Studies on Agents with Vasodilator and β-Blocking Activities. IV[1)]

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A series of novel pyridazinone derivatives (II) having a phenoxypropanolamine moiety was synthesized. Their hypotensive and β-blocking activities were evaluated after intravenous administration of the compounds to anesthetized rats. Among them, the 5-chloro-2-cyanophenoxy derivative (29) showed the promising dual activities and was selected for further studies.

Key words phenoxypropanolamine; pyridazinone; hypotensive activity; β-blocking activity; congestive heart failure

Many vasodilators cause reflex tachycardia. To overcome this drawback, we have synthesized compounds with both vasodilator and β-blocking activities.[2)] In the previous report,[2b)] we described the synthesis and pharmacological activities of a series of phenoxypropanolamine derivatives (I) having a hydrazinopyridazinyl moiety on the *N*-alkyl substituent in order to develop an effective antihypertensive agent. Among them, the *ortho*-chlorophenoxy derivative (**1**, TZC-1370) was revealed to have the most potent dual activities: the hypotensive activity was equal to that of hydralazine and the β-blocking activity was 2.7-fold more potent than that of propranolol. Thus, linking of a hydrazinopyridazine, a vasodilator, to a phenoxypropanolamine, a β-blocker, in a certain way provided a molecule with both activities. In the present study, a series of 6-aryl-4,5-dihydro-5-methylpyridazin-3(2*H*)-ones (**2**), characteristically potent vasodilators,[3)] was coupled to a β-blocker to prepare a series of novel phenoxypropanolamine derivatives having a 6-aryl-4,5-dihydro-5-methylpyridazin-3(2*H*)-one moiety on the *N*-alkyl substituent, as shown by the general formula (II).

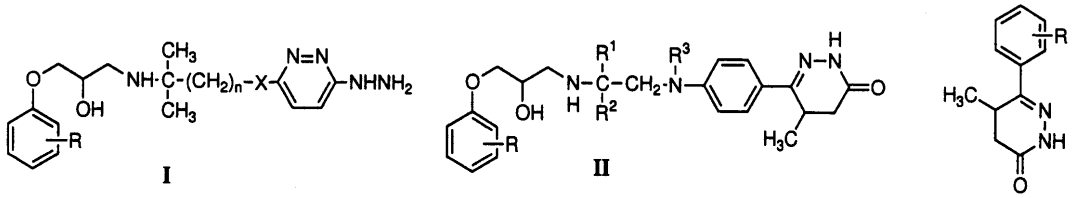
Recently, several reports have suggested that a β-blocker, *e.g.* alprenolol or metoprolol, could be beneficial in the long-term treatment of some types of congestive heart failure (CHF).[4)] At the same time, vasodilators themselves are used in the treatment of CHF. Thus, an agent with both vasodilator and β-blocking activities could be useful for the treatment of CHF by improving the decreased cardiac function without causing an increase in heart rate. Bucindolol, a potent β-blocker with vasodilator activity, has already been reported to be useful in the treatment of CHF.[5)] Moreover, the inotropic activity of some pyridazinones (**2**) makes them candidates for the treatment of CHF.[6)] From this point of view, some pyridazinone derivatives having the dual activities were synthesized for examination of their pharmacological activities in the present study.

Chemistry

The reaction of the diaminopyridazinone (**3**—**6**) with the glycidyl ether (**7**) gave the phenoxypropanolamine derivatives (II) having a pyridazinone moiety on the *N*-alkyl substituent as shown in Chart 2. The physical properties of the novel pyridazinone derivatives (II) are summarized in Table 1.

The key compounds, the diaminopyridazinones (**3**—**5**), having a hydrogen atom at the aniline nitrogen, were prepared by the procedure described in Chart 3. The anilino-pyridazinone (**42**), the starting material for **3**—**5**, was derived from acetanilide according to the method of McEvoy and Allen,[7)] while 2-methyl-2-phthaliminopropanal (**43**)[8)] was obtained by oxidation of the corresponding alcohol[9)] with dimethyl sulfoxide (DMSO). Then **42** was reductively alkylated with a slight excess of the aldehyde (**43**) and sodium cyanoborohydride to give the *N*-monoalkylated derivative (**46**). The phthaloyl group of **46** was removed with hydrazine hydrate in a usual way to afford the desired diaminopyridazinone (**3**). Compound **3** was also derived from the aminoalcohol (**49**) *via* the following reaction sequence: *N*-protection of **49** to **50**,[10)] the Parikh–Doering oxidation[11)] of **50** to the aldehyde (**51**), reductive amination of **51** to **52**, and subsequent removal of the *tert*-butoxycarbonyl group with hydrogen chloride. The α-methyl substituted and α-non-branched 1,2-diaminopyridazinones (**4** and **5**) were similarly derived from **42** and the corresponding phthalimino-aldehyde (**44** or **45**)[8)] as described above.

The synthesis of **3** *via* the anilino-pyridazinone (**42**) mentioned above was laborious and unsatisfactory on a



I II 2

1 (TZC-1370): R=2-Cl, n=1, X=O

Chart 1

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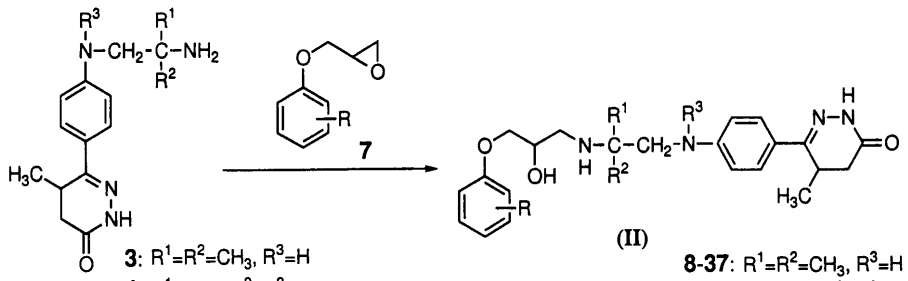

3: $R^1=R^2=CH_3$, $R^3=H$
4: $R^1=CH_3$, $R^2=R^3=H$
5: $R^1=R^2=R^3=H$
6: $R^1=R^2=R^3=CH_3$

(II)

8-37: $R^1=R^2=CH_3$, $R^3=H$
38: $R^1=CH_3$, $R^2=R^3=H$
39: $R^1=R^2=R^3=H$
40-41: $R^1=R^2=R^3=CH_3$

Chart 2

Table 1. Physical Properties of Pyridazinone Derivatives (II)

Compound No.[a]	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
8	2-Cl	94.6	167—170	$C_{24}H_{31}ClN_4O_3 \cdot C_4H_4O_4$[b]	58.48	6.14	9.74	58.48	6.19	9.72
9	2-CN	93.1	175—178	$C_{25}H_{31}N_5O_3 \cdot C_4H_4O_4$	61.58	6.24	12.38	61.63	6.15	12.35
10	2-Me	82.0	159—162	$C_{25}H_{34}N_4O_3 \cdot C_4H_4O_4$	62.80	6.91	10.10	62.81	6.81	9.97
11	2-Cl-3-Me	82.0	149—151	$C_{25}H_{33}ClN_4O_3 \cdot C_4H_4O_4$	59.12	6.33	9.51	59.00	6.51	9.65
12	2,3-Cl_2	68.3	167—170	$C_{24}H_{30}Cl_2N_4O_3 \cdot C_4H_4O_4$	55.17	5.62	9.19	55.07	5.62	9.32
13	2-CN-3-Cl	71.0	173—174	$C_{25}H_{30}ClN_5O_3 \cdot C_4H_4O_4$	58.04	5.71	11.67	58.03	5.84	11.92
14	2-CN-3-Me	82.0	164—167	$C_{26}H_{33}N_5O_3 \cdot C_4H_4O_4$	62.15	6.43	12.08	62.13	6.25	11.93
15	2-Me-3-Cl	59.3	171—174	$C_{25}H_{33}ClN_4O_3 \cdot C_4H_4O_4$	59.12	6.33	9.51	58.91	6.44	9.63
16	2,3-Me_2	69.4	170—173	$C_{26}H_{36}N_4O_3 \cdot C_4H_4O_4$	63.36	7.09	9.85	63.49	7.12	9.79
17	2-Me-3-NO_2	73.0	124—127	$C_{25}H_{33}N_5O_5 \cdot C_4H_4O_4$	58.08	6.21	11.68	57.95	6.15	11.67
18	2-NO_2-3-Me	78.6	136—138	$C_{25}H_{33}N_5O_5 \cdot C_4H_4O_4$	58.08	6.21	11.68	58.06	6.05	11.72
19	–(CH=CH)$_2$–	98.1	144—146	$C_{28}H_{34}N_4O_3 \cdot C_4H_4O_4$	65.07	6.48	9.49	65.19	6.40	9.48
20	2-CH=CH–NH-3	87.7	112—113	$C_{26}H_{33}N_5O_3 \cdot C_4H_4O_4$	62.15	6.43	12.08	61.94	6.49	11.95
21	2-CH=CMe–NH-3	80.3	206—207	$C_{27}H_{35}N_5O_3$	67.89	7.38	14.66	67.88	7.45	14.51
22	2-$(CH_2)_2$CONH-3	83.2	196—199	$C_{27}H_{35}N_5O_4$	65.69	7.14	14.18	65.51	7.26	13.89
23	2,5-Cl_2	88.3	200—202	$C_{24}H_{30}Cl_2N_4O_3 \cdot C_4H_4O_4$	55.17	5.62	9.19	55.13	5.62	9.20
24	2-Cl-5-CN	52.2	187—189	$C_{25}H_{30}ClN_5O_3 \cdot C_4H_4O_4$	58.04	5.71	11.67	57.97	5.77	11.77
25	2-Cl-5-Me	68.9	166—167	$C_{25}H_{33}ClN_4O_3 \cdot C_4H_4O_4$	59.13	6.33	9.51	59.03	6.36	9.58
26	2-Cl-5-NO_2	63.1	195—197	$C_{24}H_{30}ClN_5O_5 \cdot C_4H_4O_4$	54.23	5.52	11.29	54.15	5.47	11.29
27	2-Cl-5-CF_3	54.1	203—205	$C_{25}H_{30}ClF_3N_4O_3 \cdot C_4H_4O_4$	54.16	5.33	8.71	54.11	5.31	8.50
28	2-CN-5-Cl	70.6	196—199	$C_{25}H_{30}ClN_5O_3 \cdot C_4H_4O_4$	58.04	5.71	11.67	57.98	5.83	11.82
29	2-CN-5-Cl	70.6	154—155	$C_{25}H_{30}ClN_5O_3 \cdot C_6H_8O_4$[c]	59.27	6.10	11.15	59.26	6.05	11.31
30	2-CN-5-Me	89.3	198—201	$C_{26}H_{33}N_5O_3 \cdot C_4H_4O_4$	62.15	6.43	12.08	62.19	6.37	11.88
31	2-Me-5-Cl	61.0	197—199	$C_{25}H_{33}ClN_4O_3 \cdot C_4H_4O_4$	59.12	6.33	9.51	58.99	6.46	9.57
32	2,5-Me_2	72.8	182—185	$C_{26}H_{36}N_4O_3 \cdot C_4H_4O_4$	63.36	7.09	9.85	63.33	7.09	9.75
33	2-NO_2-5-Cl	68.0	187—190	$C_{24}H_{30}ClN_5O_5 \cdot C_4H_4O_4$	54.23	5.52	11.29	54.26	5.59	11.32
34	2,5-$(NO_2)_2$	87.9	172—174	$C_{24}H_{30}N_6O_7 \cdot C_4H_4O_4$	53.32	5.43	13.32	53.42	5.18	13.10
35	3,5-Me_2	77.1	146—149	$C_{26}H_{36}N_4O_3 \cdot C_4H_4O_4$	63.36	7.09	9.85	63.40	7.10	9.85
36	2-Cl-4-Me	85.2	176—179	$C_{25}H_{33}ClN_4O_3 \cdot C_4H_4O_4$	59.12	6.33	9.51	59.05	6.42	9.64
37	2-CN-4-OH-5-Cl	61.1[d]	144—146	$C_{25}H_{30}ClN_5O_4 \cdot C_4H_4O_4 \cdot 0.8H_2O$	55.24	5.69	11.11	55.29	5.52	10.84
38	2-Cl-5-Me	88.2	188—190	$C_{24}H_{31}ClN_4O_3 \cdot 0.5(CO_2H)_2$	59.57	6.40	11.12	59.42	6.50	11.15
39	2-Cl-5-Me	42.2	117—120	$C_{23}H_{29}ClN_4O_3$	62.08	6.57	12.59	61.90	6.65	12.55
40	2-Me	76.4	158—159	$C_{26}H_{36}N_4O_3 \cdot 0.5(CO_2H)_2$	65.17	7.50	11.26	65.26	7.45	11.33
41	2-Cl-5-Me	70.5	223—224	$C_{26}H_{35}ClN_4O_3 \cdot 0.5(CO_2H)_2$	60.95	6.82	10.53	60.85	7.00	10.56

a) The structures are shown in Chart 2. *b*) Maleate. *c*) Monoethyl maleate salt. *d*) Overall yield from **70**.

large scale, so that an alternative route of 1,4-addition was developed as shown in Chart 4. The 1,4-addition of α-aryl-4-morpholinoacetonitrile to α,β-unsaturated esters or nitriles in the presence of a catalytic amount of potassium hydroxide was reported to be a versatile way to obtain 6-arylpyridazin-3(2*H*)-ones.[12] Though compound **54**[13] was treated with crotononitrile according to this method, the reaction proceeded too slowly to afford the desired dicyano compound (**55**) efficiently. Thus, the method was modified by including a phase-transfer catalyst as follows. Addition of 1 mol% benzyltriethylammonium chloride to the reaction mixture in *N*,*N*-dimethylformamide (DMF) promoted the 1,4-addition at room temperature to afford **55**. Without purification, **55** was deprotected with 70% acetic acid to the γ-keto nitrile (**56**),[7] followed by hydrolysis to give the anilino-keto acid (**57**).[14] Compound **57** was transformed to the nitro-aniline (**58**) by Johnson's method[15] with a modification as follows. A solution of **57** in 10% sodium hydroxide was treated with either 2-nitropropane

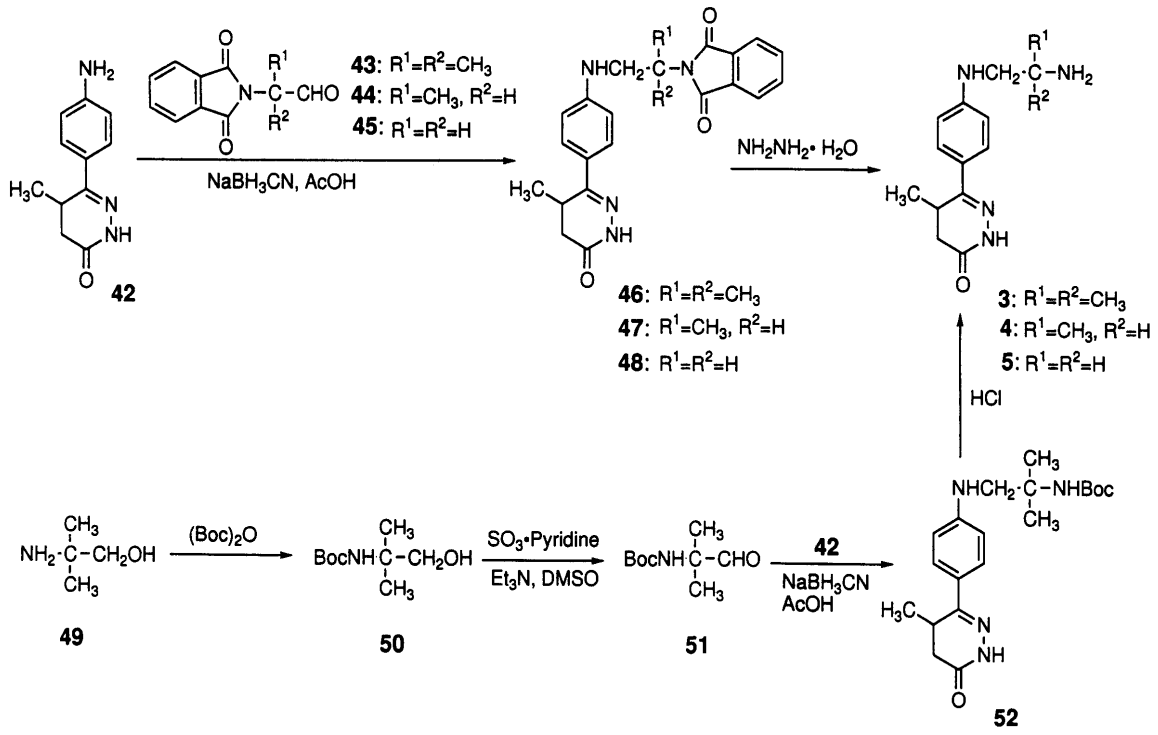

Chart 3

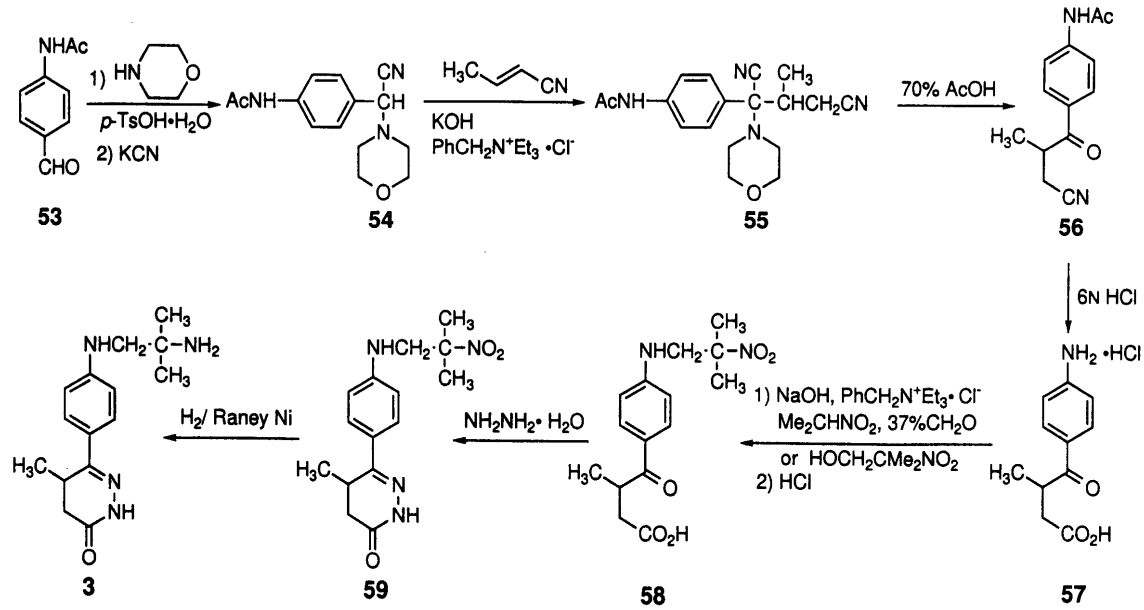

Chart 4

and formaldehyde or 2-methyl-2-nitro-1-propanol in the presence of a catalytic amount of benzyltriethylammonium chloride, followed by acidification to give the γ-keto acid (**58**) in good yield. Cyclization of **58** with hydrazine hydrate in a usual way gave the pyridazinone (**59**). The nitro group of **59** was catalytically hydrogenated over Raney nickel to afford the desired diaminopyridazinone (**3**).

Compound **6**, having a methyl group at the aniline nitrogen, was synthesized from the anilino-keto ester (**60**)[3] in the way shown in Chart 5. The reductive *N*-alkylation of **60** with aldehyde (**51**) and sodium cyanoborohydride gave the secondary amine derivative (**61**). The following reductive *N*-methylation of **61** with an excess of paraformaldehyde and sodium cyanoborohydride afforded the tertiary amine (**62**). Cyclization of the γ-keto ester (**62**) with hydrazine hydrate, followed by deprotection of the resulting pyridazinone (**63**) with hydrogen chloride afforded the diaminopyridazinone (**6**).

It was reported that a phenoxypropanolamine β-blocker was metabolized at the *para*-position of its phenoxy ring with retention of the activity.[16] Thus, we prepared the *para*-hydroxy derivative (**37**) of **28** (Chart 6). The Duff reaction of 3-chloro-4-methoxyphenol (**64**)[17] with hexamethylenetetramine in trifluoroacetic acid (TFA) gave the salicylaldehyde (**65**). Orientation of the formylation was confirmed on the basis of the NMR spectrum showing two singlet aromatic proton signals at δ 7.01 and 7.07.

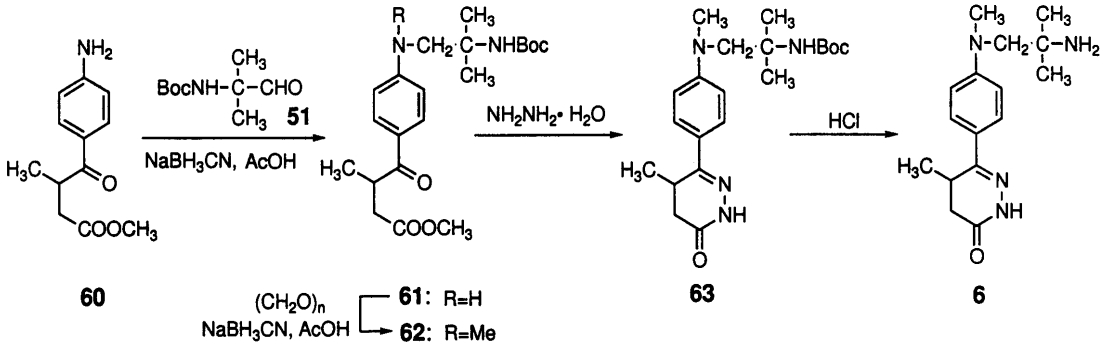

Chart 5

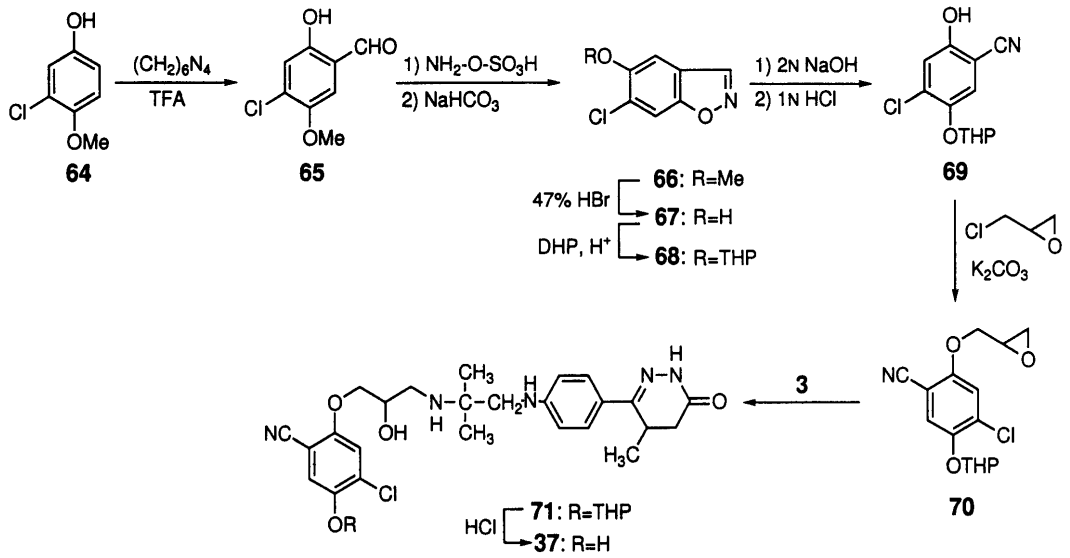

Chart 6

According to the method of Casey *et al.*,[18] condensation of the salicylaldehyde (**65**) with hydroxylamine-*O*-sulfonic acid, followed by ring closure with sodium bicarbonate gave the benzisoxazole (**66**). After demethylation of **66** with 47% hydrobromic acid, the resulting **67** was converted to the tetrahydropyranyl ether (**68**). Base-catalyzed isomerization of **68** afforded the cyanophenol (**69**), which was then reacted with excess epichlorohydrin in the presence of potassium carbonate to give the glycidyl ether (**70**). Treatment of **70** with the diaminopyridazinone (**3**) afforded **71**, and deprotection gave the desired *para*-hydroxy compound (**37**).

Pharmacology

The hypotensive and β-blocking activities of our novel pyridazinone derivatives (II) were evaluated in anesthetized rats using the reported procedures.[2a] Hydralazine and propranolol were used as reference drugs for hypotensive activity and β-blocking activity, respectively. The results are shown in Tables 2 and 3.

In our previous report,[2b] compound I, having a hydrazinopyridazinyloxy moiety on the *N*-alkyl group showed the dual activities. Replacement of the pyridazinyloxy moiety of compound I with a pyridazinylamino moiety resulted in a remarkable decrease of hypotensive activity and an increase of β-blocking activity. On the other hand, as in the case of the 2-chlorophenoxy compound **8** showing hypotensive activity equal to that of hydralazine, substitution of the hydrazinopyridazinyloxy moiety with an anilino-pyridazinone at the aniline nitrogen could be done with retention of the activity, though it was accompanied with a great increase in heart rate, probably due to intrinsic sympathomimetic activity (ISA). Smoller substituents other than a chlorine atom, such as a cyano (**9**) or a methyl (**10**) group, were examined on the basis of the finding that these substituents were preferable from the viewpoint of the dual activities in the case of compound I. In the 2-cyanophenoxy compound (**9**), the hypotensive activity was one-third of that of hydralazine and the β-blocking activity was 1.8-fold more potent than that of propranolol. In the 2-methylphenoxy compound (**10**), the hypotensive activity was equal to that of hydralazine and the β-blocking activity was one-third as potent as that of propranolol. An extreme increase in heart rate, however, was observed with both **9** and **10**, as well as **8**. Therefore, the α-naphthyloxy derivative (**19**) was examined, in view of the fact that propranolol, an α-naphthol derivative, has no ISA at all. Compound **19**, however, showed no hypotensive activity and low β-blocking activity. In the case of compounds **20** (a pindolol type), **21** (a mepindolol type) and **22** (a carteolol type), having 2,3-fused bicyclic aromatic ring in place of naphthalene, the hypotensive activity was also weak and, as for β-blocking activity, only **22** was comparable to propranolol.

In order to retain the dual activities without an increase in heart rate, several modifications of the phenoxypropanolamine moiety were carried out (Table 3). As in the case of a series of 2-chloro-5-methylphenoxy derivatives, branching at the α-carbon atom on the *N*-alkyl group of the phenoxypropanolamine (**25**, $-CMe_2-$; **38**, $-CHMe-$; **39**, $-CH_2-$) enhanced the β-blocking activity, as was expected from the results of Crowther *et al.*[19] Their hypotensive activities were also enhanced. Then we focused on α-*gem*-dimethyl substitution at the nitrogen atom of the phenoxypropanolamine moiety. Further methylation at the aniline nitrogen of **25**, however, resulted in attenuation of the hypotensive activity. Similarly, the hypotensive activity of the 2-methylphenoxy analogue (**40**) was much reduced in comparison with that of the corresponding des-methyl derivative (**10**). In a structure–activity relationship study of 6-aryl-4,5-dihydro-5-methylpyridazin-3(2*H*)-one, McEvoy and Allen observed that monoalkylamino substitution at the 6-aryl group resulted in enhancement of the antihypertensive activity and dialkylamino substitution caused attenuation of the activity.[3] Our results are compatible with theirs.

Table 2. Pharmacological Activities of Pyridazinone Derivatives (II)

Compound No.[a]	β-Blocking activity[b]	Hypotensive activity[c]	Change of heart rate[d]
8	NT	+++	++
9	1.8	+++	++
10	0.33	+++	++
11	0.1	±	−
12	0.2	++	±
13	0.33	+	±
14	0.4	+++	+
15	0.1	+	+
16	0.17	++	±
17	0.2	±	±
18	0.5	++	−
19	0.13	±	±
20	0.33	++	++
21	0.33	+	+
22	1.0	+	++
23	0.14	+++	−
24	0.1	++	−
25	0.17	+++	±
26	0.1	++	±
27	0.17	++	−
28	0.5	+++	−
29	0.45	+++	−
30	0.33	++	−
31	0.11	+++	−
32	0.13	++	−
33	0.25	++	±
34	0.2	±	+
35	0.1	++	−
36	0.01	++	+
37	0.06	++	−
Propranolol	1.0	NT	NT
Hydralazine	NT	+++	NT

Each compound was injected intravenously into anesthetized rats. *a*) The structures are shown in Chart 2. *b*) Potency relative to the ID_{50} value of propranolol. *c*) Degree of hypotension induced at 1 mg/kg: +++, ≧35 mmHg; ++, 25—34 mmHg; +, 15—24 mmHg; ±, <15 mmHg. *d*) Change of heart rate induced at 1 mg/kg: ++, ≧50 beats/min; +, 20—50 beats/min; ±, −20—20 beats/min; −, ≦−20 beats/min. NT = not tested.

In the previous study on a series of hydrazinopyridazine derivatives (I),[2b] 2,5-disubstituted phenoxy derivatives generally exhibited more potent hypotensive activities than the corresponding 2,3-disubstituted analogues. This was also the case for the pyridazinone derivatives (**23**—**34**), having 2,5-disubstituted phenoxy group, except for the 2-cyano-5-methylphenoxy compound (**30**), whose hypotensive activity was about half that of the 2-cyano-3-methyl derivative (**14**).

Therefore, introduction of a chlorine atom, or a cyano, a methyl, a nitro or a trifluoromethyl group into the phenyl ring at the 5-position of the 2-chlorophenoxy compound (**8**), which showed the best hypotensive activity among the *ortho*-monosubstituted compounds (**8**—**10**) as described above, was examined. The hypotensive activities of **24** (2-Cl-5-CN), **25** (2-Cl-5-Me), **26** (2-Cl-5-NO_2) and **27** (2-Cl-5-CF_3) were inferior to that of the corresponding 2-chloro compound (**8**) and their β-blocking activities were weak, except for **23** (2,5-Cl_2), whose hypotensive activity was equal to that of **8**, though the β-blocking activity was one-sixth that of propranolol. The 5-chloro substitution seemed to be significant for the hypotensive activity.

As the hypotensive and β-blocking activities of hydrazinopyridazine derivatives (I) varied with the mode of substitution at the phenyl ring of the aryloxypropanolamine moiety in our previous study,[2b] we introduced several aryloxy groups into the propanolamine moiety of the pyridazinone compounds. A series of 2,3-disubstituted phenoxy compounds (**11**—**18**) showed attenuation of the hypotensive and β-blocking activities in comparison with the corresponding 2-monosubstituted compounds (**8**—**10**). Among them, the 2-cyano-3-methyl analogue (**14**) exhibited appreciable activities (the hypotensive activity was one-third that of hydralazine and the β-blocking activity was two-fifths that of propranolol). For the β-blocking activity, the 2-nitro-3-methylphenoxy compound (**18**) was the best (half as active as propranolol), though the hypotensive activity was a quarter of that of hydralazine.

Table 3. Pharmacological Activities of Pyridazinone Derivatives (II)

Compound No.[a]	R	R^1	R^2	R^3	β-Blocking activity[a]	Hypotensive activity[a]	Change of heart rate[a]
10	2-Me	Me	Me	H	0.33	+++	++
25	2-Cl-5-Me	Me	Me	H	0.17	+++	−
38	2-Cl-5-Me	Me	H	H	0.15	+	−
39	2-Cl-5-Me	H	H	H	0.03	+	−
40	2-Me	Me	Me	Me	NT[a]	+	++
41	2-Cl-5-Me	Me	Me	Me	0.1	±	−

a) See footnote in Table 2.

Furthermore, substitution at the 2-position of the 5-chlorophenoxy ring was examined as follows. 2-Cyano-5-chloro- (**28**) and 2-methyl-5-chlorophenoxy derivatives (**31**) possessed potent hypotensive activity. The hypotensive activity of **28** was equal to that of hydralazine and 3 times more potent than that of the corresponding *ortho*-monosubstituted phenoxy compound (**9**). As for β-blocking activity, **28** was the best among the 2,5-disubstituted phenoxy derivatives (**23**—**34**) (half as potent as that of propranolol). On the other hand, 2-nitro substitution (**33**) was not effective for either activity.

The β-blocking activity of the 2-chloro-4-methylphenoxy compound (**36**) was weaker than that of the corresponding 2,3- or 2,5-disubstituted compound (**11** and **25**), as was expected from the fact that the *para*-substitution of 1-aryloxy-3-isopropylamino-2-propanol gave low β-blocking activity in comparison with the corresponding *ortho*- or *meta*-substitution.[20]

It was reported that in the mono-, di-, and trimethylphenoxypropanolamine β-blockers, 3,5-disubstitution afforded more potent β-blocking activity than the corresponding 2,3- and 2,5-disubstitution.[20] On the other hand, in compound **35** (3,5-Me_2) the β-blocking and hypotensive activities were about the same as those of the corresponding 2,3- and 2,5-disubstituted ones (**16** and **32**).

Conclusion

A series of novel phenoxypropanolamine derivatives (II) having a pyridazinone moiety on the *N*-alkyl group was synthesized as candidate hybrid compounds with vasodilator and β-blocking activities. Branching at α-carbon atom on the *N*-alkyl group of phenoxypropanolamine was essential for both activities to appear. In the case of the hydrazinopyridazine compound (I), any of a chlorine atom, a cyano and a methyl group at the 2-position on the phenyl ring was similarly effective for the dual activities, while in the case of the pyridazinone derivatives (II), a 2-cyano group was preferable for β-blocking activity to a 2-chlorine atom or a 2-methyl group, and an additional 5-chloro substituent afforded a better hypotensive activity without increase in heart rate. Thus, the 5-chloro-2-cyanophenoxy compound (**28**) and its monoethylmaleate salt (**29**, TZC-5665) possessed the most promising pharmacological activity in the present study. Further pharmacological evaluations of TZC-5665 suggested that it might be useful in the treatment of CHF.[21] TZC-5665 is currently under clinical trial for CHF.

Experimental

Melting points were determined with a Mettler FP-2 melting point apparatus and are uncorrected. NMR spectra were taken at 60 MHz on a Hitachi R-1200 spectrometer or at 90 MHz on a Hitachi R-90H spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Mass spectra were taken with a Shimadzu GCMS-QP 1000 instrument. Elemental analysis results were within ±0.3% of the theoretical values.

6-[4-(2-Methyl-2-phthaliminopropylamino)phenyl]-4,5-dihydro-5-methyl-pyridazin-3(2*H*)-one (46) TFA (1.7 ml) was added to a solution of *N*-(1,1-dimethyl-2-hydroxyethyl)phthalimide[9] (60.0 g, 0.274 mol), 1,3-dicyclohexylcarbodiimide (164.0 g, 0.796 mol) and pyridine (22.2 ml) in C_6H_6 (600 ml) and DMSO (300 ml). The whole was stirred overnight at room temperature and then AcOH (15 ml) and H_2O (15 ml) were added. The whole was stirred for 1 h, and the precipitates were removed by filtration. The filtrate was washed three times with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from iso-Pr_2O to give **43** (40.1 g, 67.5%) as colorless needles. mp 88—90 °C. (lit.[11] 90.1—90.6 °C). NMR ($CDCl_3$) δ: 1.68 (6H, s), 7.70—7.90 (4H, m), 9.61 (1H, s). IR (KBr): 1765, 1735, 1710 cm^{-1}. MS *m/z*: 217 (M^+), 88 (base peak).

A mixture of **42** (12.71 g, 62.6 mmol), **43** (17.66 g, 81.4 mmol), AcOH (5.6 ml, 97.9 mmol) and MeOH (300 ml) was stirred for 30 min at room temperature and a solution of $NaBH_3CN$ (2.07 g, 32.9 mmol) in MeOH (100 ml) was added dropwise to the resulting yellow solution with stirring. Stirring was continued overnight at room temperature, then the resulting precipitates were collected by filtration. Recrystallization from acetone gave **46** (17.63 g, 69.7%) as yellow crystals. mp 216—218 °C. NMR ($CDCl_3$) δ: 1.18 (3H, d, *J*=7 Hz), 1.75 (6H, s), 2.36 (1H, dd, *J*=17, 2 Hz), 2.65 (1H, dd, *J*=17, 6 Hz), 3.00—3.40 (1H, m), 3.75 (2H, d, *J*=7 Hz), 4.48 (1H, t, *J*=7 Hz), 6.62 (2H, d, *J*=9 Hz), 7.30—7.87 (4H, m), 7.51 (2H, d, *J*=9 Hz), 8.52 (1H, br s). IR (KBr): 3380, 3200, 1770, 1710, 1685, 1620 cm^{-1}. MS *m/z*: 404 (M^+), 216 (base peak). *Anal.* Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.26; H, 5.76; N, 13.68.

6-[4-(2-Phthaliminopropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (47) Compound **47** (0.62 g, 64.5%) was prepared from **42** (0.50 g, 2.46 mmol) and **44** (0.50 g, 2.96 mmol) as described above. mp 186—189 °C. NMR ($CDCl_3$) δ: 1.19 (3H, d, *J*=7 Hz), 1.57 (3H, d, *J*=7 Hz), 2.37 (1H, dd, *J*=17, 2 Hz), 2.67 (1H, dd, *J*=17, 6 Hz), 3.00—4.10 (4H, m), 4.40—4.90 (1H, m), 6.60 (2H, d, *J*=9 Hz), 7.53 (2H, d, *J*=9 Hz), 7.55—7.93 (4H, m), 8.44 (1H, br s). IR (KBr): 3365, 1770, 1700, 1615 cm^{-1}. MS *m/z*: 390 (M^+), 216 (base peak). *Anal.* Calcd for $C_{22}H_{22}N_4O_3$: C, 67.67; H, 5.68; N, 14.35. Found: C, 67.56; H, 5.62; N, 14.24.

6-[4-(2-Phthaliminoethylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (48) Compound **48** (7.13 g, 50.8%) was prepared from **42** (7.58 g, 37.3 mmol) and **45** (7.06 g, 37.3 mmol) as described above. mp 223—224 °C. NMR ($CDCl_3$) δ: 1.20 (3H, d, *J*=7 Hz), 2.38 (1H, dd, *J*=17, 2 Hz), 2.68 (1H, dd, *J*=17, 6 Hz), 3.06—3.60 (1H, m), 3.47 (2H, t, *J*=6 Hz), 3.98 (2H, t, *J*=6 Hz), 6.62 (2H, d, *J*=9 Hz), 7.55 (2H, d, *J*=9 Hz), 7.60—7.93 (4H, m), 8.43 (1H, br s). IR (KBr): 3330, 1770, 1705, 1680, 1610 cm^{-1}. MS *m/z*: 376 (M^+), 216 (base peak). *Anal.* Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.89. Found: C, 67.00; H, 5.25; N, 14.89.

6-[4-(2-*tert*-Butoxycarbonylamino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (52) Di-*tert*-butyl dicarbonate (65.0 g, 0.298 mol) was added portionwise to a solution of **49** (53.0 g, 0.596 mol) in H_2O (500 ml) with stirring at room temperature. Stirring was continued for 1 h and then the whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in *n*-hexane and the solution was allowed to stand overnight. The resulting crystals were collected by filtration to give **50** (44.41 g, 78.9%) as colorless plates. mp 57—60 °C. NMR ($CDCl_3$) δ: 1.24 (6H, s), 1.42 (9H, s), 3.20—5.50 (2H, m), 3.56 (2H, s). MS *m/z*: 158 ($M^+ - 31$), 57 (base peak).

A solution of sulfur trioxide pyridine complex (25.25 g, 0.159 mol) in DMSO (160 ml) was added in one portion to a solution of **50** (10 g, 52.9 mmol) and Et_3N (16.03 g, 0.159 mol) in DMSO (160 ml) and the whole was stirred for 30 min at room temperature. After usual work-up,[11] the residue was recrystallized from *n*-hexane to give **51** (8.58 g, 86.7%) as colorless needles. mp 86—87 °C. NMR ($CDCl_3$) δ: 1.32 (6H, s), 1.43 (9H, s), 4.95 (1H, br s), 9.38 (1H, s). IR (KBr): 3270, 1740, 1720 cm^{-1}. MS *m/z*: 158 ($M^+ - 29$), 57 (base peak).

According to the method described for **46**, a solution of **42** (2.03 g, 10 mmol), **51** (2.43 g, 13 mmol) and AcOH (0.60 g, 10 mmol) in MeOH (50 ml) was treated with $NaBH_3CN$ (0.33 g, 5.24 mmol). The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with 5% Na_2CO_3 and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give **52** (3.58 g, 95.7%) as colorless crystals. An analytical sample was recrystallized from iso-Pr_2O. mp 157—160 °C. NMR ($CDCl_3$) δ: 1.22 (3H, d, *J*=7 Hz), 1.34 (6H, s), 1.42 (9H, s), 2.18—2.95 (2H, m), 3.05—3.55 (1H, m), 3.31 (2H, s), 4.58 (1H, br s), 6.58 (2H, d, *J*=9 Hz), 7.52 (2H, d, *J*=9 Hz), 8.59 (1H, br s). IR (KBr): 3470, 3405, 3205, 1700, 1670, 1615 cm^{-1}. MS *m/z*: 374 (M^+), 216, 58 (base peak). *Anal.* Calcd for $C_{20}H_{30}N_4O_3$: C, 64.14; H, 8.07; N, 14.96. Found: C, 64.13; H, 8.19; N, 15.00.

6-[4-(2-Amino-2-methylpropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (3) Method A: A solution of **46** (13.0 g, 32.2 mmol) and hydrazine hydrate (5.0 ml, 0.1 mol) in EtOH (130 ml) was refluxed for 2 h. After cooling, the resulting precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. 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 residue was recrystallized from iso-PrOH to give **3** (7.53 g, 83.3%) as colorless crystals. mp 184—186 °C. NMR (CD_3OD) δ: 1.15 (3H, d, J=7 Hz), 1.16 (6H, s), 2.30 (1H, dd, J=17, 2 Hz), 2.69 (1H, dd, J=17, 6 Hz), 3.07 (2H, s), 3.13—3.53 (1H, m), 6.68 (2H, d, J=9 Hz), 7.58 (2H, d, J=9 Hz). IR (KBr): 3330, 3260, 1680, 1610 cm^{-1}. MS *m/z*: 274 (M^+), 217, 58 (base peak). *Anal.* Calcd for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08; N, 20.42. Found: C, 65.71; H, 8.18; N, 20.31.

Method B: A 2.3 N HCl–AcOEt solution (40 ml) was added to a solution of **52** (3.74 g, 10 mmol) in AcOEt (10 ml) with stirring at ice cooling. Stirring was continued for 1 h, then the solvent was evaporated under reduced pressure. The residue was dissolved in H_2O. The solution was alkalinized with Na_2CO_3 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from iso-PrOH gave **3** (2.06 g, 75.2%) as colorless crystals.

Method C: A solution of **59** (412.6 g, 1.36 mol) in DMF (1600 ml) was hydrogenated under atmospheric pressure at 60—65 °C using Raney nickel as a catalyst. After theoretical uptake of hydrogen, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was recrystallized from MeOH to give **3** (340.4 g, 91.5%) as colorless crystals.

6-[4-(2-Aminopropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (4) Compound **4** (96 mg, 72.2%) was prepared from **47** (0.20 g, 0.51 mmol) as described above. mp 158—162 °C. NMR (CD_3OD) δ: 1.14 (6H, d, J=7 Hz), 2.27 (1H, dd, J=17, 2 Hz), 2.69 (1H, dd, J=17, 6 Hz), 2.95—3.53 (4H, m), 6.59 (2H, d, J=9 Hz), 7.53 (2H, d, J=9 Hz). IR (KBr): 3340, 1665, 1610 cm^{-1}. MS *m/z*: 260 (M^+), 216 (base peak). *Anal.* Calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.59; H, 7.69; N, 21.48.

6-[4-(2-Aminoethylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3-(2*H*)-one (5) Compound **5** (2.82 g, 65.0%) was prepared from **48** (6.63 g, 17.6 mmol) as described above. mp 160—162 °C. NMR (DMSO-d_6) δ: 1.04 (3H, d, J=7 Hz), 2.15 (1H, d, J=17 Hz), 2.30—3.50 (7H, m), 5.96 (1H, t, J=5 Hz), 6.57 (2H, d, J=9 Hz), 7.51 (2H, d, J=9 Hz), 10.60 (1H, s). IR (KBr): 3390, 3350, 1670, 1610 cm^{-1}. MS *m/z*: 246 (M^+), 216 (base peak). *Anal.* Calcd for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.40; H, 7.32; N, 22.75.

3-(4-Acetamidobenzoyl)butyronitrile (56) According to the literature,[12] a solution of **53** (500 g, 3.07 mol), *p*-TsOH·H_2O (630 g, 3.32 mol) and morpholine (580 ml, 6.66 mol) in tetrahydrofuran (2300 ml) was refluxed for 1 h with stirring. After cooling the above solution, a solution of KCN (270 g, 4.15 mol) in H_2O (450 ml) was added dropwise to it. The whole was refluxed for 3 h with stirring and concentrated under reduced pressure. The residue was poured into ice-water and the resulting precipitates were collected by filtration to give **54** (733.6 g, 92.3%) as colorless crystals. mp 154—156 °C. (lit.[13] 152—154 °C). NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.45—2.70 (4H, m), 3.55—3.85 (4H, m), 4.77 (1H, s), 7.30—7.70 (1H, m), 7.44 (2H, d, J=9 Hz), 7.57 (2H, d, J=9 Hz). IR (KBr): 3350, 2250, 1680, 1540 cm^{-1}. MS *m/z*: 259 (M^+), 173, 131, 56 (base peak).

KOH (3.25 g, 58 mmol) was added in one portion to a solution of **54** (150 g, 0.58 mol), crotononitrile (58.2 g, 0.87 mol) and benzyltriethylammonium chloride (1.32 g, 5.8 mmol) in DMF (300 ml). The whole was stirred for 6 h at room temperature and then diluted with H_2O. The separated oily material was extracted with AcOEt. The organic layer was washed three times with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **55** (188.8 g, quantitatively) as a pale brown viscous oil, which was used for the next step without further purification. NMR ($CDCl_3$) δ: 1.07 (3H, d, J=7 Hz), 1.60—2.10 (1H, m), 2.18 (3H, s), 2.30—3.05 (6H, m), 3.50—3.95 (4H, m), 7.35 (2H, d, J=9 Hz), 7.58 (2H, d, J=9 Hz), 7.68 (1H, br s). IR (KBr): 3320, 2225, 1670, 1605, 1530 cm^{-1}. MS *m/z*: 326 (M^+), 258 (base peak).

A solution of **55** (188.8 g, 0.58 mmol) in AcOH (335 ml) and H_2O (120 ml) was stirred for 2 h at 100 °C. The solution was concentrated under reduced pressure. The residue was poured into H_2O (1000 ml) and the whole was stirred overnight. The resulting precipitates were collected by filtration to give **56** (119.5 g, 89.9%) as pale brown crystals, which were used for the next step without further purification. mp 127—130 °C. (lit.[7] mp 131—132 °C). NMR ($CDCl_3$) δ: 1.39 (3H, d, J=7 Hz), 2.22 (3H, s), 2.60—2.90 (2H, m), 3.50—4.20 (1H, m), 7.71 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 8.22 (1H, s). IR (KBr): 2250, 1675, 1540 cm^{-1}. MS *m/z*: 230 (M^+), 162, 120 (base peak).

3-(4-Aminobenzoyl)butyric Acid Hydrochloride (57) A solution of **56** (151.6 g, 0.66 mmol) in 2 N hydrochloric acid (450 ml) was stirred for 2 h at reflux temperature. After cooling, the resulting precipitates were collected by filtration and washed with acetone to give **57** (110.4 g, 68.8%) as colorless crystals. NMR (CD_3OD) δ: 1.20 (3H, d, J=7 Hz), 2.48 (1H, dd, J=17, 6 Hz), 2.96 (1H, dd, J=17, 9 Hz), 3.30—3.70 (1H, m), 7.61 (2H, d, J=9 Hz), 8.23 (2H, d, J=9 Hz). IR (KBr): 2900, 1715, 1695 cm^{-1}. MS *m/z*: 207 (M^+), 120 (base peak).

3-[4-(2-Methyl-2-nitropropylamino)benzoyl]butyric Acid (58) Method A: Compound **57** (1500 g, 6.16 mol), 2-nitropropane (670 ml, 7.43 mol), 37% formaldehyde (560 ml, 7.43 mol) and benzyltriethylammonium chloride (28.3 g, 0.124 mol) were added successively to a solution of NaOH (530 g, 12.3 mol) in H_2O (3700 ml). The whole was stirred for 4 h at reflux temperature. Then, 2-nitropropane (450 ml, 5.0 mol) and 37% formaldehyde (375 ml, 5.0 mol) were added dropwise to the solution and stirring was continued for 4 h at reflux temperature. The reaction mixture was acidified with concentrated HCl (620 ml, 7.22 mol) at 80—85 °C. After cooling, the resulting precipitates were collected by filtration and washed with H_2O. Recrystallization from MeOH gave **58** (1571 g, 82.8%) as pale yellow crystals. mp 160—161 °C. NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7 Hz), 1.66 (6H, s), 2.20—4.13 (3H, m), 2.49 (1H, dd, J=16, 6 Hz), 2.93 (1H, dd, J=16, 8 Hz), 3.70 (2H, s), 6.62 (2H, d, J=9 Hz), 7.86 (2H, d, J=9 Hz). IR (KBr): 3365, 1705, 1650, 1595, 1530 cm^{-1}. MS *m/z*: 308 (M^+), 262, 221 (base peak). *Anal.* Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.47; H, 6.55; N,8.98.

Method B: A solution of **57** (243.5 g, 1.0 mol), 2-methyl-2-nitro-1-propanol (154.7 g, 1.3 mol), benzyltriethylammonium chloride (4.56 g, 20 mmol) and NaOH (80 g, 2.0 mol) in H_2O (800 ml) was stirred for 24 h at reflux temperature and treated as described above to give **58** (267.1 g, 86.7%) as pale yellow crystals.

6-[4-(2-Methyl-2-nitropropylamino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (59) A solution of **58** (631 g, 2.05 mol) and hydrazine hydrate (298 ml, 6.15 mol) in H_2O (900 ml) was stirred for 3 h at 100 °C. After cooling, the resulting crystals were collected by filtration, washed with H_2O and dried. Recrystallization from MeOH gave **59** (549.8 g, 88.2%) as yellow crystals. mp 187—189 °C. NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7 Hz), 1.65 (6H, s), 2.40 (1H, dd, J=17, 2 Hz), 2.70 (1H, dd, J=17, 6 Hz), 3.07—3.47 (1H, m), 3.66 (2H, d, J=7 Hz), 4.27 (1H, t, J=7 Hz), 6.63 (2H, d, J=9 Hz), 7.59 (2H, d, J=9 Hz), 8.64 (1H, br s). IR (KBr): 3370, 3240, 1680, 1530 cm^{-1}. MS *m/z*: 304 (M^+), 258, 216 (base peak). *Anal.* Calcd for $C_{15}H_{20}N_4O_3$: C, 59.19; H, 6.62; N, 18.41. Found: C, 59.30; H, 6.61; N, 18.29.

Methyl 3-[4-[2-(*tert*-Butoxycarbonylamino)-2-methylpropylamino]-benzoyl]butyrate (61) A solution of $NaBH_3CN$ (0.32 g, 5.0 mmol) in MeOH (10 ml) was added dropwise to a solution of **60** (2.21 g, 10 mmol), **51** (2.42 g, 12.95 mmol) and AcOH (0.60 g, 10 mmol) in MeOH (50 ml) over a period of 2 h with stirring. The solution was further stirred for 2 h and concentrated under reduced pressure. 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 residue was recrystallized from iso-PrOH to give **61** (2.36 g, 60.2%) as colorless crystals. mp 111—112 °C. NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7 Hz), 1.35 (6H, s), 1.43 (9H, s), 2.40 (1H, dd, J=17, 6 Hz), 2.91 (1H, dd, J=17, 7 Hz), 3.38 (2H, s), 3.50—4.05 (1H, m), 3.64 (3H, s), 4.52 (1H, brs), 6.61 (2H, d, J=9 Hz), 7.84 (2H, d, J=9 Hz). IR (KBr): 3380, 3290, 1720, 1690, 1650 cm^{-1}. MS *m/z*: 392 (M^+), 217 (base peak). *Anal.* Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 63.98; H, 8.31; N, 7.10.

Methyl 3-[4-[*N*-[2-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-*N*-methylamino]benzoyl]butyrate (62) A solution of $NaBH_3CN$ (0.55 g, 8.7 mmol) in MeOH (20 ml) was added dropwise to a mixture of **61** (1.68 g, 4.29 mmol), paraformaldehyde (6.4 g), AcOH (0.97 g, 16.2 mmol) and MeOH (250 ml) over a period of 1 h with stirring at reflux temperature. The whole was refluxed for 10 h with stirring. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with 5% Na_2CO_3, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. Crystallization from iso-Pr_2O gave

62 (1.13 g, 64.9%) as colorless crystals. mp 110—112 °C. NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7 Hz), 1.30 (6H, s), 1.45 (9H, s), 2.40 (1H, dd, J=17, 6 Hz), 2.92 (1H, dd, J=17, 7 Hz), 3.39 (3H, s), 3.53—4.10 (1H, m), 3.64 (3H, s), 3.73 (2H, s), 4.51 (1H, br s), 6.77 (2H, d, J=9 Hz), 7.87 (2H, d, J=9 Hz). IR (KBr): 3350, 1740, 1690, 1660, 1605, 1530, 1170 cm^{-1}. MS m/z: 406 (M^+), 248 (base peak). *Anal.* Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 65.02; H, 8.59; N, 7.07.

6-[4-[*N*-[2-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-*N*-methylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (63) A solution of **62** (3.50 g, 8.6 mmol) and hydrazine hydrate (5.0 ml, 0.10 mol) in EtOH (50 ml) was stirred for 3 h at reflux temperature. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography. Crystallization from iso-Pr_2O gave **63** (2.94 g, 88.0%) as colorless crystals. mp 154—156 °C. NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7 Hz), 1.30 (6H, s), 1.45 (9H, s), 2.39 (1H, dd, J=17, 2 Hz), 2.69 (1H, dd, J=17, 6 Hz), 2.87—3.55 (1H, m), 3.06 (3H, s), 3.68 (2H, s), 4.49 (1H, br s), 6.80 (2H, d, J=9 Hz), 7.61 (2H, d, J=9 Hz), 8.40 (1H, br s). IR (KBr): 3340, 1715, 1675, 1615 cm^{-1}. MS m/z: 388 (M^+), 230 (base peak). *Anal.* Calcd for $C_{21}H_{32}N_4O_3$: C, 64.92; H, 8.30; N, 14.42. Found: C, 64.82; H, 8.38; N, 14.24.

6-[4-[*N*-(2-Amino-2-methylpropyl)-*N*-methylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (6) A mixture of **63** (1.94 g, 5 mmol) and 2.3 N HCl–AcOEt solution (50 ml) was stirred for 30 min at room temperature and the solvent was removed under reduced pressure. The residue was dissolved in H_2O and alkalinized with Na_2CO_3. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from iso-PrOH to give **6** (1.09 g, 75.7%) as colorless crystals. mp 178—180 °C. NMR ($CDCl_3$) δ: 1.20 (6H, s), 1.24 (3H, d, J=7 Hz), 1.71 (2H, br s), 2.39 (1H, dd, J=17, 2 Hz), 2.69 (1H, dd, J=17, 6 Hz), 2.92—3.50 (1H, m), 3.10 (3H, s), 3.33 (2H, s), 6.83 (2H, d, J=9 Hz), 7.62 (2H, d, J=9 Hz), 8.50 (1H, br s). IR (KBr): 3210, 1680, 1620 cm^{-1}. MS m/z: 288 (M^+), 231, 58 (base peak). *Anal.* Calcd for $C_{16}H_{24}N_4O$: C, 66.63; H, 8.39; N, 19.43. Found: C, 66.51; H, 8.43; N, 19.24.

6-[4-[2-[3-(2,5-Dichlorophenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (23) A solution of **3** (3.0 g, 10.9 mmol), 1-(2,5-dichlorophenoxy)-2,3-epoxypropane (2.40 g, 10.9 mmol) in *tert*-BuOH (100 ml) was stirred at 65—70 °C for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give **23** (4.77 g, 88.8%) as a colorless oil. NMR ($CDCl_3$) δ: 1.20 (6H, s), 1.20 (3H, d, J=7 Hz), 2.10—3.45 (7H, m), 3.01 (2H, br s), 4.00 (3H, br s), 4.50 (1H, br s), 6.52 (2H, d, J=9 Hz), 6.70—7.35 (3H, m), 7.49 (2H, d, J=9 Hz), 9.00 (1H, br s). IR (KBr): 1670 cm^{-1}. An analytical sample was recrystallized from EtOH as the maleate. mp 200—202 °C. MS m/z: 495 (M^++3), 493 (M^++1), 278, 276 (base peak). *Anal.* Calcd for $C_{24}H_{30}Cl_2N_4O_3 \cdot C_4H_4O_4$: C, 55.17; H, 5.62; N, 9.19. Found: C, 55.13; H, 5.62; N, 9.20.

Compounds **8**—**36** and **38**—**41** were prepared from the diaminopyridazinones (**3**—**6**) and the glycidyl ethers (**7**) as described above. The physical properties of compounds (II) are shown in Table 1.

4-Chloro-5-methoxysalicylaldehyde (65) A solution of **64** (3.50 g, 22.1 mmol) and hexamethylenetetramine (3.10 g, 22.1 mmol) in TFA (35 ml) was stirred at room temperature. An exothermic reaction occurred, and the whole was stirred for 12 h at 85 °C. The solution was concentraed under reduced pressure and ice-water was added to the residue. The whole was stirred for 30min, alkalinized with Na_2CO_3 and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. After purification by silica gel column chromatography, the residue was recrystallized from iso-Pr_2O to give **65** (1.57 g, 38.1%) as pale yellow needles. mp 135—137 °C. NMR ($CDCl_3$) δ: 3.91 (3H, s), 7.01 (1H, s), 7.07 (1H, s), 9.84 (1H, s), 10.76 (1H, s). IR (KBr): 3260, 1660 cm^{-1}. MS m/z: 188 (M^++2), 186 (M^+), 171 (base peak). *Anal.* Calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.36; H, 3.78.

6-Chloro-5-methoxybenzisoxazole (66) According to the method of Casey *et al.*,[18] **65** (2.0 g, 10.7 mmol) was treated with hydroxylamine-*O*-sulfonic acid (1.82 g, 16.1 mmol), followed by $NaHCO_3$ (2.7 g, 32.1 mmol) to give **66** (1.35 g, 68.6%) as colorless crystals. mp 99—100 °C. NMR ($CDCl_3$) δ: 3.95 (3H, s), 7.13 (1H, s), 7.69 (1H, s), 8.61 (1H, s). MS m/z: 185 (M^++2), 183 (M^+), 168 (base peak). *Anal.* Calcd for $C_8H_6ClNO_2$: C, 52.34; H, 3.29; N, 7.63. Found: C, 52.32; H, 3.21; N, 7.33.

1-[5-Chloro-2-cyano-4-(tetrahydropyran-2-yloxy)phenoxy]-2,3-epoxypropane (70) A solution of **66** (1.0 g, 5.4 mmol) in 47% hydrobromic acid (10 ml) was stirred for 1 h at 110 °C. The solution was concentrated under reduced pressure. The residue was dissolved in AcOEt, washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **67** (0.86 g, 93.0%) as pale brown crystals, which were used for the next step without purification. MS m/z: 169 (M^+).

A 2.3 N HCl–AcOEt solution (0.25 ml) was added to a solution of **67** (740 mg, 4.37 mmol) and 3,4-dihydro-2*H*-pyran (1.47 ml, 16.1 mmol) in AcOEt (20 ml) and the mixture was stirred for 40 h at room temperature. Then the solution was washed with saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give **68** (758 mg, 68.5%) as a colorless oil. NMR ($CDCl_3$) δ: 1.30—2.35 (6H, m), 3.40—4.10 (2H, m), 5.46 (1H, br s), 7.47 (1H, s), 7.68 (1H, d, J=1 Hz), 8.60 (1H, d, J=1 Hz). MS m/z: 253 (M^+), 85 (base peak).

A 2 N aqueous NaOH solution (1.2 ml) was added dropwise to an ice-cooled solution of **68** (440 mg, 1.74 mmol) in EtOH (5 ml). Stirring was continued for 10 min, then the solution was acidified with 1 N HCl (2.3 ml). The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give **69** (440 mg, quantitatively) as colorless crystals, which were used for the next step without purification. NMR ($CDCl_3$) δ: 1.30—2.25 (6H, m), 3.30—4.20 (2H, m), 5.30 (1H, br s), 6.37 (1H, br s), 7.03 (1H, s), 7.30 (1H, s). IR (liq. film): 3255, 2225 cm^{-1}. MS m/z: 253 (M^+), 169, 85 (base peak).

A mixture of **69** (440 mg, 1.74 mmol), epichlorohydrin (0.66 ml, 8.44 mmol), K_2CO_3 (260 mg, 1.88 mmol) and EtOH (10 ml) was refluxed for 1 h with stirring. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$. The solution thus obtained was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. After purification of the residue by silica gel column chromatography, recrystallization from iso-Pr_2O gave **70** (286 mg, 53.2%) as colorless crystals. mp 81—85 °C. NMR ($CDCl_3$) δ: 1.35—2.30 (6H, m), 2.65—2.95 (2H, m), 3.20—3.46 (1H, m), 3.46—4.43 (4H, m), 5.34 (1H, br s), 7.07 (1H, s), 7.38 (1H, s). IR (KBr): 2225 cm^{-1}. MS m/z: 309 (M^+), 225, 169, 85 (base peak). *Anal.* Calcd for $C_{15}H_{16}ClNO_4 \cdot 0.1H_2O$: C, 57.82; H, 5.24; N, 4.50. Found: C, 57.91; H, 5.19; N, 4.21.

6-[4-[2-[3-(5-Chloro-2-cyano-4-hydroxyphenoxy)-2-hydroxypropylamino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methylpyridazin-3(2*H*)-one (37) As described for the synthesis of **23**, **70** (86 mg, 0.28 mmol) was reacted with **3** (76 mg, 0.28 mmol) to give **71** (106 mg, 65.4%) as a colorless powder. NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7 Hz), 1.22 (6H, s), 1.40—2.10 (4H, m), 2.20—3.00 (5H, m), 3.09 (2H, s), 3.10—4.00 (3H, m), 4.06 (3H, br s), 4.20—4.70 (1H, m), 5.30 (1H, s), 6.62 (2H, d, J=9 Hz), 7.01 (1H, s), 7.35 (1H, s), 7.55 (2H, d, J=9 Hz), 8.46 (1H, br s). IR (KBr): 3380, 2230, 1680, 1620 cm^{-1}. MS m/z: 367, 283, 114 (base peak).

A 1 N aqueous HCl solution (1 ml) was added to a solution of **71** (100 mg, 0.17 mmol) in EtOH (3 ml) and the mixture was stirred for 0.5 h at room temperature. The solution was concentrated under reduced pressure and saturated $NaHCO_3$ was added to the residue. The whole was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give **37** (80 mg, 93.5%) as a colorless powder. NMR (CD_3OD) δ: 1.15 (3H, d, J=7 Hz), 1.20 (6H, s), 2.10—2.95 (4H, m), 3.11 (2H, s), 3.20—3.50 (1H, m), 4.02 (3H, br s), 6.61 (2H, d, J=9 Hz), 7.00 (1H, s), 7.12 (1H, s), 7.53 (2H, d, J=9 Hz). IR (KBr): 3300, 2230, 1680, 1620 cm^{-1}. MS m/z: 283, 114 (base peak). An analytical sample was purified as the maleate. mp 143—145 °C. *Anal.* Calcd for $C_{25}H_{30}ClN_5O_4 \cdot C_4H_4O_4 \cdot 0.8H_2O$: C, 55.24; H, 5.69; N, 11.11. Found: C, 55.29; H, 5.52; N, 10.84.

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