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Synthesis and hypotensive activity of novel 3-pyridazinyloxypropanolamines

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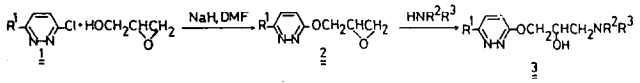
pyridazinyloxypropanolamines / hypotensive activity

Introduction

We reported earlier the synthesis of some hypotensive pyridazinylhydrazones with direct peripheral vasodilatation [2]. Now to avoid tachycardia, the most frequent side-effect of peripherally acting hypotensive agents, we combined the pyridazine ring with an 1-alkylamino-2-hydroxypropyl group, which is a structural unit in many potent β-adrenoceptor antagonists and a new series of 3-pyridazinyloxypropanolamines (see [1]) was synthesized. The hypotensive effect, the change in heart rate and adrenoceptor antagonist activity (α- and β-) of the compounds were tested.

Chemistry

First the epoxides **2** were prepared by the 'glycidol route' in one step from chloropyridazines **1** and glycidol then glycidyl ethers **2** were converted into the desired amino derivatives **3** with amines. The chloro substituent of the compounds **3** was removed by catalytic hydrogenation.



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Pharmacological results and discussion

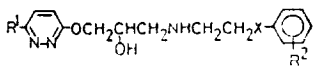
Compounds **3** were screened for hypotensive activity in a screening dose of 5 mg/kg. It was found that the substitution of the pyridazine ring did not modify the hypotensive potency considerably. Except for the fluoro substituent, the effect of the compounds containing a 2-substituted phenyl group showed higher activity than their 4-substituted isomers (*cf* **3.5** and **3.6**).

Compounds showing at least 60 mmHg decline in blood pressure at 60 min after administration and causing bradycardia were tested in a dose of 1 mg/kg for iv hypotensive and in a dose of 50 mg/kg for oral antihypertensive activity in conscious spontaneously hypertensive rats. It was established that 1,4-benzodioxane derivatives were generally more potent than the analogous 2-phenoxyethyl derivatives. Three out of 4 of the compounds were 1,4-benzodioxane derivatives exerting significant antihypertensive activity (Δ bp at least –25%): **3.20** (–37%), **3.65** (–27%), **3.67** (–24%), **3.69** (–27%).

It was found that none of the compounds exerted significant β-adrenoreceptor antagonist activity and only **3.67** showed α-adrenoceptor antagonist activity in excess of 20% (35%).

Our results suggest that there is no direct correlation between the hypotensive effect and the adrenoceptor antagonist activity of the compounds **3**. It is more possible that the peripheral vasodilating activity of the pyridazine moiety is responsible for the hypotensive effect of compounds **3**. The bradycardia

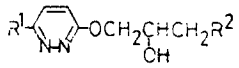
Table I. Physical data and hypotensive activity of compounds **3.1–3.38**.



Compound	R^1	R^2	*x*	*Base mp °C*	*Salt mp °C*	*Formula*	*Yield %*	*BP mmHg*	*HR min^{-1}*
3.1	Cl	H	O	101-2	158-9	$C_{15}H_{18}ClN_3O_3$•HCl	68	– 40	– 40
3.2	Cl	H	S	82-3	98-9	$C_{15}H_{18}ClN_3O_2S$•HCl	59	0	0
3.3	Cl	2-F	O	138-9	130-9	$C_{15}H_{17}ClFN_3O_3$•HCl	75	– 40	– 20
3.4	Cl	4-F	O	120-1	114-6	$C_{15}H_{17}ClFN_3O_3$•HCl	91	– 50	– 25
3.5	Cl	2-Cl	O	100-5	146-9	$C_{15}H_{17}Cl_2N_3O_3$•HCl	72	– 50	– 45
3.6	Cl	4-Cl	O	128-9	117-9	$C_{15}H_{17}Cl_2N_3O_3$•HCl	64	0	0
3.7	Cl	2,5-diCl	O	124-5	134-5	$C_{15}H_{16}Cl_3N_3O_3$•HCl	85	– 35	– 10
3.8	Cl	4-CN	O	150-2	154-6	$C_{16}H_{17}ClN_4O_3$•HCl	53	0	0
3.9	Cl	4-NO_2	O	144-6	174-6	$C_{15}H_{17}ClN_4O_5$•HCl	52	0	0
3.10	Cl	4-$CONH_2$	O	*	177-8	$C_{16}H_{19}ClN_4O_4$•HCl	62	– 30	– 40
3.11	Cl	2-OCH_3	O	83-5	90-5	$C_{16}H_{20}ClN_3O_4$•HCl	46	– 45	– 20
3.12	Cl	4-CH_2OH	O	100-2	92-6	$C_{16}H_{20}ClN_3O_4$•HCl	62	0	0
3.13	Cl	4-$CONHCH_2CH_2N/C_2H_5/_2$	O	103-5	–	$C_{22}H_{32}ClN_5O_4$	25	0	0
3.14	Cl	2-$COOCH_3$	O	118-9	140-1	$C_{17}H_{20}ClN_3O_5$•HCl	45	0	0
3.15	Cl	4-$COOCH_3$	O	117-9	133-5	$C_{17}H_{20}ClN_3O_5$•HCl	37	0	0
3.16	Cl	2-morpholinomethyl	O	124-6	130-2	$C_{20}H_{27}ClN_4O_4$•HCl	53	0	0
3.17	Cl	4-morpholinomethyl	O	110-2	187-9	$C_{20}H_{27}ClN_4O_4$•HCl	31	0	0
3.18	Cl	3-butylureido	O	oil	175-7	$C_{20}H_{28}ClN_5O_4$•HCl	84	– 30	– 60
3.19	Cl	H	CH_2O	110-3	115-8	$C_{16}H_{20}ClN_3O_3$•HCl	81	– 25	+ 15
3.20	H	H	O	98-9	155-8	$C_{15}H_{19}N_3O_3$•HCl	56	– 60	– 20
3.21	H	2-F	O	oil	85-7	$C_{15}H_{18}FN_3O_3$•HCl	61	– 35	– 50
3.22	H	4-F	O	oil	140-2	$C_{15}H_{18}FN_3O_3$•HCl	83	– 45	– 5
3.23	H	4-CN	O	100-5	182-4	$C_{16}H_{18}N_4O_3$•HCl	64	0	0
3.24	H	4-NH_2	O	*	158-9	$C_{15}H_{20}N_4O_3$•HCl	50	0	0
3.25	H	4-$COOCH_3$	O	120-4	154-6	$C_{17}H_{21}N_3O_5$•HCl	37	0	0
3.26	H	2-OCH_3	O	70-1	105-7	$C_{16}H_{21}N_3O_4$•HCl	25	– 30	– 15
3.27	H	4-morpholinomethyl	O	oil	98-9	$C_{20}H_{28}N_4O_4$•HCl	89	0	0
3.28	H	3-butylureido	O	140-2	131-3	$C_{20}H_{29}N_5O_4$•HCl	58	0	0
3.29	H	H	CH_2O	73-5	–	$C_{16}H_{21}N_3O_3$	60	0	0
3.30	phenyl	H	O	127-9	170-5	$C_{21}H_{23}N_3O_3$•HCl	70	– 40	– 30
3.31	phenyl	2-OCH_3	O	oil	116-8	$C_{22}H_{25}N_3O_4$•$C_4H_4O_4$**	40	– 35***	0
3.32	phenyl	4-$CONH_2$	O	oil	80-4	$C_{22}H_{24}N_4O_4$•HCl	47	0	0
3.33	phenyl	2-OCH_3-4-$COOCH_3$	O	103-5	65-9	$C_{24}H_{27}N_3O_6$•$C_4H_4O_4$**	50	0	0
3.34	1-pyrrolyl	H	O	120-2	187-8	$C_{19}H_{22}N_4O_3$•HCl	63	– 50	– 20
3.35	1-pyrrolyl	2-OCH_3	O	93-5	115-9	$C_{20}H_{24}N_4O_4$•HCl	76	– 40	– 10
3.36	1-pyrrolyl	4-F	O	*	156-8	$C_{19}H_{21}FN_4O_3$•HCl	50	– 40	– 50
3.37	1-imidazolyl	H	O	113-4	184-4	$C_{18}H_{21}N_5O_3$•HCl	67	– 40	– 15
3.38	1-imidazolyl	2-OCH_3	O	76-9	170-5	$C_{19}H_{23}N_5O_4$•HCl	33	– 35	– 20

*Not isolated; **maleate; ***in a dose of 1 mg/kg. BP = hypotensive activity, mean arterial blood pressure. HR = heart rate.

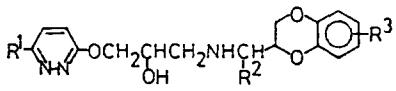
Table II. Physical data and hypotensive activity of compounds **3.39–3.64**.



Cpd	*R^1*	*R^2*	*Base °C*	*Salt °C*	*Formula*	*Yield*	*BP mmHg*	*HR min^{-1}*
3.39	Cl	amino	165-9	100-6	$C_7H_{10}ClN_3O_2$•HCl	47	0	0
3.40	Cl	2-hydroxyethylamino	134-5	100-5	$C_9H_{14}ClN_3O_3$•HCl	37	0	0
3.41	Cl	2-diethylaminoethylamino	95-8	150-3	$C_{13}H_{23}ClN_4O_2$•HCl	62	0	0
3.42	Cl	2-benzamidoethylamino	oil	100-1	$C_{16}H_{19}ClN_4O_3$•HCl	32	0	0
3.43	Cl	2-acetamidoethylamino	128-9	–	$C_{11}H_{17}ClN_4O_3$	51	0	0
3.44	Cl	2-/6-benzo-1,4-dioxanyloxy/--ethylamino	oil	184-6	$C_{17}H_{20}ClN_3O_5$•HCl	21	– 35	– 10
3.45	Cl	*tert*-butylamino	72-3	128-9	$C_{11}H_{18}ClN_3O_2$•HCl	52	– 10	– 30
3.46	Cl	1,4-dioxanylmethylamino	110-3	131-3	$C_{12}H_{18}ClN_3O_4$•HCl	68	0	0
3.47	Cl	/4-benzyl-2-morpholinyl/--methylamino	oil	225-8	$C_{19}H_{25}ClN_4O_3$•2HCl	50	0	0
3.48	Cl	1-methyl-3-phenylpropylamino	105-8	178-9	$C_{17}H_{22}ClN_3O_2$•HCl	42	0	0
3.49	Cl	1-methyl-2-/2,6-dimethoxy-phenoxy/-ethylamino	oil	115-6	$C_{18}H_{24}ClN_3O_5$•HCl	21	– 20	– 30
3.50	1-pyrrolyl	isopropylamino	111-2	125-6	$C_{14}H_{20}N_4O_2$•HCl	23	0	0
3.51	1-imidazolyl	isopropylamino	114-5	173-5	$C_{13}H_{19}N_5O_2$•HCl	20	0	0
3.52	3,5-dimethyl-1-pyrazolyl	isopropylamino	80-5	178-9	$C_{15}H_{23}N_5O_2$•HCl	26	– 20	– 20
3.53	3,5-dimethyl-1--pyrazolyl	*tert*-butylamino	96-8	138-9	$C_{16}H_{25}N_5O_2$•HCl	20	0	0
3.54	3,5-dimethyl-1--pyrazolyl	1,4-dioxanylmethylamino	115-8	157-8	$C_{17}H_{25}N_5O_4$•HCl	50	0	0
3.55	3,4,5-trimethyl-1-pyrazolyl	isopropylamino	90-7	160-2	$C_{16}H_{25}N_5O_2$•HCl	36	0	0
3.56	Cl	morpholino	94-5	190-2	$C_{11}H_{16}ClN_3O_3$•HCl	52	– 30	0
3.57	H	morpholino	57-8	160-3	$C_{11}H_{17}N_3O_3$•HCl	28	0	0
3.58	Cl	bis/2-hydroxyethyl/-amino	oil	94-5	$C_{11}H_{18}ClN_3O_4$•HCl	28	0	0
3.59	Cl	2-aminomethylmorpholino	93-5	187-9	$C_{12}H_{19}ClN_4O_3$•2HCl	33	0	0
3.60	Cl	2-phtalimidomethylmorpholino	190-5	215-7	$C_{20}H_{21}ClN_4O_5$•HCl	87	0	0
3.61	Cl	4-methylpiperazine	oil	173-5	$C_{12}H_{19}ClN_4O_2$•2HCl	87	0	0
3.62	Cl	4-/2-chlorophenyl/-piperazine	95-7	201-3	$C_{17}H_{20}Cl_2N_4O_2$•2HCl	60	– 50	– 30
3.63	Cl	/ethyl piperazine-4-carboxylate/--1-yl	80-3	180-3	$C_{14}H_{21}ClN_4O_4$•HCl	70	0	0
3.64	H	4-/4-methoxyphenyl/-piperazine	oil	186-8	$C_{18}H_{24}N_4O_3$•2HCl	42	0	0

BP = hypotensive activity, mean arterial blood pressure. HR = heart rate.

Table III. Physical data and hypotensive activity of compounds **3.65–3.74.**



Compound	*R^1*	*R^2*	*R^3*	*Base Mp°C*	*Salt Mp°C*	*Formula*	*Yield*	*BP mmHg*	*HR min^{-1}*
3.65	Cl	H	H	88-9	138-9	$C_{16}H_{18}ClN_3O_4$	67	– 50	– 50
3.66	Cl	CH_3	H	130-3	143-8	$C_{17}H_{20}ClN_3O_4$•HCl	32	– 40	0
3.67	H	H	H	85-8	158-9	$C_{16}H_{19}N_3O_4$•HCl	25	– 50	– 35
3.68	H	H	5-OCH_3	oil	80-2	$C_{17}H_{21}N_3O_4$•HCl	77	– 35	– 10
3.69	phenyl	H	H	141-2	160-2	$C_{22}H_{23}N_3O_4$•HCl	31	– 60	– 70
3.70	phenyl	H	6/7/-NO_2	oil	100-2	$C_{22}H_{22}N_4O_6$•$C_4H_4O_4$*	62	0	0
3.71	1-pyrrolyl	H	H	115-9	160-3	$C_{20}H_{22}N_4O_4$•HCl	45	0	0
3.72	1-imidazolyl	H	H	120-5	183-5	$C_{19}H_{21}N_5O_4$•HCl	49	– 60	– 40
3.73	1-imidazolyl	H	6/7/Br	130-1	114-5	$C_{19}H_{20}BrN_5O_4$•$C_4H_4O_4$*	38	– 25	– 20
3.74	3,5-dimethyl-pyrazolyl	H	H	85-9	198-9	$C_{21}H_{25}N_5O_4$•HCl	25	– 60	– 30

*Maleate. BP = hypotensive activity, mean arterial blood pressure. HR = heart rate.

may be caused by a direct action of the compounds on heart muscle as compounds **3.20**, **3.65**, **3.67** and **3.69** had an influence on rabbit papillary muscle measured according to the methods in the literature [3].

Experimental protocols

Chemistry

Melting points are not corrected. The elementary analyses (C, H, N) of the new compounds are within 0.5% of the theoretical values. The IR and ^1H NMR spectral data are in accordance with the proposed structure of the compounds.

Epoxides **2** were prepared by the 'glycidol route' from chloropyridazines **1** and glycidol in dimethylformamide by means of NaH according to the literature. New compounds (R^1, yield, mp): chloro, 42%, 92–94°C; phenyl, 76%, 104–105°C; 1-pyrrolyl, 15%, 95–99°C, 1-imidazolyl, 20%, 165–166°C. The glycidyl ethers **2** were converted into the amino derivatives **3** with amines in the usual manner in butanol at 30–35°C. The chloro substituent of the compounds **3** was removed by catalytic hydrogenation in methanol in the presence of concentrated ammonium hydroxide. Compounds **3** were recrystallized from ethanol.

Pharmacology

Compounds **3** were screened for hypotensive activity in normotensive anaesthetized cats by intravenous administration at a dose of 5 mg/kg, then 1 mg/kg at 30 min post-dose. The BP and HR values of 5 mg/kg dose given in tables I, II and III are the average of 3 animals. The antihypertensive activity of the compounds **3** was measured in conscious spontaneously hypertensive rats in a 50 mg/kg dose by the 'tail' method according to the literature [4].

The α- and β-adrenoceptor antagonist activity of the compounds **3** was measured indirectly on the basis of the change in blood pressure response caused by the compounds during the treatment with the α-antagonist adrenaline or β-agonist isoprotenerol according to the literature ([4] and [5] respectively) and were expressed in percent.

References

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