihydropyridine calcium antagonists such as diltiazem and verapamil have approximately equi-active potencies for vasodilation and cardiosupression (Taira 1987). SHRs therefore constitute a good experimental model for evaluation of new antihypertensive agents, and specifically nifedipine, acting by calcium antagonism.

Table 5. Time-evolution of ED40 (calculated dose, mg kg^{-1}, required to reduce the initial MAP by 40 mmHg) for nifedipine and compounds P4, P5, P13 and P15 in conscious SHRs.

Compound	Time after intraperitoneal administration (h)			
	1	4	8	12
Nifedipine	2·19	16·96	15·96	202·94
P4	85·43	48·14	51·42	44·03
P5	40·18	38·15	30·25	28·79
P13	29·16	23·40	15·50	16·21
P15	26·44	40·49	45·39	64·36

This study demonstrates the antihypertensive properties of new oxazolo-pyridine and pyrido-oxazine derivatives in SHRs after a single intraperitoneal dose, and confirms potent and lasting antihypertensive activity for four compounds (P4, P5, P13 and P15) which is still significant 12–24 h post-administration. Secondly, this study reveals that the most active compounds exert little influence on heart rate, in contrast with the appearance of reflex tachycardia with nifedipine. Some doses of P14 and P5 even induced bradycardia. Other calcium antagonists, e.g. diltiazem, provoke bradycardia in SHRs (Takada et al 1991).

Although initial in-vitro studies of a number of representative compounds (San Feliciano et al 1992) did not show calcium antagonist activity in smooth muscle, we cannot rule out the participation of a possible direct cardiodepressive effect in the hypotensive action. For the most active compounds, however, the bradycardia seems not to be responsible for the hypotensive activity, because some doses of these products, which did not modify the heart rate, were effective as hypotensive agents.

The more prolonged action and the different profile shown by the compounds in comparison with nifedipine suggest a clear difference in the mechanism of antihypertensive action.

Metabólites could be responsible for part of the potency and for the long-lasting antihypertensive action of compounds P4, P5, P13 and P15. Other factors, including bioavailability and serum protein binding, which is specially high for dihydropyridines (Follath & Taeschner 1988), can also influence the effect of these substances. These parameters will be analysed in future studies and will provide a more conclusive answer on the nature of the antihypertensive activity of these compounds.

From a comparison of the effect obtained with the compounds assayed and from the relative potencies of products P4, P5, P13 and P15 in reducing MAP, several structure–activity features can be deduced.

For the first family of compounds, the oxazolo[3,2-*a*]pyridines, we introduced the different structural changes represented in Fig. 1. To determine the role of ester groups we prepared some di-ester compounds P2–P5, hydroxy-esters P6 and P7 and the simplest monoester P12. The most potent and longest antihypertensive activity was found for di-ester derivatives; introduction of a hydroxy group in compound P7 resulted in behaviour similar to that of nifedipine, whereas the elimination of the ester group attached to an sp^3 carbon (P12), resulted in no appreciable modification of blood pressure levels. The incorporation of heteroaromatic substituents at C-7 was also examined. Usually the activity disappeared (P8, P9, P11); only the furyl derivative P10 caused a gradual decrease in MAP. The extent of this was less than that resulting from P2 or P4.

The influence of the size of the ring was evaluated on pyrido-oxazines P13, P14 and P15. The activity was conserved or improved in P13 and P15. The maximum effect of compound P14 was observed 30 min after administration; its behaviour was more similar to that of nifedipine.

The results of substitution of the oxygen atom by sulphur in the five-membered ring was evaluated with P19 only. This compound contained the other groups considered essential for activity, yet was completely inactive. We can, therefore, conclude that the presence of the oxygen atom in this part of the molecule is necessary for activity.

The synthesis and evaluation of P16–P18 was performed with the aim of facilitating their in-vivo hydrolytic degradation to a 1,4-dihydropyridine derivative. The loss of activity in P17 is in accord with the necessity of a small ester group. P16 and P18 showed a profile of activity similar to that of nifedipine, although after a preliminary period P18 provoked a reduction of the MAP that could be a result of the appearance of an unknown metabolite.

In conclusion, intraperitoneal administration of P4, P5, P13 and P15 resulted in a potent and long-lasting antihypertensive action in SHRs. During the course of hypotension these products exerted little influence on heart rate. We can also conclude that oxazolo-pyridine or pyrido-oxazine systems containing small ester groups, such as methyl or ethyl, and a nitrophenyl group as the aromatic substituent, seem to result in optimum activity. Further studies should be performed on the mechanism of action of oxazolo-pyridine and pyrido-oxazine derivatives as this might help the determination of better structure–activity correlations and the design, synthesis and evaluation of better antihypertensive agents among these classes of compound.

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