Novel Potassium Channel Activators. II.[1] Synthesis and Pharmacological Evaluation of 3,4-Dihydro-2*H*-1,4-benzoxazine Derivatives: Modification of the Aromatic Part

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Three new series of analogues related to 3,4-dihydro-2*H*-1,4-benzoxazine derivative 1a were synthesized and evaluated for their potassium channel activating activity. In the first series I, where the 6,7-positions were disubstituted, it was found that an electron-withdrawing substituent was preferable at the 6 position, but either an electron-withdrawing or releasing substituent without bulkiness was tolerated at the 7 position. In the second series II, where several heterocycles were introduced into the 6,7-positions, the oxadiazole derivative 6 showed more potent activity than cromakalim. In the third series III, where the benzene ring was replaced by a pyridine ring, borane complex 16 had equivalent activity to cromakalim. Especially, compound 6 showed a potent hypotensive effect with a long duration of action in the spontaneous hypertensive rat and had a lesser increasing effect on intracranial pressure in dogs than 1a and levcromakalim, showing a good profile as an antihypertensive agent.

Key words potassium channel activator; 3,4-dihydro-2*H*-1,4-benzoxazine; cromakalim; antihypertensive; intracranial pressure

Potassium channels regulated by changes in intracellular levels of adenosine triphosphate are called ATP-sensitive K^+ channels or K_{ATP} channels and are an important class of ionic channels. These channels are closed when intracellular ATP levels are elevated and opened when intracellular ATP levels decline, linking membrane potential to the metabolic state of the cell.[4] Activation of these channels in the membranes of cells such as smooth muscle cells allows K^+ ions to move out, causing transmembrane hyperpolarization and repolarization. These effects reduce intracellular calcium concentration by blocking voltage-dependent calcium channels and inhibiting intracellular calcium release, producing smooth muscle relaxation and antispasmodic action.[5] The use of potassium channel activators or openers[6] may therefore be valuable in the treatment of diseases caused by smooth muscle contraction, such as hypertension, anginapectoris, asthma,[7] and urinary incontinence,[8] as well as baldness.[9] Additionally, these agents are expected to afford cellular protection against ischemic results independent of their vasodilating actions[10] and have antilipemic effects[11] lowering low density lipoprotein (LDL) cholesterol and triglyceride, in addition to increasing high density lipoprotein (HDL) cholesterol.

There are several prototypes of this class of compounds represented by cromakalim,[12] pinacidil,[13] nicorandil,[14] and aprikalim.[15] (Chart 1) Among them, a great amount of research on structural modifications based around cromakalim, a benzopyran derivative, has been reported. As part of our chemical program based around cromakalim, we previously reported[1] the synthesis and biological activity of a new series of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives, represented by **1a**, which had a strong ATP-sensitive K^+ channel activating activity. It turned out that the 3,4-dihydro-2*H*-1,4-benzoxazine was a promising skeleton for ATP-sensitive K^+ channel activators, taking the place of the benzopyran. As shown in our previous paper, the stronger the electron-withdrawing property of the substituent at the 6 position of the 1,4-benzoxazine, the stronger its activity was. As a result of our interest in this substituent's effect, we have made a further modification of the benzene part of 1,4-benzoxazine derivative **1a**.

Here we describe the synthesis and the biological activity of 6,7-disubstituted derivatives **I**, tricyclic derivatives **II** with several heterocycles being introduced into the 6,7-positions, and pyrido-1,4-oxazine derivatives **III**, where the benzene ring was replaced by a pyridine ring (Chart 1). Levcromakalim, the active (−)-isomer of cromakalim, is under development as an antihypertensive agent and its main side effect is a headache,[16] which is considered to be caused by an increase in intracranial pressure (ICP).[17] Several examples of this headache were also observed in the case of compound **1a**. Therefore, we examined the effects of levcromakalim, compound **1a**, and compound **6**, which was a representative compound in this series, on ICP in anesthetized dogs.

Chemistry

The preparation of the 6,7-disubstituted derivatives and tricyclic derivatives followed the route outlined in Chart 2. 6-Nitro or 7-nitro monosubstituted compounds **1a** and **1b**[1] were employed as starting materials. A reduction of **1a** or **1b** with zinc metal, followed by acetylation of the crude aniline products with acetic anhydride, gave the acetamide products, which underwent a nitration reaction with nitric acid in acetic acid to yield the 6-acetamido-7-nitro derivative **2a** or 6-nitro-7-acetamido derivative **2b**, respectively. A standard acidic hydrolysis of **2a** or **2b** furnished the 6-amino-7-nitro derivative **3a** or 6-nitro-7-amino derivative **3b**, respectively. Oxidative ring closure of *o*-nitroaniline **3a** using sodium hypochlorite produced an oxadiazole *N*-oxide derivative **5**,[18] which was reduced by treatment with triethyl phosphite to give a tricyclic oxadiazole derivative **6**. Several tricyclic derivatives were prepared *via* the unstable diamino compound **7** pro-

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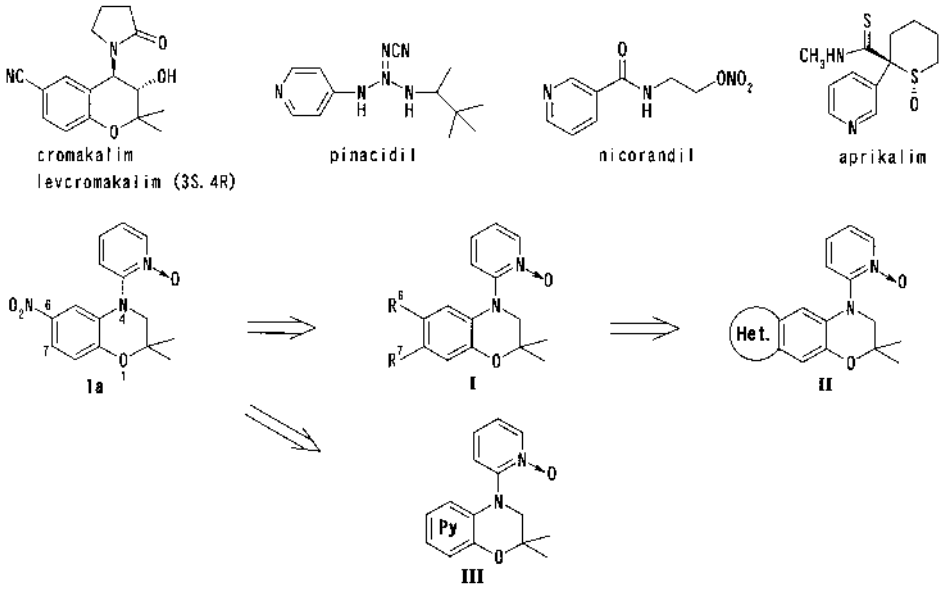
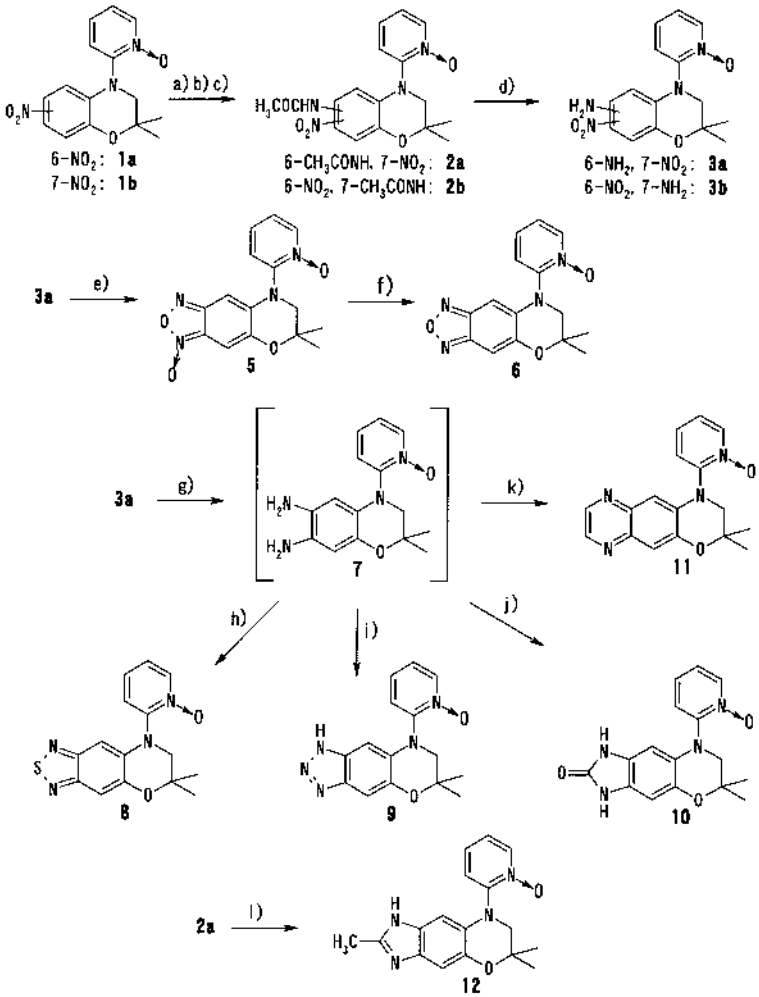
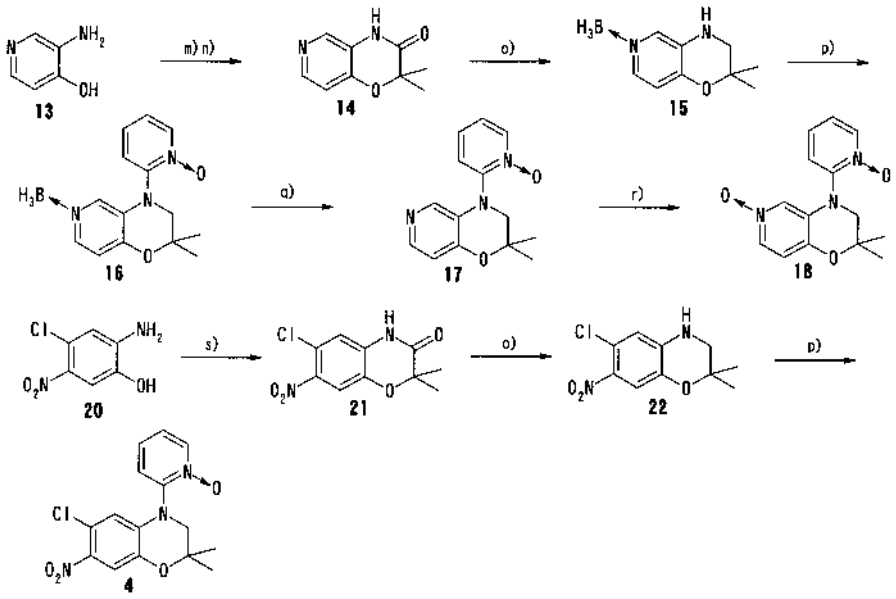


Chart 1



a) Zn, NH_4Cl, MeOH b) $(CH_3CO)_2O$, CH_2Cl_2 c) HNO_3, CH_3COOH d) HCl aq. EtOH e) NaClO, NaOH aq. EtOH f) $P(OEt)_3$, PhH g) H_2/Pd-C, EtOH h) $SOCl_2$, Et_3N i) $NaNO_2$, CH_3COOH aq. j) carbonyldiimidazole k) $(CHO)_2$, $NaHSO_3$, NH_3 aq. l) i) H_2/Pd-C, CH_3COOH ii) 100℃

Chart 2



m) $BrC(CH_3)_2COBr$, Et_3N n) K_2CO_3, DMF o) BH_3–THF p) 2-bromopyridine 1-oxide hydrochloride, NaH, DMF q) d. HCl r) m-CPBA, CH_2Cl_2 s) $BrC(CH_3)_2COOC_2H_5$, KF, DMF

Chart 3

vided by a reduction of **3a** with hydrogen over palladium-activated carbon (Pd–C) in acetic acid. 1,2,5-Thiadiazole derivative **8** was prepared by the treatment of **7** with thionyl chloride and triethylamine in refluxing benzene.[19] 1,2,5-Triazole derivative **9** was prepared by the treatment of **7** with sodium nitrite in an acetic acid aqueous solution.[20] 2-Oxoimidazoline derivative **10** was prepared by the treatment of **7** with carbonyldiimidazole in tetrahydrofuran (THF).[21] Pyrazine derivative **11** was prepared by the treatment of **7** with 40% glyoxal solution.[22] Hydrogenation of 6-acetamido-7-nitro derivative **2a** over Pd–C in acetic acid, followed by heating at 100 °C, gave the 2-methylimidazole derivative **12**.

The synthesis of pyrido-1,4-oxazine derivatives and the 6-chloro-7-nitro derivative **4** followed the route outlined in Chart 3. Treatment of 3-amino-4-pyridinol **13**[23] with 2-bromoisobutyryl bromide and triethylamine (Et_3N), followed by ring closure with potassium carbonate in *N*,*N*-dimethylformamide (DMF), gave 3,4-dihydro-3-oxo-2*H*-pyrido[4,3-*b*]-1,4-oxazine **14**. Reduction of the amide moiety of **14** with borane-THF complex gave a borane complex (**15**) of 3,4-dihydro-2*H*-pyrido[4,3-*b*]-1,4-oxazine. By nucleophilic substitution of **15** with 2-bromopyridine *N*-oxide in the presence of sodium hydride (NaH) in DMF, a borane complex, **16**, could be obtained in a good yield. With 1 N hydrochloric acid, **16** was readily converted to the corresponding pyridine derivative **17**. Treatment of **17** with *m*-chloroperbenzoic acid gave a *N*,*N'*-dioxide derivative **18**. The regioisomer of **17**, pyrido-[3,2-*b*]-1,4-oxazine derivative **19**, was prepared from 3,4-dihydro-2,2-dimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine[24] and 2-bromopyridine *N*-oxide in the presence of NaH. Cyclization of 2-amino-4-chloro-5-nitrophenol **20** with ethyl 2-bromoisobutyrate and potassium fluoride gave benzoxazinone **21**, which was reduced with borane-THF to yield **22**. The 6-chloro-7-nitro derivative **4** was prepared from **22** and 2-bromopyridine *N*-oxide in the presence of NaH.

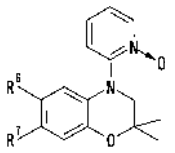
Result and Discussion

The potassium channel-activating effects of the compounds were evaluated *in vitro* in terms of their inhibitory effect (IC_{50}) on 3,4-diaminopyridine-induced rhythmic contraction in isolated dog coronary artery,[25] and their *in vivo* hypotensive activity (maximum decrease in mean blood pressure (MBP), %) in anesthetized dogs (Tables 1, 2, and 3).

Initially, a series of compounds was investigated where the disubstitution pattern in the 6,7-positions of **1a** was varied while the other parts were fixed (Table 1). The introduction of an amino group into the 7 position of **1a** afforded the 6-nitro-7-amino derivative **3b** with a retention of high activity, while, surprisingly, the 6-nitro-7-acetamido derivative **2b** resulted in almost a complete loss of activity, even at 10 μM, the cause of which might be the bulkiness of the acetamido group, because its electronic effect would be approximately the same as that of H: the σ_p value[26] of the acetamido group was 0.0, which was identical with that of H. Exchange of the substitutions in the 6,7-position of **3b** afforded the 6-amino-7-nitro derivative **3a** with a complete loss of activity. Acetylation of the 6-amino group, as in **2a**, had no effect on activity, while the introduction of a chlorine atom into the 6 position afforded the 6-chloro-7-nitro derivative **4** with activity comparable to cromakalim. From the above data, it could be speculated for 6,7-disubstituted derivatives that an electron-withdrawing substituent was preferable at the 6 position, as in the case of 6-monosubstituted derivatives,[1] which was different from the case of cromakalim, where compounds without electron-withdrawing substitution at the 6 position had potent activity.[12] Concerning the 7 position, either an electron-withdrawing or releasing substituent could be introduced, but less bulky substituents would be preferable.

In the second series of compounds, tricyclic derivatives were investigated in which several hetetrocycles were introduced into the 6,7-position of the 1,4-benzoxazine skeleton, taking the place of 6,7-disubstituents (Table 2). Compound **6**,

Table 1. 6,7-Disubstituted-2*H*-1,4-benzoxazines



Compound	R^6	R^7	*In vitro* IC_{50}[a] (μM)	*In vivo* Dose (μg/kg i.v.)	*In vivo* Max decrease in MBP[b] (%)
1a	NO_2	H	0.014	3	21
				10	49
3b	NO_2	H_2N	0.052	3	14
				10	35
2b	NO_2	CH_3CONH	>10	300	14
3a	H_2N	NO_2	>10	1000	8
2a	CH_3CONH	NO_2	>10	1000	12
4	Cl	NO_2	0.30	30	14
				100	37
Cromakalim			0.39	10	28
Levcromakalim			0.038	3	9
				10	25

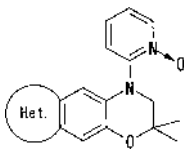
a) Drug concentration required to inhibit 3,4-diaminopyridine-induced rhythmic contraction in dog coronary artery by 50% (n=3—6). *b*) Blood pressure was measured in groups of 3—5 anesthetized dogs.

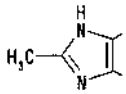
with an oxadiazole ring, was found to be more active than cromakalim. It's *N*-oxide, derivative **5**, showed retained potent activity. Transformation of the oxadiazole ring into the corresponding thiadiazole ring, as in **8**, caused a reduction in potency. Triazole derivative **9** showed a further reduction in potency. 2-Oxoimidazoline derivative **10** and 2-methylimidazole derivative **12** had a complete loss of activity, even though they had a five-membered ring like the oxadiazole ring. The oxo group and methyl group in the 2 position of the five-membered ring might not be tolerant sterically. A change in the 5-membered ring to a 6-membered ring, as in the pyrazine derivative **11**, also caused a loss of activity. Steric tolerance might only be allowed up to a 5-membered ring.

In the third series of compounds, pyrido-1,4-oxazine derivatives were investigated in which the benzene ring of the benzoxazine skeleton was changed to a pyridine ring (Table 3). Pyrido [3,2-*b*] oxazine derivative **19**, in which a N atom was introduced into the 5 position of 1,4-benzoxazine, showed no activity; however, as expected, pyrido [4,3-*b*] oxazine derivative **17**, in which the N atom was introduced into the 6 position, showed comparatively potent activity because pyridine is a well known bioisoster of nitrobenzene.[27] This result was similar to that of pyranopyridine derivatives in that only the derivative in which the N atom was introduced into the 6 position of benzopyrane showed activity.[28] *N*-Oxide derivative (**18**) of **17** lost its activity, but surprisingly, the borane-adduct derivative **16** showed potent activity, comparable to cromakalim. This is the first time to our knowledge that a borane-adduct has shown potassium channel activating activity.

The oral hypotensive effects of **3b** and **6** in conscious spontaneously hypertensive rats (SHR) were examined (Table 4). Both compounds showed more potent hypotensive activity than cromakalim. Especially, the oxadiazole derivative **6** was characterized by its long duration of activity, similar to compound **1a**. We selected **6** as a **1a** successor candidate for

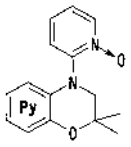
Table 2. Tricyclic Derivatives

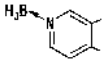


Compd.	Het.	*In vitro* IC_{50}[a] (μM)	*In vivo* Dose (μg/kg i.v.)	*In vivo* Max decrease in MBP[b] (%)
6		0.15	3	8
			10	33
5		0.17	10	10
			30	41
8		1.2	10	10
			30	33
9		3.7	30	11
			100	34
10		>10	300	−6
12		>10	NT[c]	NT
11		>10	NT	NT

a, *b*) See footnotes in Table 1. *c*) Not tested.

Table 3. Pyrido-1,4-oxazines



Compd.	Py	*In vitro*	*In vivo*	
		IC_{50} [a] (μM)	Dose (μg/kg i.v.)	Max decrease in MBP [b] (%)
19		>10	300	0
17		4.1	100 300	11 35
18		>10	300	−2
16		0.15	10 30	17 33

a, *b*) See footnotes in Table 1.

Table 4. Hypotensive Effects in SHR

Compd.	Dose (mg/kg *p.o.*)	MBP [a] Δ%			
		0.5 h	1 h	2 h	8 h
3b	0.3	−45	−37	−38	−15
6	0.3	−45	−44	−44	−25
1a	0.1	−53	−45	−43	−26
Cromakalim	0.3	−35	−32	−35	−11

a) Mean blood pressure was measured in groups of 3 SHR.

further investigation of its pharmacological property. In the rat isolated portal vein, **6** concentration-dependently inhibited the frequency of spontaneous rhythmic contractions[29] (IC_{50}: 0.10 μM), and the effect was competitively antagonized by glybenclamide, a K_{ATP} channel blocker. These data indicated that **6** was an ATP-sensitive potassium channel activator.[30]

In the clinical development, levcromakalim showed good hypotensive activity, but some patients receiving it complained of a headache as a main side effect.[16] Several examples with headache were also observed in cases involving compound **1a**. Vasodilators often have the side effect of producing headaches. In particular, nitrocompounds such as nitroglycerine have been known to cause severe headaches, and produce a marked increase in ICP,[31] which is considered to be caused by an increase in cerebral blood volume due to acute vasodilation. Therefore, we examined the effects of **6**, **1a**, levcromakalim, and two representative vasodilators on ICP in anesthetized dogs. **6** (0.3—30 μg/kg i.v.), **1a** (0.1—10 μg/kg i.v.), levcromakalim (0.3—30 μg/kg i.v.), nitroglycerin (0.1—3 μg/kg i.v.), and nicardipine (0.1—3 μg/kg i.v.), which is a Ca^{2+} antagonist often used for hypertension, produced an increase in ICP in a hypotension-dependent manner (Fig. 1). However, the extent of increased ICP by **6** was less than that of **1a**, levcromakalim, and nitroglycerin, and was almost equal to that of nicardipine. Comparing the data at

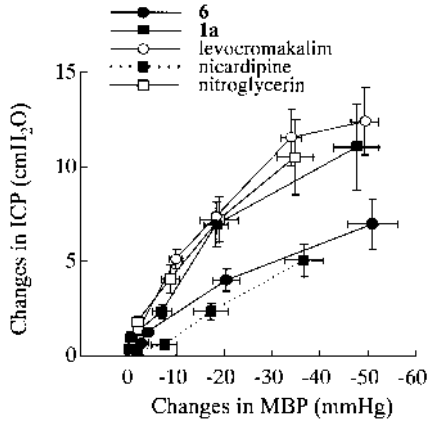


Fig. 1. Effects of **6**, **1a**, and Reference Compounds on MBP and ICP in Anesthetized Dogs

Each point represents the mean±S.E.M. of 7—8 dogs.

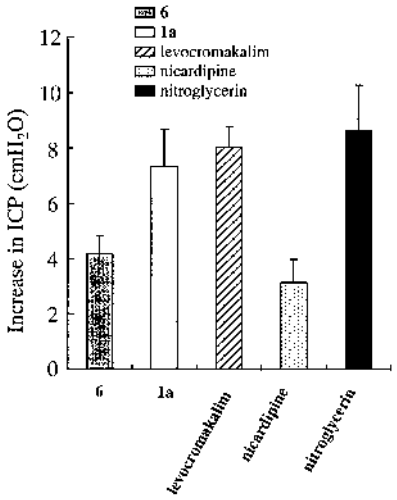


Fig. 2. Effects of **6**, **1a**, and Reference Compounds on ICP at about 30 mmHg Hypotension

Each column represents the mean±S.E.M. of 7—8 dogs.

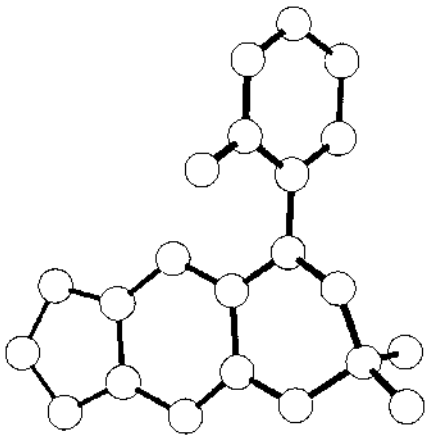


Fig. 3. X-Ray Crystal Structure of **6**

about 30 mmHg hypotension, **6** had a lesser increasing effect on ICP than **1a** and levcromakalim, providing a better profile as an antihypertensive agent than those two (Fig. 2). Although the reason for the difference in ICP between these compounds was not clear, the difference of affinity for cerebrovascular tissue between these compounds might be the

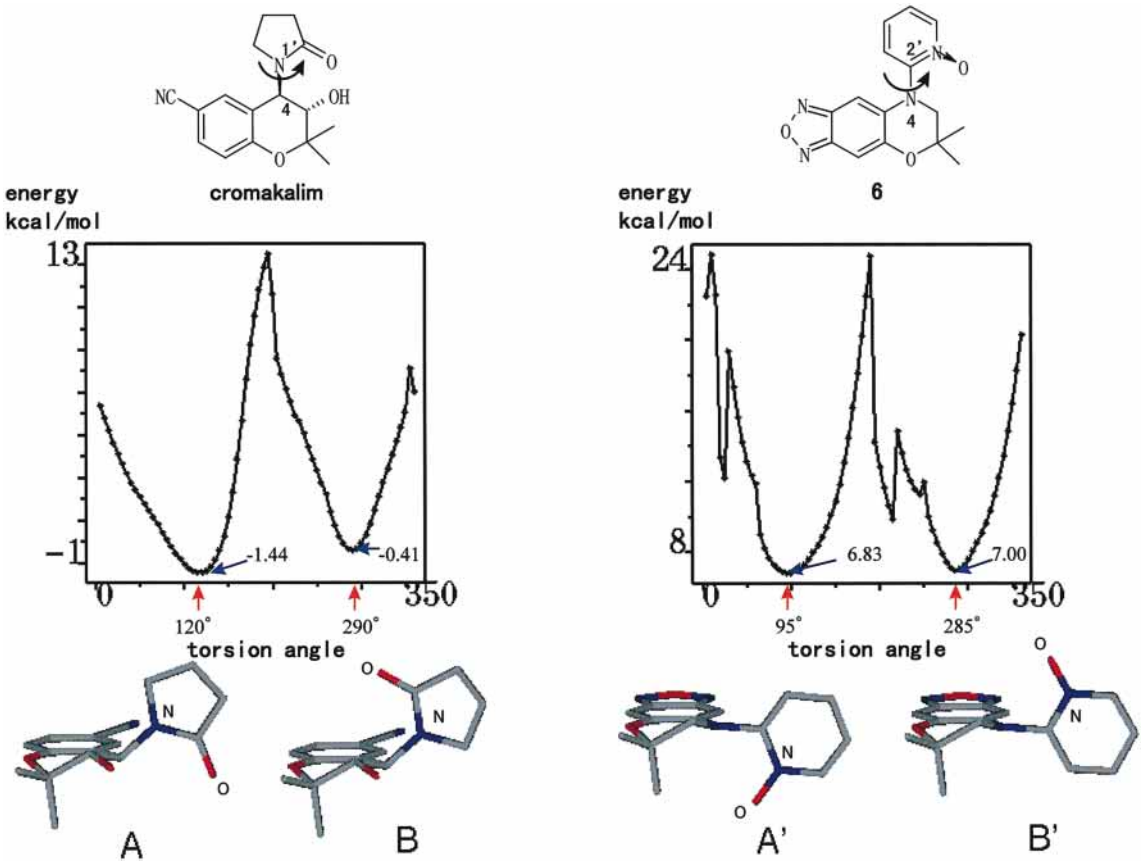


Fig. 4. Calculated Energy of Cromakalim and **6** as a Function of Rotation around the C-4/N-1′ Bond or N-4/C-2′ Bond

cause.

The X-ray crystal structure of **6** is shown in Fig 3. Although the pyridine *N*-oxide ring was orthogonal to the pseudoplane of oxazinobenzoxadiazole, like the relationship between the γ lactam ring and the bezopyrane skeleton of cromakalim, the oxygen atom of pyridine *N*-oxide, an essential atom for potent activity, was in the opposite direction to the corresponding oxygen atom of cromakalim's X-ray structure.[32] This conformational difference stirred our interest, so molecular mechanics studies of both compounds were performed using the software SYBYL6.4[33] for modeling on the basis of the X-ray data (Fig. 4). In the case of cromakalim, two energetically favored comformations were observed, in which the lactam ring was almost orthogonal to the pseudoplane of the benzopyrane, and conformation A was preferred by 1.03 kcal/mol to conformation B, which was similar in conclusion to Attwood's work.[34] But in the case of **6**, although the energetically favored conformations of the pyridine *N*-oxide ring were also orthogonal to the pseudoplane of oxazinobenzoxadiazole, the graph of energy had a symmetric double minimum form and there was no substantial difference (only 0.17 kcal/mol) between conformations A′ and B′. The conformational difference between **6** and cromakalim probably originated in the difference of the root atom of the pyridine *N*-oxide and lactam ring. The root atom was a sp^2-like nitrogen atom in **6**, but it was sp^3 carbon atom in cromakalim. The molecular overlap of **6** and cromakalim showed that **6** would take conformation B′ easily, while conformation B would not be favorable for cromakalim compared to conformation A because of steric hindrance (Fig. 5).

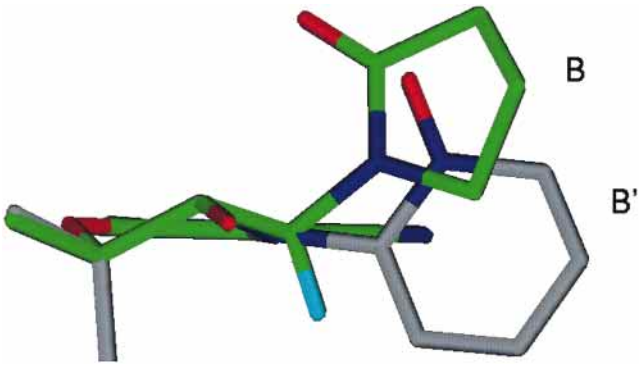


Fig. 5. Molecular Overlap of Conformation B of Cromakalim and Conformation B′ of **6**

Although the stable conformations of both compounds were clarified as above, it was not clear whether they were active conformations.

In conclusion, we synthesized a new series of 6,7-disubstituted derivatives, tricyclic derivatives, and pyrido-1,4-oxazine derivatives of 3,4-dihydro-2*H*-1,4-benzoxazine derivative **1a** and evaluated their potassium channel activating activities and hypotensive effects. It turned out that on the 6,7-disubstituted derivatives, while an electron-withdrawing substituent was preferable at the 6 position, either an electron-withdrawing or electron-releasing substituent without bulkiness was tolerated at the 7 position. On the tricyclic derivatives, the oxadiazole derivative **6** showed more potent activity than cromakalim. On the pyrido-1,4-oxazines, **17**, with the N atom being introduced into the position corresponding to the

6 position of 1,4-benzoxazine, showed relatively potent activity and its borane-adduct **16** showed equivalent activity to cromakalim. Especially, the oxadiazole derivative **6** showed a potent hypotensive effect with a long duration of action in SHR. Moreover, **6** produced a lesser increasing effect on ICP in dogs than **1a** and levcromakalim, showing a good profile as an antihypertensive agent.

Experimental

All melting points were determined on a Yanaco MP-500D micro melting point apparatus without correction. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX90Q, FX100, FX270 or FX400 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, br s=broad singlet. Mass spectra (MS) were recorded with a Hitachi M-80, JEOL JMS-DX300, or JMS-700T spectrometer. Infrared spectra (IR) were measured with a Hitachi 270-30 spectrophotometer. Elemental analyses were done with a Yanaco MT-5. HPLC was carried out using a Hitachi L-6000 pump, L-4000 UV-detector and D-2500 recorder. Silica gel F_{254} (Merck) thin-layer chromatography (TLC) plates were used. Column chromatography was done on 100—200 mesh silica gel from Wako. Anhydrous $MgSO_4$ or Na_2SO_4 were used as the drying agents for organic extraction. All solvent evaporation was performed under a vacuum. Yields were not optimized.

2-(7-Acetamido-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine 1-Oxide (2b) a) To a mixture of **1b** (8.1 g, 27 mmol), ammonium chloride (28.5 g, 530 mmol), methanol (MeOH) (140 ml), and water (140 ml), zinc powder (34.9 g, 530 mmol) was added under ice cooling, and the resulting mixture was stirred at 5 °C for 14 h. The insoluble matter was filtered off and the filtrate was concentrated, extracted with ethyl acetate (AcOEt), dried, and evaporated, giving crude 2-(7-amino-3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzoxazin-4-yl)pyridine 1-oxide (7.2 g, yield 99%). b) To a solution of the aniline obtained above (6.7 g, 25 mmol) in methylene chloride (CH_2Cl_2), was added 2.6 ml acetic anhydride under ice cooling. The mixture was stirred at room temperature (rt.) for 4 h, 20 ml MeOH was added to the reaction mixture, and the solvents were distilled off, giving crude 2-(7-acetamido-3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzoxazin-4-yl)pyridine 1-oxide (7.7 g, 100%). c) To a solution of the above acetanilide (7.7 g, 25 mmol) in 35 ml acetic acid (AcOH), a solution of a mixture of 1.3 ml fuming nitric acid and 14 ml acetic acid was added dropwise under ice cooling. The mixture was stirred at rt. for 1 h, poured into ice water, and extracted with AcOEt. The extract was washed with water, dried, evaporated, and the residue was column chromatographed with chloroform ($CHCl_3$)–hexane (1 : 1, v/v) to give **2b** (4.5 g, 47%), a part of which was recrystallized from EtOH, mp 140—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (1.5H, t, J=7 Hz, C<u>H</u>$_3$CH$_2$OH), 1.42 (6H, s), 2.26 (3H, s), 3,68 (2H, s), 7.0—7.4 (3H, m), 7.48 (1H, s), 8.2—8.4 (1H, m), 8.32 (1H, s), 10.41 (1H, br s). *Anal*. Calcd for $C_{17}H_{18}N_4O_5 \cdot 0.5C_2H_5OH$: C, 56.69; H, 5.55; N, 14.69. Found: C, 56.69; H,5.51; N, 14.70.

Compound **2a** was prepared from **1a** in a similar way: mp 230—233 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, s), 2,07 (0.3H, s, C<u>H</u>$_3$COOH), 2.17 (3H, s), 3,66 (2H, br s), 7.2—7.5 (4H, m), 7.79 (1H, s), 7.98 (1H, s), 8.3—8.4 (1H, m), 10.51 (1H, br s). *Anal*. Calcd for $C_{17}H_{18}N_4O_5 \cdot 0.1CH_3COOH$: C, 56.70; H, 5.09; N, 15.38. Found: C, 56.61; H, 5.06; N, 15.61.

2-(7-Amino-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine 1-Oxide (3b) d) To a suspension of **2b** (0.5 g, 1.3 mmol) in 6 ml ethanol (EtOH) was added 6 ml of 5 N HCl. The mixture was stirred at 100 °C for 2 h, poured into ice water, neutralized with sodium bicarbonate ($NaHCO_3$), extracted with $CHCl_3$, dried, and evaporated. The residue was recrystallized from EtOH to give **3b** (0.36 g, 87%), mp 285—289 °C (decomp.). ^{1}H-NMR (DMSO-d_6) δ: 1.35 (6H, s), 3.63 (2H, s), 6.42 (1H, s), 6.85 (1H, s), 7.1—7.3 (3H, m), 7.39 (1H, dd), 7.56 (1H, d), 8.33 (1H, d). *Anal*. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.80; H, 5.15; N, 17.50.

Compound **3a** was prepared from **2a** in a similar way, mp 234—238 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.34 (6H, s), 3.54 (2H, br s), 5.73 (1H, s), 7.02 (2H, br s), 7.31 (1H, s), 7.32—7.74 (3H, m), 8.36—8.45 (1H, m). *Anal*. Calcd for $C_{15}H_{14}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.75; H,5.14; N, 17.67.

7,8-Dihydro-6,6-dimethyl-8-(2′-pyridyl)-6*H*-[1,4]oxazino[2,3-*f*][2,1,3]benzoxaziazole 3,1′-Dioxide (5) e) To a mixture of **3a** (8.5 g, 27 mmol), 500 ml EtOH, 45.7 ml 1 N aqueous solution of sodium hydroxide and 13.5 ml of water, was slowly added dropwise a 37.5 ml solution of sodium hypochlorite with 5% or more of available chlorine at rt. The reaction mixture was poured into ice water, extracted with AcOEt, washed with 2% sodium thiosulfate solution and brine, dried, and evaporated. The residue was recrystallized from EtOH to give **5** (6.7 g, 79%), mp 209—210 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, s), 3.64 (2H, br s), 6.03 (1H, s), 6.79 (1H, s), 7.3—7.5 (3H, m), 8.3—8.4 (1H, m). *Anal*. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.36; H, 4.56; N, 17.86.

2-(7,8-Dihydro-6,6-dimethyl-6*H*-[1,4]oxazino[2,3-*f*][2,1,3]benzoxaziazol-8-yl)pyridine 1-Oxide (6) f) To a suspension of **5** (6.6 g, 21 mmol) in 60 ml toluene, was added dropwise triethyl phosphite (3.6 ml, 21 mmol), and the mixture was heated under reflux for 14 h. The solvent was evaporated and the residue was recrystallized from EtOH to give **6** (3.1 g, 49%), mp 202.5—205.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (6H, s), 3.2—4.0 (2H, br s), 6.40 (1H, s), 7.05 (1H, s), 7.2—7.6 (3H, m), 8.3—8.4 (1H, m). IR (KBr) cm^{-1}: 1510, 1410, 1350, 1270. *Anal*. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.45; H, 4.79; N, 18.73.

2-(7,8-Dihydro-6,6-dimethyl-6*H*-[1,2,5]thiadiazolo[3,4-*g*][1,4]benzoxazin-8-yl)pyridine 1-Oxide (8) g) To a suspension of **3a** (0.60 g, 1.9 mmol) in 30 ml AcOH, was added a catalytic amount of 10% Pd–C powder, then catalytic hydrogenation was performed at ordinary temperature and pressure. The catalyst was filtered off and the solvent was evaporated to give crude 2-(6,7-diamino-3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzoxazin-4-yl)pyridine 1-oxide (**7**), which was immediately used for the succeeding reaction. h) To a suspension of the above diamine **7** in a mixture of 8 ml benzene and 2.1 ml Et_3N, was slowly added dropwise a solution of 0.36 ml thionyl chloride in 6 ml benzene, and the mixture was heated under reflux for 15 min. The reaction mixture was poured into ice water, extracted with AcOEt, dried, and evaporated. The residue was column chromatographed with CHC_{13}–MeOH (70 : 1, v/v) to give **8**, which was recrystallized from EtOH (0.093 g, 16%), mp 173—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (6H, s), 3.73 (2H, br s), 6.87 (1H, s), 7.2—7.6 (4H, m), 8.3—8.4 (1H, m). *Anal*. Calcd for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82; S,10.20. Found: C, 57.10; H, 4.67; N, 17.55; S, 10.16.

2-(1,6,7,8-Tetrahydro-[1,2,3]triazo[4,5-*g*][1,4]benzoxazin-8-yl)pyridine 1-Oxide (9) i) To a solution of crude **7** obtained from **3a** (0.55 g, 1.7 mmol) by method g in 0.5 ml AcOH and 1 ml water, was added a solution of 0.14 g sodium nitrite in 0.5 ml water at rt., the mixture was heated at 80 °C for one min, and a solution of 0.52 g sodium hydroxide and 16 g sodium chloride in 70 ml water was added to the reaction mixture, followed by extraction with AcOEt. The extract was dried and evaporated. The residue was column chromatographed with $CHCl_3$–MeOH (10 : 1, v/v) to give **9**, which was recrystallized from EtOH (0.28 g, 54%), mp 262—264.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (6H, s), 3.61 (2H, s), 6.36 (0.5H, s), 6.73 (0.5H, s), 7.0—7.8 (4H, m), 8.3—8.4 (1H, m), 14.91 (0.5H, br s), 15.16 (0.5H, br s). *Anal*. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.58; H, 5.09; N, 23.59.

2-(7,8-Dihydro-6,6-dimethyl-2-oxo-6*H*-[1,4]oxazino[2,3-*f*]benzimidazolin-8-yl)pyridine 1-Oxide (10) j) Crude **7** obtained from **3a** (0.63 g, 2 mmol) by method g was dissolved in 10 ml THF, then 0.32 g carbonyldiimidazole in 5 ml THF was added under ice cooling, and the mixture was stirred overnight at rt. The precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in water, washed with $CHCl_3$ and allowed to stand at rt. The crystals which separated out were collected by filtration to give **10** (0.13 g, 21%), mp 220—225 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 2.05 (3H, s, N<u>H</u>, H_2<u>O</u>), 3.80 (2H, br s), 6.18 (1H, s), 6.36 (1H, s), 6.8—7.0 (1H, m), 7.2—7.4 (2H, m), 8.2—8.4 (1H, m), 9.95 (1H, s), 10.11 (1H, s). *Anal*. Calcd for $C_{16}H_{16}N_4O_3 \cdot H_2O$: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.89; H, 5.39; N, 16.88.

2-(8,9-Dihydro-7,7-dimethyl-7*H*-[1,4]oxazino[2,3-*g*]quinoxalin-9-yl)pyridine 1-Oxide (11) k) Crude **7** obtained from **3a** (0.63 g, 2 mmol) by method g was dissolved in 12 ml water, then a mixture of 0.6 ml ammonia solution, 0.6 g sodium bisulfite and 0.42 g 40% aqueous solution of glyoxal was added, and the resulting mixture was stirred at rt. for 20 min, extracted with $CHCl_3$, washed with water, dried, and evaporated to give **11**, which was recrystallized from EtOH (0.15 g, 24%), mp 228—230 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (6H, s), 3.78 (2H, br s), 7.12 (1H, s), 7.2—7.4 (2H, m), 7.5—7.7 (2H, m), 8.3—8.4 (1H, m), 8.5—8.7 (2H, m). *Anal*. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.00; H, 5.31; N, 17.90.

2-(7,8-Dihydro-2,6,6-trimethyl-6*H*-[1,4]oxazino[2,3-*f*]benzimidazol-8-yl)pyridine 1-Oxide (12) l) To a solution of **2a** (0.5 g, 1.4 mmol) in 10 ml AcOH, was added 40 mg 10% Pd–C to perform catalytic hydrogenation. The reaction mixture was filtered by the use of celite, and the filtrate was stirred at 100 °C for 30 min. After cooling, the solvent was evaporated, neutralized by the addition of a saturated aqueous solution of $NaHCO_3$ and extracted

with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was column chromatographed with $CHCl_3$–MeOH (1 : 1, v/v) to give **12**, which was recrystallized from EtOH–isopropyl ether (0.18 g, 41%), mp 165—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 2.52 (3H, s), 3.61 (0.8H, q, J=7 Hz, $((CH_3)_2C\underline{H})_2O$), 3.80 (2H, s), 3.92 (2.5H, br s, N$\underline{H}$, $\underline{H}_2O$), 6.80 (1H, s), 6.9—7.5 (4H, m), 8.2—8.3 (1H, m). *Anal*. Calcd for $C_{17}H_{18}N_4O_2 \cdot 0.4((CH_3)_2CH)_2O \cdot 0.6H_2O$: C, 64.36; H, 6.90; N, 15.48. Found: C, 64.26; H, 7.12; N, 15.51.

3,4-Dihydro-2,2-dimethyl-3-oxo-2*H*-pyrido[4,3-*b*]-1,4-oxazine (14) m) To a solution of 3-amino-4-pyridinol (2.5 g, 23 mmol) in 25 ml THF and 2.3 g Et_3N was slowly added dropwise 2-bromoisobutyryl bromide (5.2 g, 23 mmol) in 10 ml THF below 0 °C. The reaction mixture was poured into ice water and extracted several times with $CHCl_3$. The extract was dried and concentrated to give crude 2-bromo-*N*-(4-hydroxypyridin-3-yl)-2-methylpropionamide (3.0 g, 51%). n) To a solution of the above bromide (3.0 g, 12 mmol) in 30 ml DMF, potassium carbonate (0.80 g, 6 mmol) was added. The mixture was heated at 50 °C for 7 h, poured into ice water and extracted 3 times with AcOEt. The extract was dried and concentrated to give **14**, which was recrystallized from AcOEt–ether (0.88 g, 43%), mp 191—193 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (6H, s), 6.91 (1H, d, J=6 Hz), 8.12—8.23 (2H, m), 8.6 (1H, br s). *Anal*. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.43; H, 5.50; N, 15.69.

3,4-Dihydro-2,2-dimethyl-2*H*-pyrido[4,3-*b*]-1,4-oxazine-6-borane (1/1) (15) o) **14** (0.8 g, 4.5 mmol) was added to 23 ml of a 1.0 M solution of borane–THF under ice cooling. The mixture was heated at 60 °C for 1 h, then carefully diluted with 4 ml MeOH, heated at 60 °C for 1 h, and evaporated. After adding 4 ml ammonia solution (15%), the residue was extracted with $CHCl_3$. The extract was dried, and evaporated to give **15**, which was crystallized from EtOH–ether–hexane (0.69 g, 94%), mp 118—120 °C (decomp.). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, s), 2.1—2.8 (3H, broad peak), 3.15 (2H, s), 4.26 (1H, br s), 6.72 (1H, d, J=6 Hz), 7.80 (1H, d, J=6 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 2370, 2310, 1520. FAB-MS *m/z*: 177.1198 (Calcd for $C_9H_{14}BN_2O$ $(M-H)^-$: 177.1200).

3,4-Dihydro-2,2-dimethyl-4-(1-oxide-2-pyridyl)-2*H*-pyrido[4,3-*b*]-1,4-oxazine-6-borane (1/1) (16) p) To a solution of **15** (0.5 g, 3 mmol) in 4 ml DMF, sodium hydride (60% in oil, 0.24 g, 6 mmol) was added and the mixture was stirred for 10 min. 2-Bromopyridine *N*-oxide hydrochloride (0.64 g, 3 mmol) was added under ice cooling. After removing the ice bath, a spontaneous rise in temperature up to 30 °C was observed. The whole was poured into ice water and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated to give **16**, which was crystallized from EtOH (0.65 g, 82%), mp 211 °C (decomp.). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (6H, s), 2.66 (0.7H, s, H_2O) 3.65 (2H, s), 3.15 (2H, s), 6.89 (1H, d, J=7 Hz), 7.21—7.44 (3H, m), 7.56 (1H, br s), 7.92 (1H, d, J=7 Hz), 8.26—8.36 (1H, m). IR (KBr) cm^{-1}: 2370, 2320, 1520, 1500, 1310, 1280. *Anal*. Calcd for $C_{14}H_{18}BN_3O_2 \cdot 0.3H_2O$: C, 60.81; H, 6.78; N, 15.20. Found: C, 60.80; H, 6.49; N, 14.93. FAB-MS *m/z*: 270 $(M+2H-H)^+$.

2-(3,4-Dihydro-2,2-dimethyl-2*H*-pyrido[4,3-*b*]-1,4-oxazin-4-yl)pyridine 1-Oxide (17) q) **16** (1.0 g, 3,7 mmol) was added to 37 ml 1 N HCl and the mixture was stirred at 60 °C for 20 min, concentrated, made alkaline with an aqueous solution of sodium hydroxide, and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated to give **17**, which was crystallized from $CHCl_3$–AcOEt (0.88 g, 92%), mp 150—152 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, s), 1.81 (1.5H, s, $\underline{H}_2O$) 3.77 (2H, s), 6.81 (1H, d, J=7 Hz), 6.95—7.42 (3H, m), 8.01—8.07 (2H, m), 8.22—8.31 (1H, m). IR (KBr) cm^{-1}: 3400, 1520, 1500, 1380, 1280. *Anal*. Calcd for $C_{14}H_{15}N_3O_2 \cdot 0.7H_2O$: C, 62.30; H, 6.12; N, 15.57. Found: C, 62.11; H, 6.34; N, 15.44.

3,4-Dihydro-2,2-dimethyl-4-(2′-pyridyl)-2*H*-pyrido[4,3-*b*]-1,4-oxazine 6,1′-Dioxide (18) r) To a solution of **17** (0.33 g, 1.2 mmol) in 5 ml CH_2Cl_2, *m*-chloroperbenzoic acid (0.33 g, 1.4 mmol) was added. The mixture was stirred at rt. for 16 h, diluted with aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ several times. The extract was dried, then evaporated to give **18**, which was crystallized from MeOH–AcOEt (0.32 g, 91%): mp 251—252 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (6H, s), 3.61 (2H, s), 6.85 (1H, d, J=7 Hz), 7.01 (1H, d, J=2 Hz), 7.31—7.67 (4H, m), 8.29—8.37 (1H, m). IR (KBr) cm^{-1}: 1520, 1500, 1380, 1280. *Anal*. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.26; H, 5.48; N, 15.28.

2-(3,4-Dihydro-2,2-dimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-4-yl)pyridine 1-Oxide (19) This compound was prepared from 3,4-dihydro-2,2-dimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine[24] and 2-bromopyridine *N*-oxide by using procedure p, mp 101—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, s), 1.90 (0.5H, s, $\underline{H}_2O$), 3.78 (2H, s), 6.76 (1H, dd), 7.0—7.6 (4H, m), 7.7—7.8 (1H, m), 8.2—8.4 (1H, m). *Anal*. Calcd for $C_{14}H_{15}N_3O_2 \cdot 0.1H_2O$: C, 64.90; H, 5.91; N, 16.22. Found: C, 64.86; H, 6.03; N, 16.12.

6-Chloro-3,4-dihydro-2,2-dimethyl-7-nitro-3-oxo-2*H*-1,4-benzoxazine (21) s) To a suspension of potassium fluoride (40 g, 690 mmol) and ethyl 2-bromoisobutyrate (40 ml, 300 mmol) in 200 ml DMF was added 2-amino-4-chloro-5-nitrophenol **20** (49 g, 260 mmol), and the mixture was stirred at 60 °C for 4 d. It was poured into ice water to yield precipitates, which were isolated and crystallized from 2-propanol to give **21** (37 g, 56%), a part of which was recrystallized from EtOH, mp 243—245 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (6H, s), 7.04 (1H, s), 7.68 (1H, s), 11.23 (1H, s). *Anal*. Calcd for $C_{10}H_9Cl\,N_2O_4$: C, 46.80; H, 3.53; N, 10.92; Cl, 13.81. Found: C, 46.84; H, 3.46; N, 10.90; Cl, 13.91.

6-Chloro-3,4-dihydro-2,2-dimethyl-7-nitro-2*H*-1,4-benzoxazine (22) This compound was prepared from **21** by using procedure o, mp 139—140.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 3.18 (2H, d), 4.71 (1H, s), 6.57 (1H, s), 7.54 (1H, s). *Anal*. Calcd for $C_{10}H_{11}Cl\,N_2O_3$: C, 49.50; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 49.45; H, 4.53; N, 11.52; Cl, 14.57.

2-(6-Chloro-3,4-dihydro-2,2-dimethyl-7-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine 1-Oxide (4) This compound was prepared from **22** and 2-bromopyridine *N*-oxide by using procedure p, mp 179—180.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 3.60 (2H, br s), 6.46 (1H, s), 7.1—7.5 (3H, m), 7.60 (1H, s), 8.2—8.4 (1H, m). *Anal*. Calcd for $C_{15}H_{14}Cl\,N_3O_4$: C, 53.66; H, 4.20; N, 12.52; Cl, 10.56. Found: C, 53.58; H, 4.25; N, 12.39; Cl, 10.61.

X-Ray Crystallography of 6 Crystals of **6** were grown from EtOH as colorless prisms. Diffraction intensities were collected from a crystal of dimensions 0.2*0.2*0.1 mm^3 on a Riga AFC5R four-circle diffractometer. Of the total 2005 unique reflections (complete for $2\theta<120.0°$), 1477 satisfied the criterion ($F>3\sigma$) and only these were used in the solution and refinement of the structure. Crystal data: $C_{15}H_{14}N_4O_3$, M.W.=298.30, monoclinic, space group $P2_1/n$, a=15.35(1) Å, b=9.350(4) Å, c=9.643(5) Å, β=90.15(5)°, V=1384(1) Å^3, Z=4, Dc=1.432 g/cm^3, CuK_α radiation, graphite-monochromated, λ=1.54178 Å. The structure was solved by a direct method using MULTAN84,[35] and the final refinement was done by the blocked-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The final *R* value was 0.084.

Biological Test i) Effects on 3,4-Diaminopyridine-Induced Rhythmic Contractions[25]: The left coronary circumflex branch or the anterior-descending branch of mongrel dogs of either sex was isolated in Krebs–Henseleit solution and cut into rings about 2 mm in width. A ring segment was fixed to a stainless steel hook and suspended in a Krebs–Henseleit bath (37 °C) aerated with 95%O_2–5%CO_2 under a tension load of 1.0 g, and isometric contractions were recorded. The specimen was allowed to stabilize for 30 min, then rhythmic contractions were induced by the addition of 3,4-diaminopyridine(10 mM). When the amplitude and frequency of the rhythmic contractions became substantially steady, a cumulative addition of the test compound to the organ bath was started. The concentration–response curves for the amplitude and frequency of contractions were constructed and efficacy was evaluated. The inhibitory effect (IC_{50}) on the frequency of contractions is shown in Tables 1, 2, and 3. ii) Hypotensive Effects in Dogs (i.v.): Mongrel dogs of either sex were anesthetized with pentobarbital (30 mg/kg, i.v.). The experiment was performed under artificial respiration after tracheal intubation. After a thoractomy, blood pressure was measured. The test compound was administered through a cannula in the femoral vein. The MBP-lowering (percent reduction) effect is shown in Tables 1, 2, and 3. iii) Hypotensive Effects in SHR (*p.o.*): Spontaneously hypertensive rats (SHR) of the Okamoto–Aoki strain were anesthetized with pentobarbital, 60 mg/kg i.p. An indwelling cannula was placed in the left common carotid artery and the other end of the cannula was led out extracorporeally from the posterior neck. After a stabilization period of 4—5 postoperative days, blood pressure was measured without the restraint of anesthesia. The test compound was suspended in 0.5% methylcellulose solution and the suspension was orally administered in a volume of 5 ml/kg. MBP-lowering in Δ% is shown in Table 4. iv) Effects on Intracranial Pressure (ICP) in Dogs (i.v.): Mongrel dogs of either sex were anesthetized with pentobarbital (30 mg/kg, i.v. bolus, 3—5 mg/kg/h infusion). A needle (22 gauge) was stabbed in the cranium between the occipital bone and the first cervical vertebrae. ICP was measured by a low pressure transducer (TP-400T, Nihon Koden) through a polyethylene tube filled with physiological saline. Blood pressure was measured by a pressure transducer through a cannula inserted in the right femoral artery. The test compound was administered through a cannula indwelt in the femoral vein. The mean blood pressure and ICP are shown in Fig. 1.

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