Studies on Agents with Vasodilator and β-Blocking Activities. I

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A series of hydrazinopyridazine derivatives combined with a β-blocking side chain were synthesized. When they were given intravenously to anesthetized rats, some of them exhibited both hypotensive and β-blocking activities. Their structure–activity relationships for hypotensive and β-blocking activities are discussed. Compound 11c had the best profile and was selected for further study.

Keywords phenoxypropanolamine; hydrazinopyridazine; antihypertensive agent; β-blocking activity; hypotensive activity; heart rate

Extensive efforts have been made to find safer and more effective antihypertensive agents and to improve patient compliance and quality of life (QOL) since the early treatment of hypertensive patients with sympatholytics.[1] Now we have available a variety of antihypertensive agents with several mechanisms of action, such as vasodilation, β-blockade, diuresis, inhibition of angiotensin converting enzyme, Ca-antagonism, *etc.* The aim of our current research is to find superior vasodilators with β-blocking activity.

Though vasodilators reduce blood pressure by directly relaxing peripheral vascular smooth muscle, the reduction in blood pressure leads to a reflex increase in sympathetic tone, followed by increases in heart rate, cardiac output and plasma renin activity, which attenuate the antihypertensive effect. It was reported that these undesirable effects of vasodilators could be eliminated by simultaneous treatment with β-blockers, and at the same time, that the possible increase in peripheral vascular resistance induced by β-blockers was eliminated by concomitant use of vasodilators.[2] In fact, the combined use of a vasodilator and a β-blocker has occasionally been adopted for treatment of hypertension.[1,3] However, the use of two drugs with different characteristics of absorption, metabolism, and excretion presents difficulties in synchronizing the two actions. Therefore, the use of a single molecule with both activities should be favorable. Labetalol (**1**) and niprazilol (**2**) may meet the case[4] (Chart 1).

Hydralazine (**3**) and its six-membered monocyclic analogue, hydrazinopyridazine,[5] seemed to be suitable parent compounds upon which to bestow β-blocking activity because of their potent and long-lasting antihypertensive activity. Several novel hydrazinopyridazine and phthalazine derivatives having β-blocking side chains were therefore synthesized and their pharmacological activities were examined.

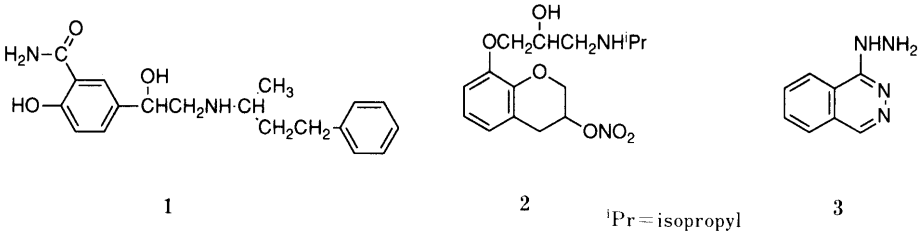
Chemistry

A series of 3-alkoxy-6-hydrazinopyridazines (**10**) were synthesized from 3,6-dichloropyridazine[6] (**4**) *via* chloropyridazines (**9**), as shown in Chart 2.

Phenols (**5**) were converted to the epoxy alcohols (**6**) by reaction with excess epichlorohydrin in the presence of potassium carbonate. Reaction of **6** with 3,6-dichloropyridazine (**4**) in the presence of sodium hydride yielded the corresponding epoxypyridazines (**7b—e**).

In the case of phenoxypyridazine (**7a**), an alternative route was adopted because of difficulty with selective monoglycidylation. Reaction of **4** with catechol in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) yielded the mono-ether (**8**), which was then treated with epichlorohydrin in a usual manner to produce **7a**.

Amination of **7** yielded the corresponding propanolamines (**9**). Reaction of the chlorides (**9**) with excess hydrazine hydrate yielded the desired products (**10**). Condensation of **10** with acetone followed by recrystallization or chromatography gave the hydrazones (**11**) in poor yields of 5—40%. The isomeric compounds (**11i, j**), whose β-blocking side chain was located at the *meta* or *para* position to the pyridazinyloxyethyl moiety, were derived from the corresponding hydroxyphenethyl alcohol by the same method as described above. The isopropylidene group of **11** was removed by hydrolysis with hydrochloric acid or more favorably by hydrazone exchange reaction using hydrazine hydrate to afford the desired hydrazine compounds (**10**).



1 2 3

iPr = isopropyl

Chart 1

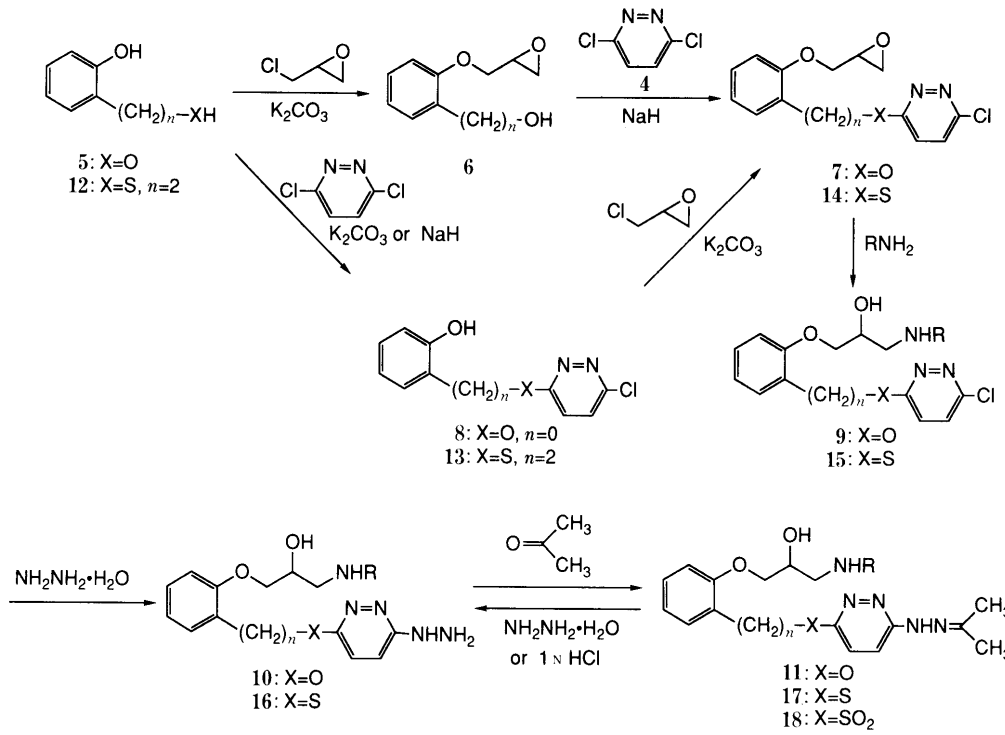


Chart 2

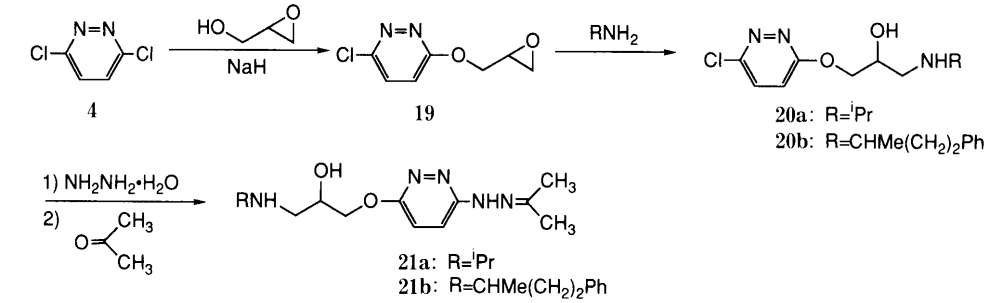


Chart 3

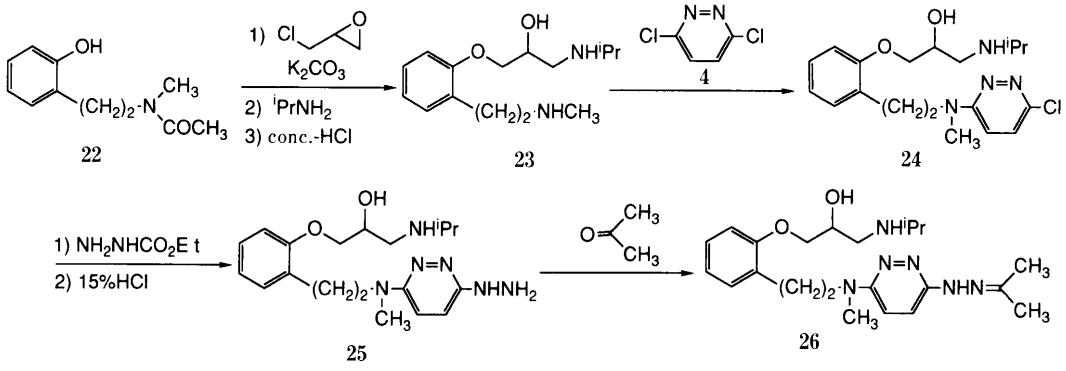


Chart 4

Dorigotti *et al.*[7] prepared compound **21**, having a β-blocking side chain and a hydrazino group on the pyridazine ring, from **4** and glycerol-1,2-acetonide, and confirmed it to have the desired pharmacological activities to some extent. Those results seemed so interesting for our purpose that some compounds of this type were similarly synthesized (Chart 3).

Thus, the reaction of **4** with glycidol in the presence of sodium hydride gave the epoxide (**19**) in a yield of 72.4%. Ring opening of **19** with primary amines yielded the propanolamines (**20**), which were then treated with hydrazine hydrate followed by condensation with acetone to afford the hydrazones (**21**).

Pyridazinylthio analogues (**16**) were also synthesized by the method shown in Chart 2. Selective *S*-arylation of **4** with 2-(2-mercaptoethyl)phenol[8] in the presence of 2 eq of sodium hydride produced the thioether (**13**) in a yield of 70.2%. Glycidylation of **13** with epichlorohydrin and

subsequent amination in a usual manner yielded the propanolamines (**15**). Reaction of **15** with excess hydrazine hydrate provided the desired products (**16**) in good yields, and they were treated with acetone to produce the hydrazone derivatives (**17**).

Treatment of **15** with acetic anhydride in pyridine provided the *N*,*O*-diacetyl derivative, which was converted to the sulfone by oxidation using *m*-chloroperbenzoic acid. The sulfone was treated with excess hydrazine hydrate and then acetone to yield the hydrazone (**18**).

The pyridazinylamino derivative (**25**) was also synthesized according to the procedure shown in Chart 4.

The methylamine (**23**) was obtained by glycidylation and subsequent amination of *N*-(*o*-hydroxyphenethyl)-*N*-methylacetamide[9] (**22**) followed by deacetylation with concentrated hydrochloric acid. Reaction of **23** with 3,6-dichloropyridazine (**4**) at 110 °C gave the aminopyridazine (**24**). Apparently steric bulkiness of the isopropyl group prevents the attack at the nitrogen atom of the β-blocking side chain. In a series of 3-amino-6-chloropyridazines, replacement of the chlorine atom by nucleophilic substitution was rather difficult due to the electron-donating 3-amino group.[10] According to the method of Carpi,[11] **24** was treated with ethoxycarbonylhydrazine[12] at 140—150 °C, but the reaction proceeded so slowly that instead, **24** was converted to the ammonium salt to activate the chlorine atom. The hydrochloride salt of **24** smoothly reacted with ethoxycarbonylhydrazine, as expected. The resulting carbazate was then hydrolyzed with 15% hydrochloric acid to give the hydrazino derivative (**25**) in a 66.2% yield. Treatment of **25** with acetone also provided the hydrazone compound (**26**). These results are summarized in Tables I—III.

Finally, we attempted to modify the hydrazino moiety of 1-hydrazinophthalazine (hydralazine) (**3**) and some 3-hydrazinopyridazine analogues according to the procedures shown in Charts 5 and 6.

Hydralazine (**3**) was condensed with the appropriate hydroxybenzaldehydes in the presence of equimolar sodium acetate to produce the benzylidene derivatives (**27**), which were then reacted with excess epibromohydrin under basic conditions to yield the epoxy compounds (**28**). As an alternative method, **3** was condensed directly with the epoxyaldehydes[13] to provide **28** in good yields. The desired propanolamines (**29**) were derived from **28** by treatment with the primary amines. In addition, according to the method of Pollak and Tisler,[14] the hydrazone (**29c**) was cyclized to *s*-triazolo[3,4-*a*]phthalazine (**30**) with bromine in acetic acid. In the same way as **3**, pyridazine compounds[5,15] (**31**) were reacted with the epoxyaldehydes and subsequently with isopropylamine to produce the benzylidene derivatives (**32**).

Finally, the hydralazine (**3**) was treated with the phenyl carbamates[16] (**33**) to yield the semicarbazide derivatives (**34**). These results are shown in Table IV.

TABLE I. Physical Properties of Epoxy Pyridazines

Compd. No.	*n*	Position	Yield (%)	Recrystn. solvent	mp (°C)	Formula[a]
7a	0	2	63.6	EtOH	69—71	$C_{13}H_{11}ClN_2O_3$
7b	1	2	68.0	EtOH	80—81	$C_{14}H_{13}ClN_2O_3$
7c	2	2	74.1	EtOH	54—56	$C_{15}H_{15}ClN_2O_3$
7d	3	2	35.0	EtOH	62—64	$C_{16}H_{17}ClN_2O_3$
7e	4	2	63.8	EtOH	70—72	$C_{17}H_{19}ClN_2O_3$
7f	2	3	73.4	EtOH	51—53	$C_{15}H_{15}ClN_2O_3$
7g	2	4	57.4	EtOH	71—73	$C_{15}H_{15}ClN_2O_3$
14	2	2	89.1	EtOH	82—84	$C_{15}H_{15}ClN_2O_2S$
19			72.4	iso-Pr_2O	92—95	$C_7H_7ClN_2O_2$

a) All compounds gave satisfactory analyses for C, H, N.

Pharmacology

The hypotensive and β-blocking activities of these compounds were examined in anesthetized rats using the procedures described in Experimental. Hydralazine and propranolol were used as reference drugs. The results are shown in Tables III and V.

Compound **21**, which has a hydrazino group and a β-blocking side chain on the pyridazine ring, did not show any hypotensive activity at the dose of 1 mg/kg i.v. On the other hand, compounds **11** were active.

TABLE II. Physical Properties of Chloro Pyridazines

Compound No.	*n*	Position	R	Yield (%)	Recrystn. solvent	mp (°C)	Formula[a]
9a	0	2	iso-Pr	89.8	C_6H_6	103—105	$C_{16}H_{20}ClN_3O_3$
9b	1	2	iso-Pr	93.7	C_6H_6	98—99	$C_{17}H_{22}ClN_3O_3$
9c	2	2	iso-Pr	92.5	C_6H_6	86—88	$C_{18}H_{24}ClN_3O_3$
9d	2	2	*tert*-Bu	81.8	iso-Pr_2O	82—85	$C_{19}H_{26}ClN_3O_3$
9e	2	2	CMe_2CH_2OH	59.9	C_6H_6	82—83	$C_{19}H_{26}ClN_3O_4$
9f	2	2	$CH_2CH_2Ph(3,4\text{-}OMe)_2$	62.6	MeOH–acetone	182—183	$C_{25}H_{30}ClN_3O_5 \cdot 0.5(CO_2H)_2$
9g	3	2	iso-Pr	86.5	iso-Pr_2O	80—81	$C_{19}H_{26}ClN_3O_3$
9h	4	2	iso-Pr	89.0	C_6H_6	105—106	$C_{20}H_{28}ClN_3O_3$
9i	2	3	iso-Pr	82.5	Et_2O	70—71	$C_{18}H_{24}ClN_3O_3$
9j	2	4	iso-Pr	94.4	C_6H_6	100—102	$C_{18}H_{24}ClN_3O_3$
15a	2	2	iso-Pr	92.4	C_6H_6	108—110	$C_{18}H_{24}ClN_3O_2S$
15b	2	2	*tert*-Bu	86.2	iso-Pr_2O	77—80	$C_{19}H_{26}ClN_3O_2S$
20a			iso-Pr	80.2	iso-Pr_2O	83—84	$C_{10}H_{16}ClN_3O_2$
20b			$CHMe(CH_2)_2Ph$	45.9	iso-Pr_2O	98—102	$C_{17}H_{21}ClN_3O_2$
24	2	2	iso-Pr	78.6	MeOH–acetone	125—128	$C_{19}H_{27}ClN_4O_2 \cdot 2HCl \cdot 0.5H_2O$

a) See footnote a) in Table I.

TABLE III. Physical and Pharmacological Properties of Hydrazino Pyridazines and Related Compounds

Compound No.	Yield (%)	Recrystn. solvent	mp (°C)	Formula[a]	β-Blocking activity[b]	Hypotensive activity[c]
10c	79.3	EtOH	191—194	$C_{18}H_{27}N_5O_3 \cdot 2HCl$	1/10	++
10d	49.3	EtOH	179—182	$C_{19}H_{29}N_5O_3 \cdot 2HCl$	1/10	++
11a	5.2	Acetone	124—126	$C_{19}H_{27}N_5O_3$	1/30	±
11b	28.7	Et_2O	101—104	$C_{20}H_{29}N_5O_3$	1/15	±
11c	35.6	Acetone	126—128	$C_{21}H_{31}N_5O_3$	1/3	+++
11d	23.9	Acetone	112—113	$C_{22}H_{33}N_5O_3$	1/8	++
11e	25.5	Acetone	104—106	$C_{22}H_{33}N_5O_4$	1/4	++
11f	30.2	EtOH	135—138	$C_{32}H_{37}N_5O_5$[d]	1/10	±
11g	37.2	Acetone	88—90	$C_{22}H_{33}N_5O_3$	1/30	+++
11h	39.4	Acetone	142—145	$C_{23}H_{35}N_5O_3 \cdot 2HCl$	1/5	+
11i	29.4	Acetone	109—111	$C_{21}H_{31}N_5O_3$	1/60	+
11j	29.7	Acetone	121—122	$C_{21}H_{31}N_5O_3$	<1/300	+++
16a	77.1	EtOH	181—183	$C_{18}H_{27}N_5O_2S \cdot 2HCl$	1/6	++
17a	60.5	Acetone	132—134	$C_{21}H_{31}N_5O_2S$	1/5	+++
17b	59.8	EtOH–acetone	143—145	$C_{22}H_{33}N_5O_2S \cdot 2HCl$	1/10	+++
18	23.2	MeOH–acetone	116—118	$C_{21}H_{31}N_5O_4S \cdot 0.2H_2O$	1/10	+
21a	32.1	MeOH–acetone	201—205[e]	$C_{13}H_{23}N_5O_2 \cdot 2HCl$	1/300	±
21b	17.8	EtOH–acetone	167—171[f]	$C_{20}H_{28}N_5O_2 \cdot 2HCl$	1/100	±
25	66.2	Dioxane–EtOH–H_2O	129—133	$C_{19}H_{30}N_6O_2 \cdot 4HCl \cdot H_2O$	4/5	+++
26	59.1	MeOH–acetone	116—118	$C_{22}H_{34}N_6O_2 \cdot 3HCl \cdot H_2O$	4/5	+++
Propranolol					1	
Hydralazine						+++

a) See footnote *a*) in Table I. *b*) Potency relative to propranolol. *c*) Hypotensive activity is rated as follows: ±, <15 mmHg; +, 15—24 mmHg; ++, 25—34 mmHg; +++, ≧35 mmHg. *d*) Benzylidenehydrazone. *e*) Lit.[7] mp 218—220 °C (dec.). *f*) Lit.[7] mp 170—175 °C (dec.).

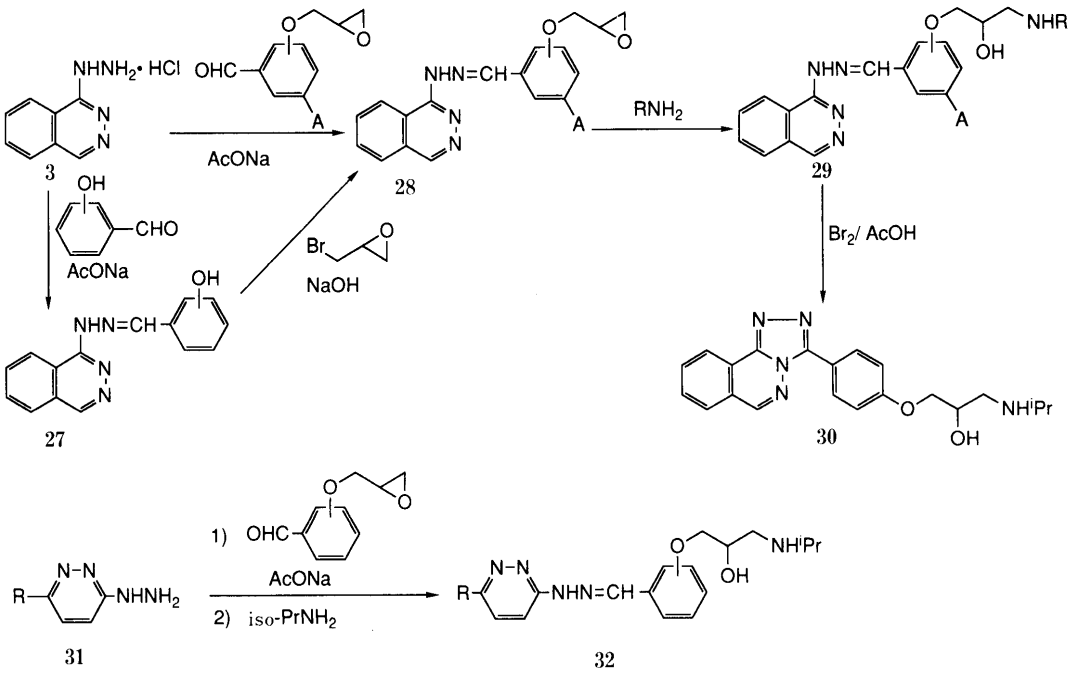


Chart 5

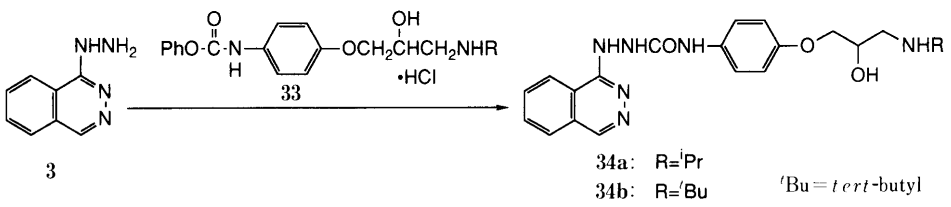


Chart 6

Among a series of 3-alkoxy-6-hydrazonopyridazines (**11a—j**), **11c** showed the most potent hypotensive and β-blocking activities. When the length (*n*) of the methylene chain between the benzene ring and the pyridazine ring was varied from 0 to 4, the highest activities appeared at *n* of 2. Shortening or lengthening of the methylene chain

TABLE IV. Physical Properties of Benzylidenehydrazones and Related Derivatives

Compound No.	Position	R	A	Yield (%)	Recrystn. solvent	mp (°C)	Formula[a]
27a	2		H	97.0	Acetone	212—215	$C_{15}H_{12}N_4O$
27b	3		H	89.6	Acetone	232—234	$C_{15}H_{12}N_4O$
28a	2		H	30.6 (89.6)[b]	$CHCl_3$	169—171	$C_{18}H_{16}N_4O_2$
28b	3		H	26.5 (80.8)	EtOH	129—131	$C_{18}H_{16}N_4O_2$
28c	4		H	67.2 (91.2)	Acetone	169—171	$C_{18}H_{16}N_4O_2$
28d	4		OMe	65.9	MeOH	161—162	$C_{19}H_{18}N_4O_3$
28e	4		Br	84.0	MeOH	171—173	$C_{18}H_{15}BrN_4O_2 \cdot 0.1H_2O$
29a	2	iso-Pr	H	67.5	MeOH	180—182	$C_{21}H_{25}N_5O_2$
29b	3	iso-Pr	H	72.3	EtOH	123—125	$C_{21}H_{25}N_5O_2$
29c	4	iso-Pr	H	93.0	MeOH	186—188	$C_{21}H_{25}N_5O_2$
29d	4	*tert*-Bu	H	90.8	MeOH	180—181	$C_{22}H_{27}N_5O_2$
29e	4	$CH_2CH_2Ph(3,4\text{-}OMe)_2$	H	43.8	EtOH	123—124	$C_{28}H_{31}N_5O_4$
29f	4	iso-Pr	OMe	76.9	MeOH	158—159	$C_{22}H_{27}N_5O_3$
29g	4	iso-Pr	Br	87.2	MeOH	183—184	$C_{21}H_{24}BrN_5O_2 \cdot 0.1H_2O$[c]
30	4	iso-Pr		52.0	EtOH	186—189	$C_{21}H_{23}N_5O_2$
32a	4	$O(CH_2CH_2)_2N$–		67.7	MeOH	238—241	$C_{21}H_{30}N_6O_3$
32b	4	$(CH_2{=}CHCH_2)_2N$–		87.4	EtOH	146—149	$C_{23}H_{32}N_6O_2$
32c	2	Et_2N–		33.0	Hexane	65—68	$C_{21}H_{32}N_6O_2$
32d	3	Et_2N–		76.9	iso-PrOH	142—144	$C_{21}H_{32}N_6O_2$
32e	4	Et_2N–		69.0	EtOH	182—184	$C_{21}H_{32}N_6O_2$
32f	4	EtO–		69.7	EtOH	196—199	$C_{19}H_{27}N_5O_3$
34a	4	iso-Pr		10.0	MeOH	176—178	$C_{21}H_{26}N_6O_3 \cdot 0.5H_2O$[d]
34b	4	*tert*-Bu		27.7	MeOH	184—187	$C_{22}H_{28}N_6O_3 \cdot 0.4H_2O$

a) See footnote *a*) in Table I. *b*) Yield from **3** and epoxyaldehyde. *c*) Calcd: N, 15.22. Found: N, 14.89. *d*) Calcd: N, 20.03. Found: N, 19.62.

TABLE V. Biological Activies of Benzylidenehydrazone and Related Derivatives

Compound No.	β-Blocking activity[a]	Hypotensive activity[a]
29a	1/10	±
29b	1/10	±[b]
29c	1/3[c]	+++[b]
29d	1/30	±[d]
29e	1/7	±[b]
29f	1/7	+[b]
29g	1/10	±[b]
30	1/500	±[e]
32a	1/100	+
32b	1/30	+++
32c	1/6	+++[f]
32d	1/30	+++[d]
32e	1/20	+++
32f	1/3	±[d]
34a	1/10	±[d]
34b	1/5	±[d]

a) See footnote in Table III. *b*) 30 mg/kg, i.p. *c*) No detectable inhibition of depressor response at a dose producing 80% inhibition of tachycardia. *d*) 3 mg/kg, i.v. *e*) 10 mg/kg, i.v. *f*) 3 mg/kg, i.p.

resulted in reduction of these activities. Migration of the β-blocking side chain to the *meta* or *para* position reduced the potency, although the *para* isomer **11j** retained high hypotensive activity. Replacement of the isopropyl group of the β-blocking side chain on **11c** with other alkyl groups gave compounds less potent than **11c**. Replacement of the pyridazine ether oxygen of **11c** with another hetero atom retained the activities, and the N-analogue (**26**) exhibited the highest β-blocking activity in this series. Oxidation of the thioether to the sulfone, however, reduced the potency. Removal of the isopropylidene group generally caused lower activities than that of the hydrazones, except for the N-analogue (**25**), which retained the activities.

Finally, compounds in which the β-blocking side chain was attached to the hydrazino moiety were examined. Conversion of the hydrazino group to the benzylidene hydrazone resulted in a marked decrease of hypotensive and β-blocking activities. In a series of phthalazine compounds, it is notable that compound **29c**, which has a β-blocking side chain at the *para* position, exhibited hypotensive and β_1-selective blocking activities. On the other hand, in a series of pyridazine analogues (**32**), β-blocking activities were very weak, though hypotensive activities were more potent than that of **29c**. The semicarbazides (**34**) showed no hypotensive activity.

Thus, **11c** (TZC-8159), with the hydrazonopyridazinyloxyethyl group in the *ortho* position to the β-blocking side chain, was found to have the most favorable pharmacological profile of long-lasting hypotensive and β-blocking activities. The S- and N-analogues of **11c** also showed potent activities. Further pharmacological study on **11c** is in progress.

Experimental

Melting points were determined with a Mettler FP-2 melting point apparatus and are uncorrected. NMR spectra were determined on a Hitachi R-20A spectrometer with tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard. Mass spectra were obtained with a Shimadzu GCMS-QP 1000 instrument. Elemental analyses were within ±0.3% of the theoretical values.

3-Chloro-6-[2-[2-(2,3-epoxypropoxy)phenyl]ethoxy]pyridazine (7c) A mixture of *o*-hydroxyphenethyl alcohol (**5c**) (13 g, 94.2 mmol), epichlorohydrin (52 g, 0.562 mol) and K_2CO_3 (13 g, 94.2 mmol), was refluxed for 2 h with stirring. The precipitates were removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the oily residue was purified by distillation to yield **6c** (13.5 g, 73.9%)

as a colorless oil, bp 158—160 °C (1 mmHg). NMR ($CDCl_3$) δ: 2.10 (1H, t, J=5 Hz), 2.60—3.10 (4H, m), 3.20—3.50 (1H, m), 3.60—4.40 (4H, m), 6.70—7.40 (4H, m). MS m/z: 194 (M^+).

A solution of **6c** (13 g, 67 mmol) in dry C_6H_6 (30 ml) was added dropwise to a mixture of **4** (10 g, 67.1 mmol), 60% NaH (3.3 g, 82.5 mmol) and dry C_6H_6 (30 ml), with stirring at room temperature. The mixture was then refluxed for 1 h with stirring. After cooling, the precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield **7c** (8.57 g, 74.1%) as colorless crystals. An analytical sample was recrystallized from EtOH, mp 54—56 °C. NMR ($CDCl_3$) δ: 2.70—3.00 (2H, m), 3.18 (2H, t, J=7 Hz), 3.20—3.60 (1H, m), 3.80—4.40 (2H, m), 4.70 (2H, t, J=7 Hz), 6.70—7.50 (6H, m). MS m/z: 306 (M^+). *Anal.* Calcd for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.52; H, 4.93; N, 9.18.

Compounds **7b**—**g** and **19** were derived from **4** and the appropriate epoxy-alcohol (**6**) or glycidol, as described above.

3-Chloro-6-(2-hydroxyphenoxy)pyridazine (8) A mixture of **4** (7.54 g, 50 mmol), catechol (5.5 g, 50 mmol), K_2CO_3 (9 g, 65 mmol) and DMF (60 ml) was stirred at 100 °C for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in 1 N NaOH. The solution was extracted with $CHCl_3$. The aqueous layer was acidified with 10% HCl, and the resulting precipitates were collected by filtration and dried. Recrystallization from $CHCl_3$ yielded **8** (5.17 g, 46.5%) as colorless crystals, mp 147—149 °C. MS m/z: 222 (M^+). *Anal.* Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.59. Found: C, 53.76; H, 2.95; N, 12.53.

3-Chloro-6-[2-(2-hydroxyphenyl)ethylthio]pyridazine (13) A solution of 2-(2-mercaptoethyl)phenol (**12**) (30 g, 0.195 mol) in dry C_6H_6 (200 ml) was added dropwise to a mixture of **4** (34.6 g, 0.232 mol), 60% NaH (17.63 g, 0.441 mol) and dry C_6H_6 (200 ml), with stirring over a period of 30 min. The whole was then refluxed for 30 min with stirring, acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was recrystallized from $CHCl_3$–Et_2O to yield **13** (36.5 g, 70.2%) as colorless needles, mp 147—149 °C. NMR ($CDCl_3$) δ: 2.75—3.60 (4H, m), 6.63—7.60 (5H, m), 7.38 (2H, s). MS m/z: 266 (M^+). *Anal.* Calcd for $C_{12}H_{11}ClN_2OS$: C, 54.03; H, 4.16; N, 10.50. Found: C, 54.08; H, 4.04; N, 10.73.

3-Chloro-6-[2-[2-(2,3-epoxypropoxy)phenyl]ethylthio]pyridazine (14) **13** (32.0 g, 0.12 mol) was treated with epichlorohydrin as described for **6c** to yield **14** (34.5 g, 89.1%) as colorless crystals, mp 82—84 °C. NMR ($CDCl_3$) δ: 2.68—3.28 (4H, m), 3.28—3.78 (3H, m), 3.80—4.40 (2H, m), 6.70—7.40 (4H, m), 7.24 (2H, s). MS m/z: 322 (M^+). *Anal.* Calcd for $C_{15}H_{15}ClN_2O_2S$: C, 55.81; H, 4.68; N, 8.89. Found: C, 55.81; H, 4.78; N, 8.89.

1-[2-[2-(3-Chloro-6-pyridazinyloxy)ethyl]phenoxy]-3-isopropylamino-2-propanol (9c) A solution of **7c** (1.0 g, 3.26 mmol) and isopropylamine (4 ml) in EtOH (20 ml) was stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from C_6H_6 to yield **9c** (1.10 g, 92.5%) as colorless crystals, mp 86—88 °C. NMR ($CDCl_3$) δ: 1.10 (6H, d, J=6 Hz), 2.50—3.20 (5H, m), 3.13 (2H, t, J=7 Hz), 4.03 (3H, br s), 4.70 (2H, t, J=7 Hz), 6.70—7.40 (4H, m), 6.90 (1H, d, J=9 Hz), 7.33 (1H, d, J=9 Hz). MS m/z: 365 (M^+). *Anal.* Calcd for $C_{18}H_{24}ClN_3O_3$: C, 59.09; H, 6.61; N, 11.49. Found: C, 59.21; H, 6.65; N, 11.59.

Compounds **9**, **15** and **20** were derived from the corresponding epoxides (**7**, **14** and **19**) and the appropriate amines, as described above.

1-[2-[2-(3-Isopropylidenehydrazino-6-pyridazinyloxy)ethyl]phenoxy]-3-isopropylamino-2-propanol (11c) A solution of **9c** (10 g, 27.4 mmol) and hydrazine hydrate (200 ml) in EtOH (100 ml) was refluxed for 5 h with stirring. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The solution was washed three times with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dissolved in acetone (30 ml). This solution was kept overnight in a refrigerator. The resulting precipitates were collected by filtration and recrystallized from acetone to yield **11c** (3.91 g, 35.6%) as pale yellow crystals, mp 126—128 °C. NMR ($CDCl_3$) δ: 1.05 (6H, d, J=6 Hz), 1.90 (3H, s), 2.00 (3H, s), 2.50—3.30 (5H, m), 3.10 (2H, t, J=7 Hz), 4.02 (3H, br s), 4.61 (2H, t, J=7 Hz), 6.60—7.40 (4H, m), 6.85 (1H, d, J=9 Hz), 7.50 (1H, d, J=9 Hz). MS m/z: 401 (M^+). *Anal.* Calcd for $C_{21}H_{31}N_5O_3$: C, 62.82; H, 7.78; N, 17.44. Found: C, 62.79; H, 7.72; N, 17.32.

Compounds **11**, **17** and **21** were obtained from the corresponding chlorides (**9**, **15** or **20**) according to the method described above.

1-[2-[2-(3-Hydrazino-6-pyridazinyloxy)ethyl]phenoxy]-3-isopropylamino-2-propanol Dihydrochloride (10c) Method A: A solution of **11c** (4.01 g, 10 mmol) and hydrazine hydrate (10 g, 0.2 mol) in EtOH (40 ml) was refluxed for 2 h with stirring. The reaction mixture was treated as described above, and the residue was acidified with ethanolic HCl. The solvent was removed under reduced pressure, and the residue was dissolved in EtOH and kept overnight in a refrigerator. The resulting precipitates were collected by filtration and recrystallized from EtOH to yield **10c** (3.44 g, 79.3%) as colorless crystals, mp 191—194 °C. NMR (D_2O) δ: 1.43 (6H, d, J=6 Hz), 2.90—3.80 (3H, m), 3.20 (2H, t, J=7 Hz), 4.00—4.70 (3H, m), 4.59 (2H, t, J=7 Hz), 6.85—7.50 (4H, m), 7.32 (1H, d, J=9 Hz), 7.50 (1H, d, J=9 Hz). MS m/z: 361 (M^+). *Anal.* Calcd for $C_{18}H_{27}N_5O_3 \cdot 2HCl$: C, 49.77; H, 6.73; N, 16.12. Found: C, 49.77; H, 6.69; N, 16.23.

Method B: A solution of **11c** (1.0 g, 2.49 mmol) in 1 N HCl (40 ml) was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was treated as described above to yield **10c** (792 mg, 73.2%) as colorless crystals.

Compound **10d** was similarly prepared from **11d**.

1-[2-[2-(3-Hydrazino-6-pyridazinylthio)ethyl]phenoxy]-3-isopropylamino-2-propanol Dihydrochloride (16a) A solution of **15a** (1.0 g, 2.62 mmol) and hydrazine hydrate (20 ml) in EtOH (10 ml) was refluxed for 5 h with stirring. The reaction mixture was treated as described above to yield **16a** (0.91 g, 77.1%) as colorless crystals, mp 181—183 °C. NMR (D_2O) δ: 1.40 (6H, d, J=6 Hz), 2.70—3.80 (7H, m), 4.00—4.50 (3H, m), 6.70—7.70 (6H, m). MS m/z: 377 (M^+). *Anal.* Calcd for $C_{18}H_{27}N_5O_2S \cdot 2HCl$: C, 47.99; H, 6.49; N, 15.55. Found: C, 47.69; H, 6.34; N, 15.44.

1-[2-[2-(3-Isopropylidenehydrazino-6-pyridazinylsulfonyl)ethyl]phenoxy]-3-isopropylamino-2-propanol (18) A solution of **15a** (2.0 g, 5.25 mmol) and acetic anhydride (12.5 ml, 13.3 mmol) in pyridine (12.5 ml) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was poured into ice-water. The separated oily material was extracted with AcOEt. The organic layer was washed with 5% Na_2CO_3 and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to yield the *N,O*-diacetyl derivative (2.03 g, 83.2%) as a colorless oil. NMR ($CDCl_3$) δ: 1.20, 1.26 (6H, two d, J=6 Hz), 2.08 (3H, s), 2.16 (3H, s), 2.75—3.30 (2H, m), 3.30—3.89 (4H, m), 3.90—4.50 (3H, m), 5.20—5.60 (1H, m), 6.68—7.35 (4H, m), 7.21 (2H, s).

m-Chloroperbenzoic acid (1.83 g, 10.6 mmol) was added portionwise to a solution of the *N,O*-diacetyl derivative (2.0 g, 4.3 mmol) in $CHCl_3$ (60 ml), under ice-cooling with stirring. The whole was stirred overnight at room temperature, washed with 5% Na_2CO_3 and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to yield the sulfone (1.87 g, 87.5%) as a colorless oil. NMR ($CDCl_3$) δ: 1.23, 1.33 (6H, two d, J=6 Hz), 2.16 (3H, s), 2.18 (3H, s), 2.90—4.60 (9H, m), 5.10—5.70 (1H, m), 6.40—7.35 (4H, m), 7.50 (1H, d, J=9 Hz), 7.80 (1H, d, J=9 Hz).

A solution of the sulfone (1.85 g, 3.72 mmol) and hydrazine hydrate (45 ml) in EtOH (21 ml) was treated as described for the preparation of **11c** to yield **18** (387 mg, 23.2%) as pale yellow crystals, mp 116—118 °C. NMR (CD_3OD) δ: 1.15 (6H, d, J=6 Hz), 2.08 (6H, s), 2.70—3.21 (5H, m), 3.58—4.32 (5H, m), 6.55—7.25 (4H, m), 7.38 (1H, d, J=9 Hz), 7.75 (1H, d, J=9 Hz). MS m/z: 449 (M^+). *Anal.* Calcd for $C_{21}H_{31}N_5O_4S \cdot 0.2H_2O$: C, 55.66; H, 6.98; N, 15.46. Found: C, 55.69; H, 7.03; N, 15.49.

1-[2-[2-[*N*-(3-Chloro-6-pyridazinyl)-*N*-methylamino]ethyl]phenoxy]-3-isopropylamino-2-propanol Dihydrochloride Hemihydrate (24) A mixture of *N*-(*o*-hydroxyphenethyl)-*N*-methylacetamide (**22**) (14.6 g, 75.6 mmol), epichlorohydrin (100 ml, 1.28 mol) and K_2CO_3 (14.6 g, 0.106 mol) was refluxed for 2 h with stirring. The precipitates were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was distilled to yield the epoxy compound (17.7 g, 93.9%) as a colorless oil, bp 160—170 °C (0.1 mmHg).

A solution of the epoxy compound (17.7 g, 71.1 mmol) and isopropylamine (18 ml) in MeOH (90 ml) was refluxed for 1 h with stirring. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O and acidified with HCl-saturated ether. The resulting precipitates of the propanolamine were collected by filtration (23.0 g, 93.9%).

A solution of the propanolamine (23 g, 66.8 mmol) in concentrated HCl (200 ml) was heated at 120 °C for 15 h, then concentrated under

reduced pressure. The residue was made alkaline with saturated K_2CO_3 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated to yield **23** (16.3 g, 91.8%) as a pale brown viscous oil.

A mixture of **23** (40.7 g, 0.153 mol) and **4** (34.2 g, 0.23 mol) was heated at 110 °C for 2 h with stirring. After cooling, the mixture was dissolved in $CHCl_3$ (200 ml) and acetone (200 ml). A solution of concentrated HCl (31 ml) in acetone (150 ml) was added to this solution with stirring under ice-cooling. Stirring was continued for 30 min, then the resulting precipitates were collected by filtration and recrystallized from MeOH–acetone to yield **24** (55.37 g, 78.6%) as colorless crystals, mp 125—128 °C. NMR (D_2O) δ: 1.42 (6H, d, J=7 Hz), 2.75—3.70 (5H, m), 3.25 (3H, s), 3.85—4.55 (5H, m), 6.80—7.65 (6H, m). MS *m/z*: 378 (M^+). *Anal.* Calcd for $C_{19}H_{27}ClN_4O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 49.52; H, 6.56; N, 12.15. Found: C, 49.76; H, 6.57; N, 12.03.

1-[2-[2-[*N*-(3-Hydrazino-6-pyridazinyl)-*N*-methylamino]ethyl]phenoxy]-3-isopropylamino-2-propanol Tetrahydrochloride Monohydrate (25) **24** (50 g, 0.11 mol) was added portionwise over a period of 10 min to ethoxycarbonylhydrazine (48 g, 0.46 mol) at 140 °C and the mixture was further heated for 2 h with stirring. After cooling, 15% HCl (750 ml) was added to the reaction mixture and the whole was refluxed for 6 h. The solvent was evaporated off under reduced pressure, and the residue was dissolved in a solution of H_2O (35 ml), dioxane (185 ml) and EtOH (10 ml). After standing overnight in a refrigerator, the resulting crystals were collected by filtration to yield **25** (36.5 g, 66.2%) as colorless crystals, mp 129—133 °C. NMR (CD_3OD) δ: 1.44 (6H, d, J=7 Hz), 2.90—4.65 (10H, m), 3.36 (3H, s), 6.70—7.85 (4H, m), 7.41 (1H, d, J=9 Hz), 7.71 (1H, d, J=9 Hz). MS *m/z*: 374 (M^+). *Anal.* Calcd for $C_{19}H_{30}N_6O_2 \cdot 4HCl \cdot H_2O$: C, 42.38; H, 6.74; N, 15.61. Found: C, 42.55; H, 6.98; N, 15.91.

1-[2-[2-[*N*-(3-Isopropylidenehydrazino-6-pyridazinyl)-*N*-methylamino]ethyl]phenoxy]-3-isopropylamino-2-propanol Trihydrochloride Monohydrate (26) A solution of **25** (36.5 g, 72.8 mmol) and acetone (250 ml) in MeOH (250 ml) was refluxed for 1.5 h with stirring. The solvent was removed under reduced pressure, and the residue was dissolved in acetone (150 ml). This solution was kept overnight in a refrigerator, and the resulting precipitates were collected by filtration and recrystallized from MeOH–acetone to yield **26** (23.3 g, 59.1%) as pale yellow crystals, mp 116—118 °C. NMR (CD_3OD) δ: 1.40 (6H, d, J=7 Hz), 2.08 (3H, s), 2.13 (3H, s), 2.75—3.60 (5H, m), 3.06 (3H, s), 3.78 (2H, d, J=7 Hz), 4.00—4.55 (3H, m), 6.60—7.25 (4H, m), 7.56 (2H, s). MS *m/z*: 414 (M^+). *Anal.* Calcd for $C_{22}H_{34}N_6O_2 \cdot 3HCl \cdot H_2O$: C, 48.76; H, 7.25; N, 15.51. Found: C, 48.69; H, 7.00; N, 15.80.

1-[4-(2,3-Epoxypropoxy)benzylidenehydrazino]phthalazine (28c) Method A: A suspension of **3** (5.0 g, 25.4 mmol), *p*-hydroxybenzaldehyde (3.1 g, 25.4 mmol) and absolute AcONa (3.1 g, 37.8 mmol) in EtOH (200 ml) and H_2O (50 ml) was refluxed for 2 h with stirring. After cooling, the precipitates were collected by filtration and washed with H_2O to yield **27c** (4.46 g, 66.3%) as yellow crystals, mp 206—210 °C. NMR (DMSO-d_6) δ: 6.80 (2H, d, J=9 Hz), 7.45—8.45 (5H, m), 7.84 (2H, d, J=9 Hz), 8.35 (1H, s), 9.77 (1H, s), 11.90 (1H, br s). MS *m/z*: 264 (M^+).

Epibromohydrin (4.11 g, 30 mmol) was added to a solution of **27c** (2.64 g, 10 mmol) and 1 N NaOH (12 ml) in H_2O (50 ml), under ice-cooling with stirring. Stirring was continued for 2 h at room temperature, then the resulting precipitates were collected by filtration and recrystallized from acetone to yield **28c** (2.15 g, 67.2%) as yellow crystals, mp 169—171 °C. NMR ($CDCl_3$) δ: 2.68—3.05 (2H, m), 3.10—3.50 (1H, m), 3.85—4.45 (2H, m), 6.95 (2H, d, J=8 Hz), 7.10—8.60 (7H, m), 8.46 (1H, s), 10.60 (1H, br s). MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.36; H, 5.03; N, 17.58.

Method B: A suspension of **3** (9.8 g, 50 mmol), *p*-(2,3-epoxypropoxy)-benzaldehyde (8.9 g, 50 mmol) and absolute AcONa (4.1 g, 50 mmol) in EtOH (300 ml) was stirred for 2 h at room temperature. The precipitates were collected by filtration and washed with H_2O. Recrystallization from MeOH gave **28c** (14.6 g, 91.2%) as yellow crystals.

Compounds **27** and **28** were similarly prepared.

1-[4-(3-Isopropylamino-2-hydroxypropoxy)benzylidenehydrazino]-phthalazine (29c) A mixture of **28c** (3.0 g, 9.4 mmol), isopropylamine (50 ml) and MeOH (150 ml) was stirred for 2 h at reflux temperature. The solvent was removed under reduced pressure and the residue was recrystallized from MeOH to give **29c** (3.3 g, 93%) as yellow needles, mp 186—188 °C. NMR (DMSO-d_6) δ: 1.02 (6H, d, J=6 Hz), 2.45—3.10 (3H, m), 3.20 (2H, br s), 3.97 (3H, br s), 6.95 (2H, d, J=9 Hz), 7.50—8.45 (5H, m), 7.94 (2H, d, J=9 Hz), 8.38 (1H, s), 11.93 (1H, br s). MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{21}H_{25}N_5O_2$: C, 66.47; H, 6.64; N, 18.46. Found: C, 66.25; H, 6.58; N, 18.28.

Hydrazone derivatives (**29**) were prepared from the corresponding epoxide (**28**) and various primary amines. Pyridazine derivatives (**32**) were also prepared from the hydrazino compounds (**31**) by the method desdribed above. The results are shown in Table IV.

3-[4-(3-Isopropylamino-2-hydroxypropoxy)phenyl]-*s*-triazolo[3,4-*a*]-phthalazine (30) A solution of Br_2 (160 mg, 2 mmol) in AcOH (2 ml) was added dropwise to a mixture of **29c** (379 mg, 1 mmol), absolute AcONa (131 mg, 1.6 mmol) and AcOH (10 ml), with stirring at room temperature. Stirring was continued for 2 h, then the solvent was removed under reduced pressure. The residue was made alkaline with aqueous Na_2CO_3 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from EtOH to yield **30** (196 mg, 52%) as colorless crystals, mp 186—189 °C. NMR (DMSO-d_6) δ: 1.03 (6H, d, J=6 Hz), 2.40—3.00 (3H, m), 3.20 (2H, br s), 4.01 (3H, br s), 7.17 (2H, d, J=9 Hz), 7.70—8.70 (4H, m), 8.30 (2H, d, J=9 Hz), 9.10 (1H, s). MS *m/z*: 377 (M^+). *Anal.* Calcd for $C_{21}H_{23}N_5O_2$: C, 66.82; H, 6.14; N, 18.56. Found: C, 66.78; H, 6.05; N, 18.62.

1-(1-Phthalazinyl)-4-[4-(3-isopropylamino-2-hydroxypropoxy)phenyl]-semicarbazide (34a) A mixture of **3** (320 mg, 2.0 mmol), the carbamate (**33a**) (835 mg, 2.2 mmol) and MeOH (15 ml) was stirred for 16 h at reflux temperature, then the solvent was removed under reduced pressure. The residue was dissolved in H_2O and made alkaline with 1 N NaOH. The resulting precipitates were collected by filtration and recrystallized from iso-PrOH to yield **34a** (84 mg, 10%) as yellow crystals, mp 176—178 °C. NMR (DMSO-d_6) δ: 0.99 (6H, d, J=6 Hz), 2.30—2.90 (2H, m), 3.00—3.50 (3H, m), 3.82 (3H, br s), 6.80 (2H, d, J=9 Hz), 7.30—7.90 (6H, m), 8.10—8.75 (3H, m). MS *m/z*: 224, 186, 109 (base peak). *Anal.* Calcd for $C_{21}H_{26}N_6O_3 \cdot 0.5H_2O$: C, 60.12; H, 6.45; N, 20.03. Found: C, 59.97; H, 6.15; N, 19.62.

Pharmacological Methods All experiments were performed with groups of three male Wistar rats (300—400 g) anesthetized with pentobarbital-Na (60 mg/kg, i.p.). Arterial blood pressure was measured directly from the femoral artery *via* a catheter using a pressure transducer, and heart rate was counted from the arterial blood pressure pulse waves. Injection of drugs was performed through a catheter inserted in the abdominal *vena cava via* the femoral artery.

β-Blocking activities of test compounds, cumulatively injected, were measured in terms of the antagonism of the tachycardia induced by i.v.-injected isoproterenol (0.1 μg/kg). From the dose–inhibition curves, ID_{50} values (the dose of test compounds producing 50% inhibition of isoproterenol-induced tachycardia) were calculated and the relative potencies with respect to propranolol were determined (Tables III and V).

Hypotensive activities of test compounds were also determined by measuring the decrease in arterial blood pressure at the dose of 1 mg/kg i.v. The maximal decreases in blood pressure during 40 min are also shown in Tables III and V.

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