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Synthesis, antihypertensive and α-adrenoceptor activity of novel 2-aminoalkyl-3(2*H*)-pyridazinones*

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Summary — A number of 2-phenoxyalkylaminoalkyl- and 2-[1,4]benzodioxanylmethylaminoalkyl-3(2*H*)-pyridazinones were synthesized and tested for hypotensive and antihypertensive activity as well as for α_1- and α_2-adrenoceptor binding affinities. Some derivatives, *eg* **5.5**, **5.9**, **5.12**, **6.4** and **6.10**, showed strong hypotensive/antihypertensive effect and high affinity for α_2- and α_1-adrenoceptors. Compound **5.5** was selected for clinical study. In its mode of action a potassium channel opening activity may also be involved.

2-phenoxyalkylaminoalkyl-, 2-[1,4]benzodioxanylmethylaminoalkyl-3(2*H*)-pyridazinones / antihypertensive, α-adrenoceptor blocking activity

Introduction

The practical importance of selective α_1-adrenoceptor blockers, such as prazosine, doxazosine and trimazosine in the treatment of hypertension has already been well established. In addition, possible therapeutic value of peripherally acting postsynaptic α_2-adrenoceptor antagonists has also been emphasized [1].

Combining these types of mode of action in a single molecule also seemed to be a favourable approach to finding novel antihypertensive drugs.

In our program, the above findings as well as earlier results [2] were considered in designing new compounds with a novel type of combined mode of action.

Thus, a novel series of 2-aminoalkyl-3(2*H*)-pyridazinones containing [1,4]benzodioxanylmethyl or phenoxyalkyl group as potentially effective α-adrenoceptor blocking subunits was synthesized and tested for hypotensive and antihypertensive activity. Adrenoceptor effects of the potent compounds were also investigated in receptor binding studies.

Chemistry

2-Aminoalkyl-3(2*H*)-pyridazinones listed in tables I and II were prepared in 3 different paths as outlined in scheme 1.

In route A 3(2*H*)-pyridazinones **1** were *N*-alkylated with tertiary chloroalkylamines **2** (Method A–C) affording 2-aminoalkyl-3(2*H*)-pyridazinones **3** and **4**, *ie* the *N*-benzyl derivatives of **5** and **6**. The benzyl group was subsequently removed by catalytic hydrogenation (Method D).

In route B 2-chloropropyl-3(2*H*)-pyridazinones readily obtained from 3-hydroxyalkoxypyridazines by intramolecular $O \rightarrow N$ alkyl rearrangement [3], were reacted with the appropriate primary or secondary **8** amines (Method E) to give **5**, **6** or **9**, respectively.

Compounds unsubstituted on the pyridazinone moiety ($R^1 = R^2 = R^3 = H$) could also be prepared from the corresponding 6-chloro derivatives by hydrogenolytic dehalogenation (Method F).

*This work is dedicated to the memory of Géza Szilágyi
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Abbreviations: Bd: 2-[1,4]Benzodioxanylmethyl; Bzl: benzyl; DMF: dimethylformamide; EtOH: ethanol; EtOAc: ethyl acetate; HR: heart rate; id: intraduodenal; KOBu^t: potassium *tert*-butylate; MABP: mean arterial blood pressure; ME: 2-morpholinoethyl; MeOH: methanol; PE: 2-phenoxyethyl; PP: 3-phenoxypropyl; iPrOH: isopropanol; PTE: 2-(phenylthio)-ethyl; TBAB: tetrabutylammonium bromide.

Table I. List of 2-aminoalkyl-3(2*H*)-pyridazinones **3–6**, **9**.

Compd	*R¹*	*R²*	*R³*	*R⁴*	*R⁵*	*R⁶*	*n*	*Method*	*Salt*	*Mp (°C)*	*Yield (%)*
3.1	H	H	H	H	Bd	Bzl	1	A	HCl	164–166	53
3.2	$COOC_2H_5$	H	H	H	Bd	Bzl	1	A	HCl	153–155	50
3.3	morpholino	H	H	H	Bd	Bzl	1	A	HCl	154–156	93
3.4	4-(ethoxycarbonyl-1-piperazinyl	H	H	H	Bd	Bzl	1	A	HCl	162–165	43
3.5	3,5-dimethyl-1-pyrazol	H	H	H	Bd	Bzl	1	A	HCl	114–116	50
3.6	1-imidazolyl	H	H	H	Bd	Bzl	1	A	HCl	193–195	88
3.7	H	H	H	H	Bd	Bzl	2	B	base	oil	85
3.8	CH_3	H	H	H	Bd	Bzl	2	C	fumarate	oil	70
3.9	morpholino	H	H	H	Bd	Bzl	2	C	HCl	193–196	31
4.1	H	H	H	H	PE	Bzl	1	A	HCl	152–154	30
4.2	$COOC_2H_5$	H	H	H	PE	Bzl	1	A	HCl	88–89	39
4.3	morpholino	H	H	H	PE	Bzl	1	A	HCl	100–103	38
4.4	dimethylamino	H	H	H	PE	Bzl	1	A	base	oil	36
4.5	4-(ethoxycarbonyl)-1-piperazinyl	H	H	H	PE	Bzl	1	A	HCl	150–152	70
4.6	1-imidazolyl	H	H	H	PE	Bzl	1	A	HCl	153–156	80
4.7	3,5-dimethyl-1-pyrazolyl	H	H	H	PE	Bzl	1	A	HCl	188–189	76
4.8	3,5-dimethyl-5-nitro-1-pyrazolyl	H	H	H	PE	Bzl	1	A	HCl	157–159	57
4.9	dimethylamino	H	H	H	PE	Bzl	2	A	base	oil	60
4.10	Cl	CH_3	H	H	PE	Bzl	1	A	HCl	145–146	65
5.1	H	H	H	H	Bd	H	1	D	HCl	163–165	62
5.2	$COOC_2H_5$	H	H	H	Bd	H	1	D	HCl	185–188	73
5.3	1-imidazolyl	H	H	H	Bd	H	1	D	2HCl	192–195	73
5.4	3,5-dimethyl-1-pyrazolyl	H	H	H	Bd	H	1	D	fumarate	77–78	68
5.5	H	H	H	H	Bd	H	2	D	HCl	130–134	80
5.6	Cl	H	H	H	Bd	H	2	E	HCl	162–165	21
5.7	CH_3	H	H	H	Bd	H	2	D	fumarate	oil	45
5.8	phenyl	H	H	H	Bd	H	2	D	$HCl \cdot H_2O$	55–59	62
5.9	morpholino	H	H	H	Bd	H	2	D	HCl	185–189	85
5.10	1-imidazolyl	H	H	H	Bd	H	2	D	HCl	136–138	24
5.11	6-[1,4]benzodioxanyl	H	H	H	Bd	H	2	D	fumarate	170–172	92
5.12	H	H	CH_3	H	Bd	H	2	D	fumarate	178–179	70
5.13	H	CH_3	H	H	Bd	H	2	D	fumarate	122–123	60
5.14	H	H	H	CH_3	Bd	H	2	D	HCl	120–122	80
6.1	H	H	H	H	PE	H	1	D	HCl	160–161	89
6.2	Cl	H	H	H	PE	H	1	E	HCl	133–135	62
6.3	$COOC_2H_5$	H	H	H	PE	H	1	D	HCl	183–184	38
6.4	dimethylamino	H	H	H	PE	H	1	D	HCl	160–162	67
6.5	morpholino	H	H	H	PE	H	1	D	2HCl	143–145	78
6.6	1-imidazolyl	H	H	H	PE	H	1	D	2HCl	200–203	60
6.7	4-(ethoxycarbonyl)-1-piperazinyl	H	H	H	PE	H	1	D	HCl	147–149	80
6.8	3,5-dimethyl-1-pyrazolyl	H	H	H	PE	H	1	D	HCl	98–99	60
6.9	H	H	H	H	PE	H	2	F	HCl	138–139	45
6.10	Cl	H	H	H	PE	H	2	E	HCl	115–117	26
6.11	1-pyrrolyl	H	H	H	PE	H	2	E	HCl	143–145	31
6.12	dimethylamino	H	H	H	PE	H	2	D	HCl	171–174	93
6.13	H	H	H	H	PP	H	2	F	HCl	150–153	68
6.14	Cl	H	H	H	PP	H	2	E	HCl	120–125	20
6.15	H	H	H	H	2-F-PE	H	2	F	HCl	87–88	39
6.16	Cl	H	H	H	2-F-PE	H	2	E	HCl	98–99	25
6.17	Cl	H	H	H	4-F-PE	H	2	E	HCl	130–135	30
6.18	Cl	H	H	H	2-Cl-PE	H	2	E	HCl	130–135	22
6.19	Cl	H	H	H	2-MeO-PE	H	2	E	HCl	156–158	32
6.20	Cl	H	H	H	4-$CONH_2$-PE	H	2	E	HCl	143–145	30
6.21	Cl	H	H	H	PTE	H	2	E	HCl	106–108	30
6.22	Cl	H	H	H	H	H	2	I	HCl	245–248	38
6.23	H	H	H	H	ME	H	2	F	2HCl	206–207	60
6.24	Cl	H	H	H	ME	H	2	E	2HCl	205–208	35
6.25	morpholino	H	H	H	CH_3	H	1	D	HCl	174–178	83
9.1	H	H	H	H	CH_3	CH_3	2	F	HCl	145–146	20
9.2	Cl	H	H	H	CH_3	CH_3	2	E	HCl	170–172	99
9.3	Cl	H	H	H	phthalimido		2	J	base	136–139	61
9.4	morpholino	H	H	H	CH_3	Bzl	1	A	base	oil	53
9.5	Cl	H	H	H	4-(4-MeOPh)-1-piperazinyl		2	E	HCl $0.5\ H_2O$	173–175	30

Table II. List of 2-[3-(2-[1,4]benzodioxanylmethylamino)propyl]-4,5-dihydro-3(2*H*)-pyridazinones **11**, **12**.

Compd	R^1	R^6	*Method*	*Salt*	*MP (°C)*	*Yield*
11.1	H	Bzl	C	fumarate	oil	63
11.2	CH_3	Bzl	C	fumarate	oil	63
12.1	H	H	D	HCl	128–129	71
12.2	CH_3	H	D	fumarate	oil	61
12.3	phenyl	H	B, D	fumarate	78–79	60
12.4	6-[1,4]benzodioxanyl	H	B, D	fumarate	171–172	72

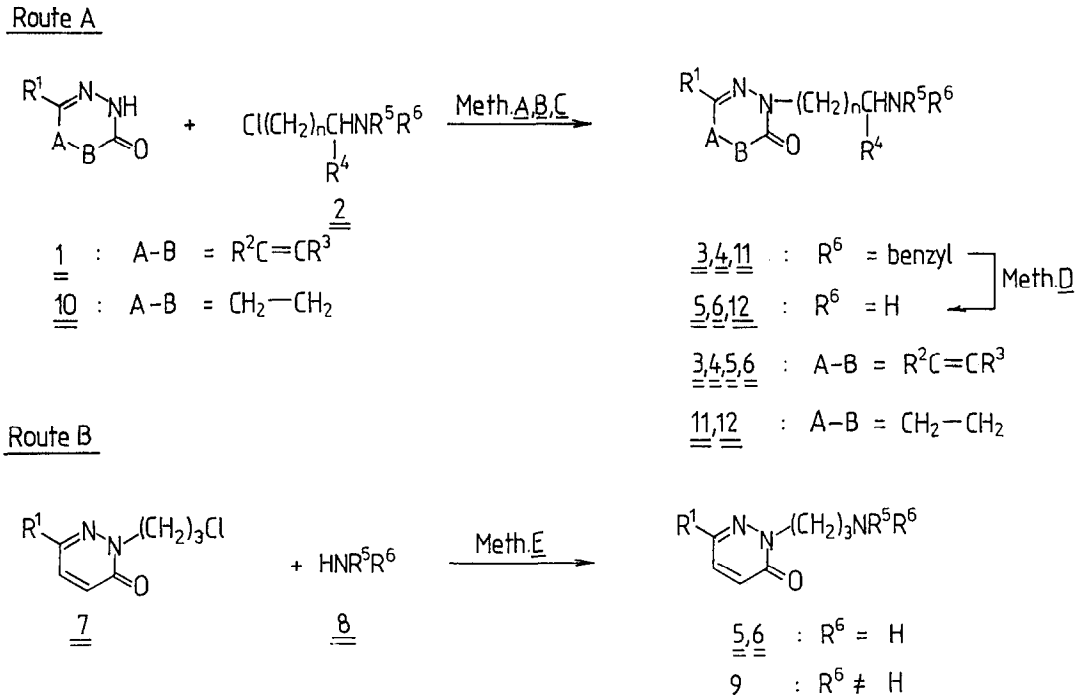
The synthesis of **15.1** and **15.2**, the *O*-aminoalkyl isomers of **5.6** and **5.5**, respectively, was accomplished by a completely different pathway as shown in scheme 2. Treatment of 3,6-dichloropyridazine with amino alcohol **14** in the presence of potassium *tert*-butylate (Method G) furnished the expected pyridazinyloxypropylamine derivative **15.1**, which was smoothly dehalogenated according to method F to give **15.2**.

Alkylation of 4,5-dihydro-3(2*H*)-pyridazinones **10** with *N*-benzyl-*N*-chloropropyl amine **2**, and then removing the benzyl group as described for compounds **5** and **6** in route A, afforded 2-aminoalkyldihydropyridazinones **12** in good yield. The possible formation of compounds **12** under conditions employed for debenzylation, catalytic hydrogenation of fully unsaturated 3(2*H*)-pyridazinones **5** and **6** was also investigated. At atmospheric pressure, less than 5% of compounds **12** were however formed, while at higher pressure (2 MPa), starting from **5.5**, besides the 4,5-dihydro derivative **12.1** and unchanged starting material, the corresponding tetrahydropyridazinone **16** could also be separated (scheme 3).

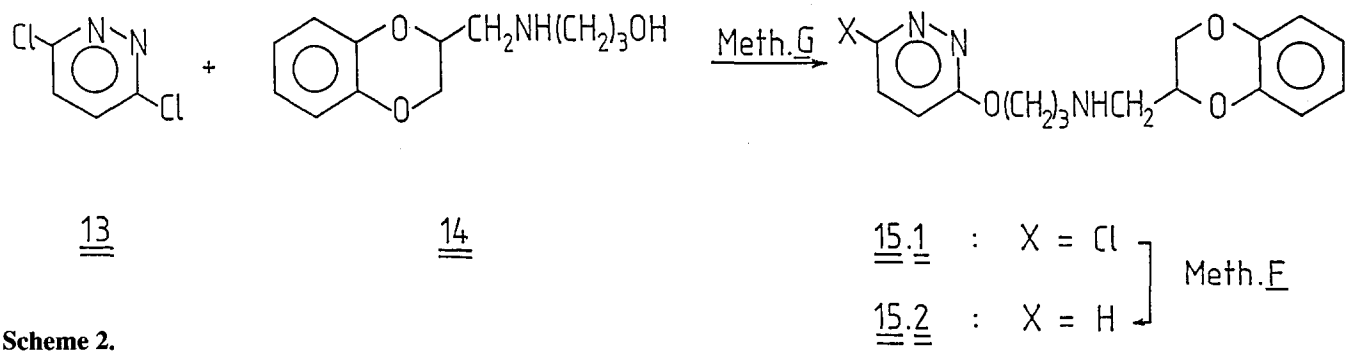
Results and interpretation of biological properties

Hypotensive activity of compounds was determined after intravenous and intraduodenal administration to normotensive anaesthetized cats. The decrease in the mean arterial blood pressure and effect on heart rate is shown in table III.

Compounds with a strong hypotensive effect were also tested for antihypertensive activity by oral ad-



Scheme 1.



13 14

15.1 : X = Cl
15.2 : X = H

Scheme 2.

ministration to conscious spontaneously hypertensive rats. These results are summarized in table IV.

The affinities of pyridazinones for α_1- and α_2-adrenoceptors in rat myocardial membranes and human platelet membranes respectively were determined by radioligand receptor binding with [^{3}H]-prazosine and [^{3}H]yohimbine as selective ligands, respectively. The results of these studies are summarized in table III.

Hypotensive/antihypertensive structure–activity relationships

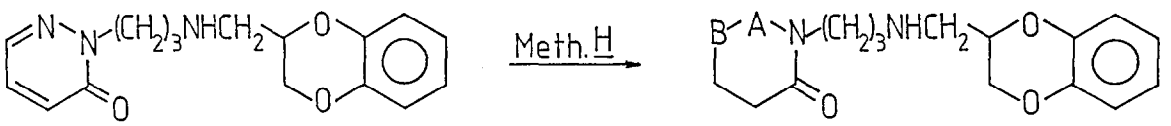
As amino substituent, 2-benzodioxanylmethyl or phenoxyalkyl group is essential but clearly not sufficient for hypotensive action in this class of substances. While compounds **5.4–5.14** and **6.4–6.19** showed moderate to high hypotensive effect (decrease in MABP in normotensive cats), their benzyl derivatives **3**, **4**, and compounds **5.1–5.3**, **6.1–6.3** as well as the *N*-alkyl, *N*,*N*-di-alkyl analogues **6.24**, **6.25**, **9.1–9.5** did not reduce the blood pressure at all.

A comparison of benzodioxanylmethylaminoalkyl-3(2*H*)-pyridazinones **5** with phenoxyalkylamino derivatives **6** indicates that the latter are usually less active (**5.5** *vs* **6.9**, **6.13**; **5.4** *vs* **6.8**).

The possible substitution patterns of the pyridazine part of the molecules were exhaustively studied in both series. Replacing the *N*-substituted amide function by an ether type linkage (**5.5** *vs* **15.2** and **5.6** *vs* **15.1**) reduced the hypotensive effect. Unsubstituted compounds (**5.5**, **5.14**, **6.9**, **6.13**, **6.15**) and derivatives with electron-releasing substituent, such as *eg* methyl (**5.7**), morpholino (**5.9**) or dimethylamino group (**6.4**), generally decreased the MABP to a higher extent than those with electron-withdrawing substituent (*eg* **5.10**, **6.13**). Electronic effects thus appear to be more important than steric effects as also evidenced by the similar blood pressure lowering effect of the positional isomers **5.7**, **5.12** and **5.13**. 4,5-Disubstitution with both electron donor and acceptor substituents markedly reduced the hypotensive effect [4].

Effect of the saturation of the 4,5-double bond on the hypotensive effect is not so clear. While the unsubstituted compound **5.5** is considerably more potent than the corresponding 4,5-dihydro compound **12.1**, only slight differences could be observed for 6-substituted derivatives, and a reverse correlation might be valid in these cases (**5.7** *vs* **12.2**, **5.8** *vs* **12.3**).

Substitution on the phenyl ring of phenoxyethylamino derivatives **6.15–6.20** caused different responses in hypotensive and antihypertensive effects.



5.5

12.1 : A–B = CH=N
16 : A–B = CH_2–NH

Scheme 3.

Table III. Blood pressure and HR effects in normotensive cats (1 mg/kg id) and radioligand binding data for compounds **5**, **6**, **12** and **15**.

Compd No	*Decrease in MABP* [a] *(Δ mmHg)*	*HR (Δ min–1)* [a]	*Radioligand binding, pKi* [b] *[^{3}H]prazosine (α_1)*	*[^{3}H]yohimbire (α_2)*
5.1	0	0	5.47 ± 0.14 (2)	6.67 ± 0.31 (2)
5.4	–10	0	–	–
5.5	–60	–35	7.03 ± 0.09 (10)	7.51 ± 0.01 (6)
5.6	–30	0	–	–
5.7	–20	0	–	–
5.8 [c]	–25	0	8.16 ± 0.10 (2)	8.57 (1)
5.9	–60	–50	7.73 ± 0.33	8.29 ± 0.13
5.10	–10	0	6.21 ± 0.14 (2)	7.06 ± 0.08 (2)
5.11	–20	0	–	–
5.12	–30 (20)	+20	7.22 ± 0.27	7.38 ± 0.15
5.13	–40 (20)	0	7.01 ± 0.35	7.09 ± 0.08
5.14	–40	–5	6.23 ± 0.04	7.81 ± 0.16
6.4	–35	–10	6.16 ± 0.13	8.12 ± 0.33
6.5	0	0	–	–
6.6	0	0	–	–
6.7	0	0	–	–
6.8	–10 (10)	0	–	–
6.9	–40	+10	6.01 (1)	–
6.10	–25 (20)	–5	6.37 ± 0.13	6.69 ± 0.12
6.11	–15 (30)	–25	–	–
6.12	–15	0	6.49 ± 0.09 (2)	7.56 ± 0.32 (2)
6.13	–20	–15	6.01 ± 0.14	5.80 ± 0.09
6.15	–35	+20		
6.17	–10	0	–	–
6.18	–25	–5	–	–
6.19[d]	–20	–15	–	–
6.20	0	0	–	–
6.23	–25 (15)	–15 (15)	–	–
12.1	–15	+10	–	–
12.2	–35	–10	–	–
12.3	–40	+5	7.57 ± 0.09	8.27 ± 0.15
15.1	0	0	–	–
15.2	–15	0	–	–
Prazosine	–	–	9.55 ± 0.07 (11)	6.05 ± 0.08 (4)
Yohimbine	–	–	6.12 ± 0.05 (6)	8.79 ± 0.05 (14)
Idazoxan	–	–	5.40 ± 0.06	7.49 ± 0.06 (4)
Phentolamine	–	–	7.37 ± 0.15 (4)	7.61 ± 0.06 (4)

[a]After 30 min unless otherwise noted. [b]Determined in rat myocardial membranes with [^{3}H]prazosine and in human platelet membranes with [^{3}H]yohimbine, respectively. Values are the means of 3 separate determinations ± SEM unless otherwise noted. [c]Highly toxic in 5 mg/kg dose. [d]Measured with 5 mg/kg dose

The *ortho* halogen derivatives exerted a similar, or even higher hypotensive effect than the corresponding unsubstituted compounds (**6.9** *vs* **6.15**; **6.10** *vs* **6.18**), whereas the antihypertensive effect (decrease in MABP in SHR) of **6.10** was stronger than that of **6.18**. The other modifications on the phenyl ring failed to improve the hypotensive/antihypertensive effect.

Concerning the chain length between the pyridazinone and amine nitrogen, linear propylene seems to be superior to ethylene (*eg* **5.5** *vs* **5.1** or **6.9** *vs* **6.1**) or α-methylethylene (**5.5** *vs* **5.14**).

α-Adrenoceptor structure–affinity relationships

A number of compounds displayed α_2-adrenoceptor affinity comparable to, or greater than idazoxan. Enhanced affinity upon a phenyl or electronreleasing substitution on the pyridazinone moiety could be observed in both the benzodioxanylmethyl and phenoxyalkyl series (*eg* **5.8**, **5.9**, **6.4**).

Several compounds showed significant but much weaker α_1-adrenoceptor affinity than prazosine. In the benzodioxanylmethylamino series, a phenyl or an

Table IV. Blood pressure and HR effects in spontaneously hypertensive rats for selected compounds **5**, **6** and **12**.

Compd No	*Dose (mg/kg po)*	*Decrease in MABP (Δ %)* [a]	*HR (Δ min^{-1})* [a]
5.5	25	–24 (8)	+2
	3	–12	–6
5.9	25	–10	–5
6.4	20	0	0
6.9	50	–30	+3
6.10	50	–30	+10
	25	0	0
6.15	50	–10	+10
6.18	50	–10	+10
12.3	50	–10	+10
Prazosine	2.5	–50	+2
Phentolamine	50	–27	+25
	25	–5	+3

[a]After 5 h unless otherwise stated

electron-releasing substituent at the 6-position also increased the α_1-adrenoceptor binding affinity (*eg* **5.8**, **5.9**).

It seems therefore plausible to postulate that an amino nitrogen in R^1 or a phenyl group at the 6-position as well as the ring nitrogen(s) may represent important anchoring points for both α_1- and α_2-adrenoceptor binding.

For α_1-adrenoceptor affinity, a linear propylene chain between the amide and amino nitrogen might be a basic requirement (**5.5** *vs* **5.1**, **5.14**), whereas for α_2-adrenoceptor binding affinity, ethylene or α-methylethylene can still be well tolerated (*eg* **6.4**, **5.14**).

Conclusion

Several compounds of the presented chemical class of 2-aminoalkyl-3(2*H*)-pyridazinones exhibit pronounced hypotensive/antihypertensive effect and high affinity for α_2-adrenoceptors.

Compounds combining moderate α_1- and α_2-adrenoceptor affinities may, however, also exert a strong hypotensive/antihypertensive effect.

Compound **5.5** (GYKI-12 743) was selected for phase I clinical study. In *in vivo* experiments, it had α_1- and postjunctional α_2-adrenoceptor blocking activity. However, it did not block cardiac presynaptic α_2-adrenoceptors [5]. Consequently its antihypertensive effect appeared without tachycardia in different hypertensive models. This observation adds experimental support to the view that a further subdivision of α_1- and α_2-adrenoceptors is due as has recently been concluded by Docherty in his excellent review [6].

Moreover, in preliminary experiments, compound **5.5** also exerted potassium channel activation activity comparable to cromakaline [7].

The recent findings on possible common features of $5HT_{1A}$-receptors and α_2-adrenoceptors, as well as molecular modelling on structural requirements for such bindings of some structurally related compounds [8, 9], prompted us to perform such studies.

These experiments are now in progress and results will be published separately.

Experimental protocols

Chemistry

Melting points were determined on a Boetius apparatus and are uncorrected. The elementary analyses (C, H, N) of the new compounds were within ± 0.4% of the theoretical values. The IR and ^{1}H NMR spectrum data were in accordance with the structure of compounds prepared. Hydrochlorides and fumarates were prepared in ethanol in the usual manner.

The known starting materials **1** [11–19] and **2** [20–26] were synthesized according to the published procedures, while the novel derivatives are described below.

*Synthesis of novel starting materials **1** and **2***
6-Substituted-3(2H)-pyridazinones (procedures I–III)
Procedure I. A mixture of 0.06 mol of the appropriate 6-substituted-3-chloropyridazine and 7.84 g (0.08 mol) of KOAc in 100 ml of AcOH was stirred under reflux for 10 h. The solvent was evaporated *in vacuo* and the residue was taken up in chloroform. The crystals were collected by filtration, washed with water and recrystallized from EtOH.
6-(1-Imidazolyl)-3(2*H*)-pyridazinone, yield 55%, mp 240–241°C. 6-(4-Ethoxycarbonyl-1-piperazinyl)-3(2*H*)-pyridazinone, yield 60%, mp 163–165°C.

6-(3,5-Dimethyl-1-pyrazolyl)-3(2H)-pyridazinone
Procedure II. 2.09 g (0.01 mol) of 3-chloro-6-(3,5-dimethyl-1-pyrazolyl)-pyridazine were dissolved in 160 ml of an aqueous solution of NaOH (12%) and heated under reflux for 2 h. The hot mixture was adjusted to pH 2 with an aqueous solution of HCl (36%). The precipitate was filtered off, washed with water and recrystallized from EtOH to give 1.14 g (60%) of the title compound, mp 263–266°C.

6-(6-[1,4]Benzodioxanyl)-3(2H)-pyridazinone
Procedure III. 9.28 g (0.04 mol) of 6-(6-[1,4]benzodioxanyl)-4,5-dihydro-3(2*H*)-pyridazinone (prepared from 3-(6-[1,4]-benzodioxanylcarbonyl)propionic acid with hydrazine hydrate (72%) in 86% yield, mp 214–216°C) were dissolved in 700 ml of chloroform and to this solution 40 g of activated MnO_2 [10] were added. The mixture was stirred under reflux for 20 h, and the precipitate was filtered and washed with chloroform. The filtrate was evaporated to dryness and the residue was taken up in Et_2O. The crystals were collected by filtration to give 7.18 g (78%) of the title compound, mp 225–226°C.

ω-Aminopropanols (procedure IV–V)
Procedure IV. A mixture of 0.10 mol of appropriate alkyl chloride and 0.20 mol of aminopropanol derivative was stirred at 130°C for 2 h and then at 165°C for 8 h. After cooling, 70 ml

of an aqueous solution of NaOH 20%) were added to the mixture and extracted with benzene. The organic layer was dried and evaporated *in vacuo*.
3-[*N*-(2-Phenoxyethyl)amino]propanol, yield 84%, oil.
3-[*N*-(2-[1,4]Benzodioxanylmethyl)amino]-3-methylpropanol, yield 41%, oil.
Procedure V. A mixture of 1.0 mol *N*-substituted aminopropanol derivative, 139.2 g (1.1 mol) of benzyl chloride, 15.0 g (0.1 mol) of NaI, 16.1 g (0.05 mol) of TBAB and 414.0 g (3 mol) of anhydrous K_2CO_3 in 2000 ml of toluene was heated under reflux for 3 h. After filtration, the filtrate was extracted with an aqueous solution of HCl (10%), then the aqueous layer was adjusted to pH 9 and extracted with dichloromethane. The organic layer was dried and evaporated *in vacuo*.
3-[*N*-Benzyl-*N*-(2-[1,4]benzodioxanylmethyl)amino]propanol, yield 82% oil.
3-[*N*-Benzyl-*N*-(2-phenoxyethyl)amino]propanol, yield 77%, oil.

ω-Chloroalkylamines
Procedure VI. To a solution of 0.82 mol of appropriate aminoalkanol in 1000 ml of dichloromethane 59.0 ml (0.82 mol) of $SOCl_2$ were dropwise added at rt. The mixture was heated under reflux for 4 h, then the precipitate was filtered off and washed with acetone.
N-Benzyl-*N*-(2-[1,4]benzodioxanylmethyl)-*N*-(3-chloropropyl)amine hydrochloride, yield 98%, mp 144–145°C.
N-Benzyl-*N*-(3-chloropropyl)-*N*-(2-phenoxyethyl)amine hydrochloride, yield 84%, mp 124–127°C.
N-(2-[1,4]Benzodioxanylmethyl)-*N*-(3-chloro-2-butyl)amine hydrochloride, yield 80%, mp 154–156°C.
N-Benzyl-*N*-(2-[1,4]benzodioxanylmethyl)-*N*-(3-chloro-2-butyl)amine, yield 62%, oil.

*Synthesis of 2-aminoalkyl-3(2H)-pyridazinones **5**, **6**, **9**, **11**, **12**. Alkylation of 3(2H)-pyridazinones with N-benzyl-N(ω-chloroalkyl)amines **2***
Method A. A mixture of 0.01 mol of Na-salt of the appropriate 3(2*H*)-pyridazinone (**1**) (prepared from 0.01 mol of pyridazinone) with 0.01 mol of NaOEt in EtOH) and 0.01 mol of amine **2** in 15 ml of EtOH was stirred at reflux for 6 h. After filtration, the solvent was evaporated *in vacuo* and the crude base was treated with a solution of HCl in EtOH.
Method B. A mixture of 0.12 mol of K-salt of the appropriate 3(2*H*)-pyridazinone (**1** or **10**, resp), 0.12 mol of amine **2** and 7.74 g (0.024 mol) of TBAB in 350 ml of benzene was stirred under reflux for 3 h. The mixture was extracted with an aqueous solution of HCl (4%). The aqueous phase was separated and adjusted to pH 9–10 with an aqueous solution of NaOH (4%) and extracted with dichloromethane. The organic layer was separated and after evaporation of the solvent, the product was obtained by treatment of the crude base with the appropriate acid.
Method C. A mixture of 0.01 mol of K-salt of the appropriate 3(2*H*)-pyridazinone (**1** or **10**, resp) (prepared from 0.01 mol of pyridazinone with 0.01 mol of KOH in MeOH), 0.01 mol of amine **2**, 1.19 g (0.0037 mol) of TBAB and 0.62 g (0.011 mol) of powdered KOH in 60 ml of toluene was stirred under reflux for 5 h. The mixture was washed with an aqueous solution of NaOH (8%) and then with water. The organic phase was dried and evaporated *in vacuo*. The residue was taken up in EtOH and treated with the appropriate acid.

*Debenzylation of compounds **3**, **4** and **11***
Method D. A solution of 0.10 mol of the appropriate *N*-benzyl derivative (**3**, **4** or **11**, respectively) in 370 ml of EtOH was treated with 40 ml of an aqueous solution of HCl (10%). The mixture was hydrogenated with palladium on charcoal (10%) in a Parr apparatus. After the calculated value had been reached, the catalyst was filtered off. The solvent was removed *in vacuo* and the residue dissolved in water and adjusted to ph 9 with an aqueous solution of NaOH (20%). The solution was extracted with dichloromethane. The organic layer was separated and after evaporation of the solvent, the product was obtained by treatment of the crude base with the appropriate acid.

*Reaction of 2-N-3-chloropropyl-3(2H)-pyridazinones 7 with amines **8***
Method E. A mixture of 0.04 mol of the appropriate 3(2*H*)-pyridazinone derivative **7** (for the preparation of **6.2**, 6-chloro-2-*N*-2-chloroethyl-3(2*H*)-pyridazinone was used), 0.34 mol of amine **8** and 4.20 g (0.03 mol) of anhydrous K_2CO_3 in 34 ml of DMF was stirred at 95–100°C for 16 h. After filtration the solvent was evaporated *in vacuo*. The residue was taken up in 100 ml of an aqueous solution of NaOH (4%) and extracted with EtOAc. The solvent was evaporated *in vacuo* and the residue was treated with the appropriate acid in EtOH.
Compound **9.3** was similarly obtained using potassium phthalimide. The reaction was carried out at 120°C for 5 h. The product was separated after treatment with water.

Dehalogenation of 6-chloropyridazine derivatives
Method F. In a Parr apparatus a mixture of 0.08 mol of the appropriate 6-chloro derivative, 6.16 g (0.11 mol) of KOH and 3 g of palladium on charcoal (10%) in 600 ml of EtOH was hydrogenated at rt. After the calculated hydrogen consumption, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was triturated with iPrOH and filtered. The solvent was removed *in vacuo* and the crude base was treated with the appropriate acid in EtOH.

*Synthesis of 3-(3-aminopropoxy)pyridazines **15***
*3-[3-(N-2-[1,4], Benzodioxanylmethylamino)propoxy]-6-chloropyridazine hydrochloride **15.1***
Method G. To a stirred solution of 6.69 g (0.03 mol) of **14** and 4.50 g (0.04 mol) of KOBu^t in 60 ml of Bu^{t}OH, 4.50 g (0.03 mol) of **13** were added dropwise at rt. The mixture was stirred at 40°C for 1 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in water and extracted with chloroform, then treated with HCl in EtOH. Yield 48%, mp: 164–167°C.
15.2 was obtained from **15.1** by method F. Yield 42%, mp 151–153°C.

*Hydrogenation of **5.5** at 2 MPa (20 atm) pressure*
Method H. A solution of 7.52 g (0.025 mol) of **5.5** in 80 ml of EtOH containing 8 ml of water and 1.3 ml of an aqueous solution of HCl (35%) was hydrogenated at 40°C and 2 MPa pressure in the presence of 1.4 g of palladium on charcoal (10%) for 3 h. After filtration, the filtrate was evaporated to dryness and the residue was taken up in an aqueous solution of NaOH (10%). The solution was extracted with dichloromethane. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica using an 1:1 mixture of MeOH–EtOAc as eluent to give **12.1** (55%), **16** (20% as HCl salt, mp 55–59°C) and unchanged **5.5** (15%).

*2-(3-Aminopropyl)-6-chloro-3(2H)-pyridazinone **6.22***
Method I. A solution of 1.0 g (0.003 mol) of **9.3** and 0.16 ml of 98% hydrazine hydrate in 50 ml of EtOH was stirred at

50°C for 2 h. The separated crystals were filtered off and the filtrate was evaporated to dryness. The residue was taken up in EtOH and treated with HCl in EtOH.

Pharmacology

Hypotensive effect in normotensive anaesthetized cats
The tracheae of mongrel cats of either sex weighing 2.0–5.0 kg anaesthetized by ip administration of 35 mg/kg of pentobarbital sodium (Nembutal®) was intubated to secure undisturbed respiration. The right femoral artery and vein were cannulated. The mean arterial blood pressure was recorded by Statham P 23 Db pressure transducer connected to a Hellige polygraph. A biotachometer coupler integrated the heart rate from the phasic blood pressure. Compounds were administered *via* the right femoral vein in a dose of 5 mg/kg and the effective substances were also tested by ip administration in a dose of 1 mg/kg.

Antihypertensive effect
in conscious spontaneously hypertensive rats
Systolic blood pressure and heart rate recorded by tail-cuff technique using a modified non-invasive method [27] were determined before dosing and at various time-intervals over a 24 h-period by a 5-channel semiautomatic apparatus. The compounds to be tested were given orally.

α-Adrenoceptor radioligand binding assay
α_1-Adrenoceptor binding assay in rat myocardial membranes with [^{3}H]prazosine was performed by the described method [28]. Hearts from male Sprague–Dawley rats were homogenized in 0.25 M saccharose, 5 mM Tris-HCl buffer (pH = 7.4) with Ultraturrax at 4°C for 4 x 10 s and centrifuged at 40 000 *g* for 20 min. The resulting pellets were resuspended in 50 mM Tris–HCl buffer containing 1 mM EDTA, 4 μM phenylmethylsulfonyl fluoride and centrifuged twice as before.

In binding experiments 0.4–0.5 mg of myocardial membrane was incubated with 0.8 nM [^{3}H]prazosine (Amersham, 24.4–26.0 Ci/mmol) and various concentrations of unlabelled drugs in a final volume of 1 ml at 30°C for 30 min. Nonspecific binding was obtained in the presence of 1 μM unlabelled prazosine–HCl. The incubation was terminated by adding of 3.5 ml of ice-cold buffer and filtering the samples over glass-fiber filters (Whatman GF/B) and the filters were washed twice with 3.5 ml of buffer.

α_2-Adrenoceptor binding studies with [^{3}H]yohimbine were performed according to a previously described method [29].

Platelet-rich plasma was obtained from venous blood of healthy human volunteers and centrifuged at 16 000 *g* in ice-cold 50 mM Tris–HCl buffer containing 100 mM NaCl, 5 mM EDTA (pH = 7.2) for 10 min, and the procedure repeated twice.

[^{3}H]Yohimbine binding was carried out by incubating the platelets (0.4–0.5 mg protein) with 3 nM [^{3}H]yohimbine (Amersham, 90 Ci/nmol) and various concentrations of drugs in a final volume of 250 μl at 20°C for 30 min. Non-specific binding was determined in the presence of 1 μM unlabelled yohimbine–HCl. The reaction was terminated by adding of 10 ml of ice-cold buffer and filtered through Whatman GF/C filters. The radioactivity was measured by liquid scintillation system. Protein concentration was determined according to the published procedure [30].

K_i values were determined using the formula of Cheng and Prusoff [31].

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