Novel Potassium Channel Activators: Synthesis and Structure–Activity Relationship Studies of 3,4-Dihydro-2*H*-1,4-benzoxazine Derivatives

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Strong potassium channel-activating effects were found among a series of novel 4-substituted 3,4-dihydro-2*H*-1,4-benzoxazine derivatives. The key step in preparation was the nucleophilic substitution of 3,4-dihydro-2*H*-1,4-benzoxazine (3) with activated halogenopyridines, such as halogenopyridine *N*-oxides (15a—c) and the borane adduct (15d) of 4-bromopyridine. Structure–activity relationship studies identified 2-(3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine-1-oxide (16a: YM934) as the optimal compound. This compound (16a) showed a more potent oral antihypertensive effect than cromakalim in conscious spontaneously hypertensive rats.

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

In recent years potassium channel activators have attracted attention because of their clinical potential in various diseases. Activation of potassium channels in the membrane of cells such as smooth muscle cells allows K^+ ions to move out, causing membrane hyperpolarization and repolarization. These effects inhibit calcium influx by blocking voltage-dependent calcium channels and produce smooth muscle relaxation and antispasmodic action. The use of potassium channel activators may therefore be valuable in the treatment of diseases caused by smooth muscle contraction, such as asthma, hypertension, angina pectoris, and urinary incontinence, as well as baldness.[1]

There are several prototypes of this class of compounds, including cromakalim,[2] pinacidil,[3] nicorandil,[4] and aprikalim[5] (Fig. 1). Among these, our attention has focused on cromakalim, a benzopyran derivative, because it possesses the most potent activity. To date, many benzopyran derivatives have been reported. Regarding structural modification of the benzopyran skeleton, replacement of the oxygen atom at the 1 position by other atoms such as sulfur, carbon, and nitrogen has been done,[6] but replacement of the carbon atom at the 4 position has not been investigated. Further, the hydroxyl group at the 3 position is not necessary for activity, because the activities of the corresponding dehydration compounds (II) parallel those of the dihydrobenzopyranols (I).[2,7] We therefore designed a novel skeleton, 3,4-dihydro-2*H*-1,4-benzoxazine (III), arising from replacement of the carbon atom at the 4 position of 3,4-dihydro-2*H*-benzopyran with a nitrogen atom (Fig. 2), and synthesized a series of novel 3,4-dihydro-2*H*-1,4-benzoxazine derivatives. Some of them showed strong potassium channel-activating effects.

Chemistry

Intermediate 3,4-dihydro-2*H*-1,4-benzoxazines (**3**) were prepared as shown in Chart 1. When R^2 or R^3 was not a cyano group, method I was employed. Treatment of 2-aminophenols (**1**) with bromoacetyl bromide and triethylamine (Et_3N), followed by ring closure with potassium carbonate or sodium hydroxide,[8] gave 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines (**2**). These compounds (**2**) were also prepared by Shridhar's method b.[9] Selective reduction of the amide moiety of **2** with borane–tetrahydrofuran (THF) complex gave **3a**—**c**. When R^2 was not a cyano or nitro group, method II was employed. Treatment of 2-nitrophenols (**4**) with bromoacetaldehyde and potassium carbonate gave the ethers (**5**). Ring closure was accomplished by reduction with hydrogen over Raney nickel to give **3d**—**g**. The 6-cyano analogue (**3h**) was prepared by treatment of the 6-bromo analogue (**3e**) with copper(I) cyanide in *N*,*N*-dimethylformamide (DMF).[10]

Introduction of the lactam ring into the 4 position of 3,4-dihydro-2*H*-1,4-benzoxazines was carried out as shown in Chart 2. Nitrosation of **3** with sodium nitrite and acetic acid followed by reduction of the resulting nitroso compound with formamidinesulfinic acid gave 4-amino-3,4-dihydro-2*H*-1,4-benzoxazines (**6**), which were treated with 4-chlorobutyryl chloride or 5-chlorovaleryl chloride, followed by ring closure with potassium *tert*-butoxide to give lactam derivatives (**7a**—**c**). Ketone derivatives (**9b**—**d**) were prepared *via* amides (**8**), which were reduced by borane–THF complex followed by Swern oxidation of the resulting alcohols (**11**). In the reduction

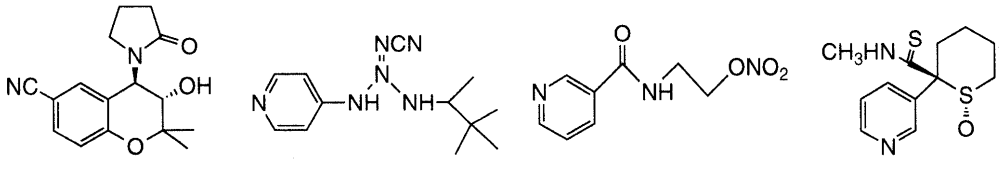

Fig. 1

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of the cyclopentanone **8b**, the *cis* alcohol **11b**[11] was produced predominantly. Treatment of cyclopentene oxide with **3h** and sodium hydride in DMF gave the *trans* alcohol (**11a**),[12] which was oxidized to the ketone **9a**. In order to prepare the lactone **10**, **3h** was treated with α-bromo-γ-butyrolactone and Et_3N. Treatment of cyclopentanone with *N*-bromosuccinimide in the presence of a catalytic amount of dibenzoyl peroxide followed by reaction of the crude product with **3** and Et_3N in THF gave 5-oxo-1-cyclopentenyl derivatives (**12a, b**). The oxime derivative **14** was prepared from the reaction of **12a** and *O*-methylhydroxylamine in pyridine. Dehydration of **3h** and 1,2-diketone derivatives with *p*-toluenesulfonic acid in toluene gave **13a, b**. The 2- or 3-pyridine *N*-oxide derivatives **16** were obtained by nucleophilic substitution of **3** with halogenopyridine *N*-oxides[13] in the presence of sodium hydride in DMF (Chart 3). However, no 4-pyridine *N*-oxide derivative (**16c**) was obtained from 4-bromopyridine *N*-oxide at 90 °C, though by using the borane adduct of 4-bromopyridine, the 4-pyridine borane adduct derivative (**17**) could be obtained at room temperature in a good yield. Consequently, the reactivity of the borane adduct of 4-bromopyridine (**15d**) was much higher than that of the *N*-oxide analogue. The borane adduct (**17**) was readily converted to the 4-pyridyl derivative (**18c**) with 1 N hydrochloric acid. Treatment of **18c** with *m*-chloroperbenzoic acid gave the 4-pyridine *N*-oxide derivative (**16c**). Reduction of the pyridine *N*-oxide derivatives (**16a, b**) with phosphorus trichloride gave the corresponding pyridine derivatives (**18a, b**). The 2- and 3-picolyl derivatives (**20a, b**) were prepared by treatment of **3a** with the respective picolyl chloride and Et_3N. But treatment of **3a** with 4-picolyl chloride and Et_3N gave no 4-picolyl derivative (**20c**), so **20c** was prepared *via* the amide derivative (**21**), followed by reduction with borane–THF complex. Oxidation of **20a—c** with *m*-chloroperbenzoic acid gave picoline *N*-oxide derivatives (**19a—c**, respectively). Acetamide derivatives (**22a—c**) were prepared directly by reaction of the ester (**23**) with ammonium

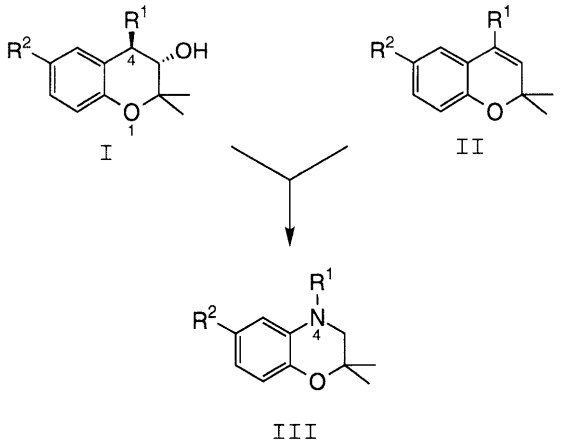
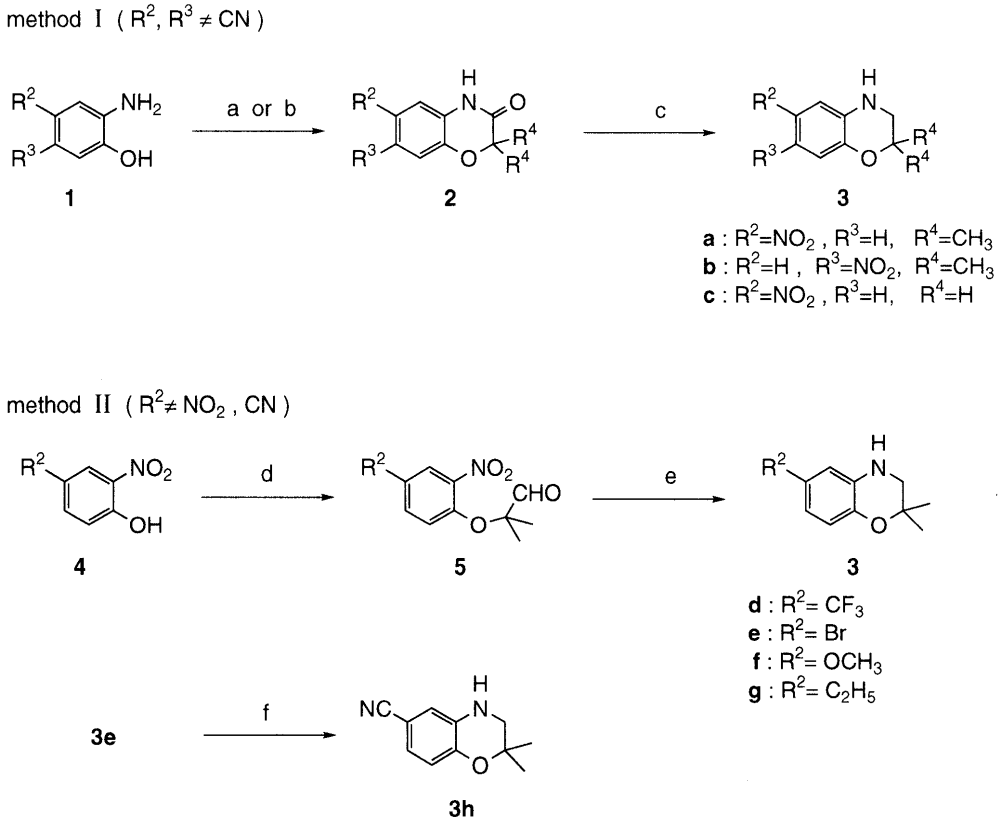
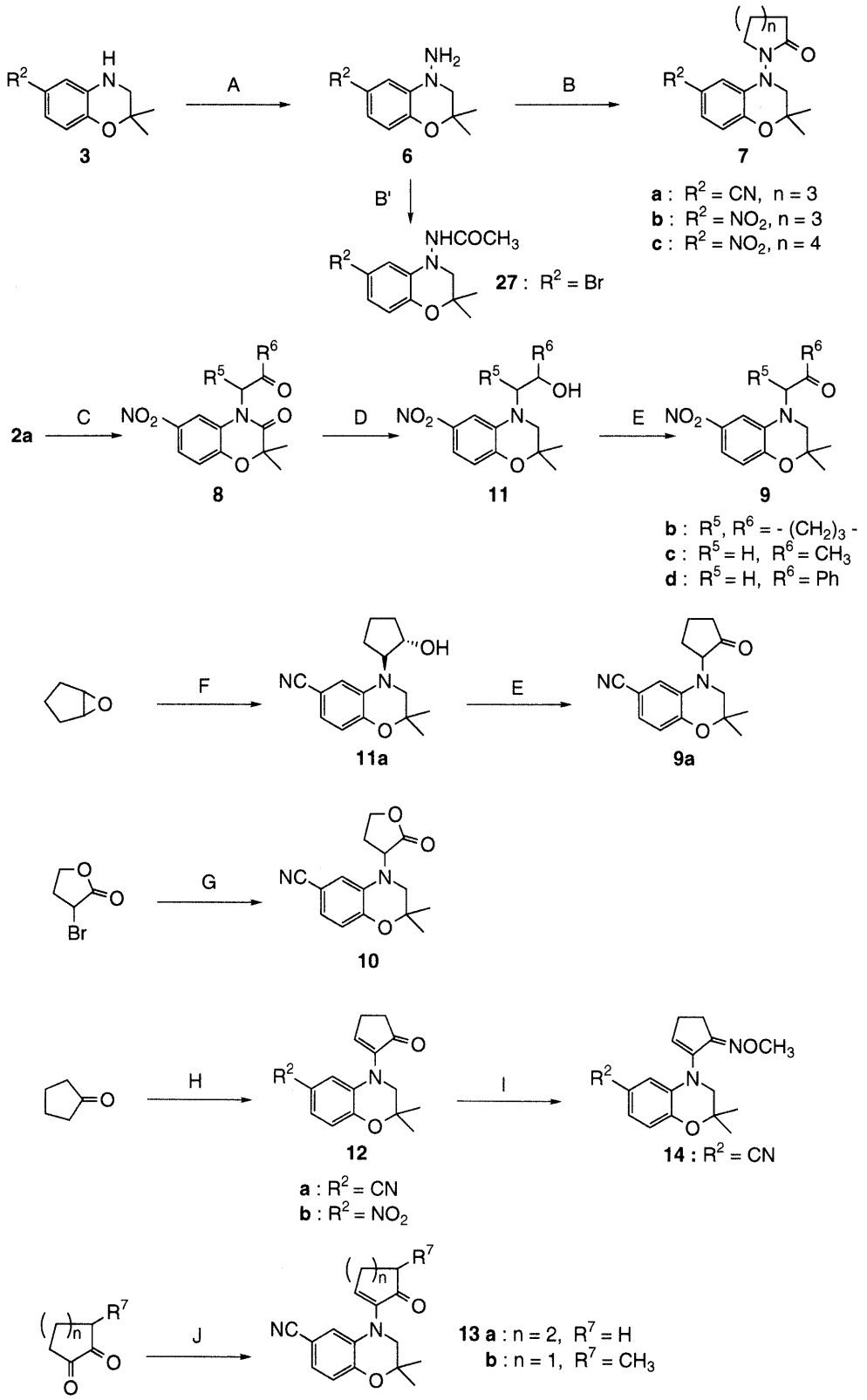


Fig. 2



a) i) $BrCOC(R^4)_2Br$, Et_3N / THF ; ii) K_2CO_3 / DMF or aq. NaOH[8] b) $BrC(Me)_2COOEt$, KF / DMF[9] c) BH_3 / THF d) $BrC(Me)_2CHO$ e) H_2, Raney Ni / EtOH f) CuCN / DMF, 150°C

Chart 1



A) i) $NaNO_2$ / AcOH - MeOH ; ii) $H_2NC(=NH)SO_2H$, aq. NaOH B) i) $Cl(CH_2)_nCOCl$, Et_3N / CH_2Cl_2 ; ii) t-BuOK / DMF B') CH_3COCl, Et_3N / CH_2Cl_2 C) $ClCH(R^5)COR^6$, NaH / THF or DMF D) BH_3 / THF E) Swern oxidation F) **3h**, NaH / DMF G) **3h**, Et_3N H) i) NBS, $(PhCO)_2O_2$; ii) **3**, Et_3N / THF I) H_2NOCH_3 / Py J) **3h**, p-TsOH / toluene, reflux

Chart 2

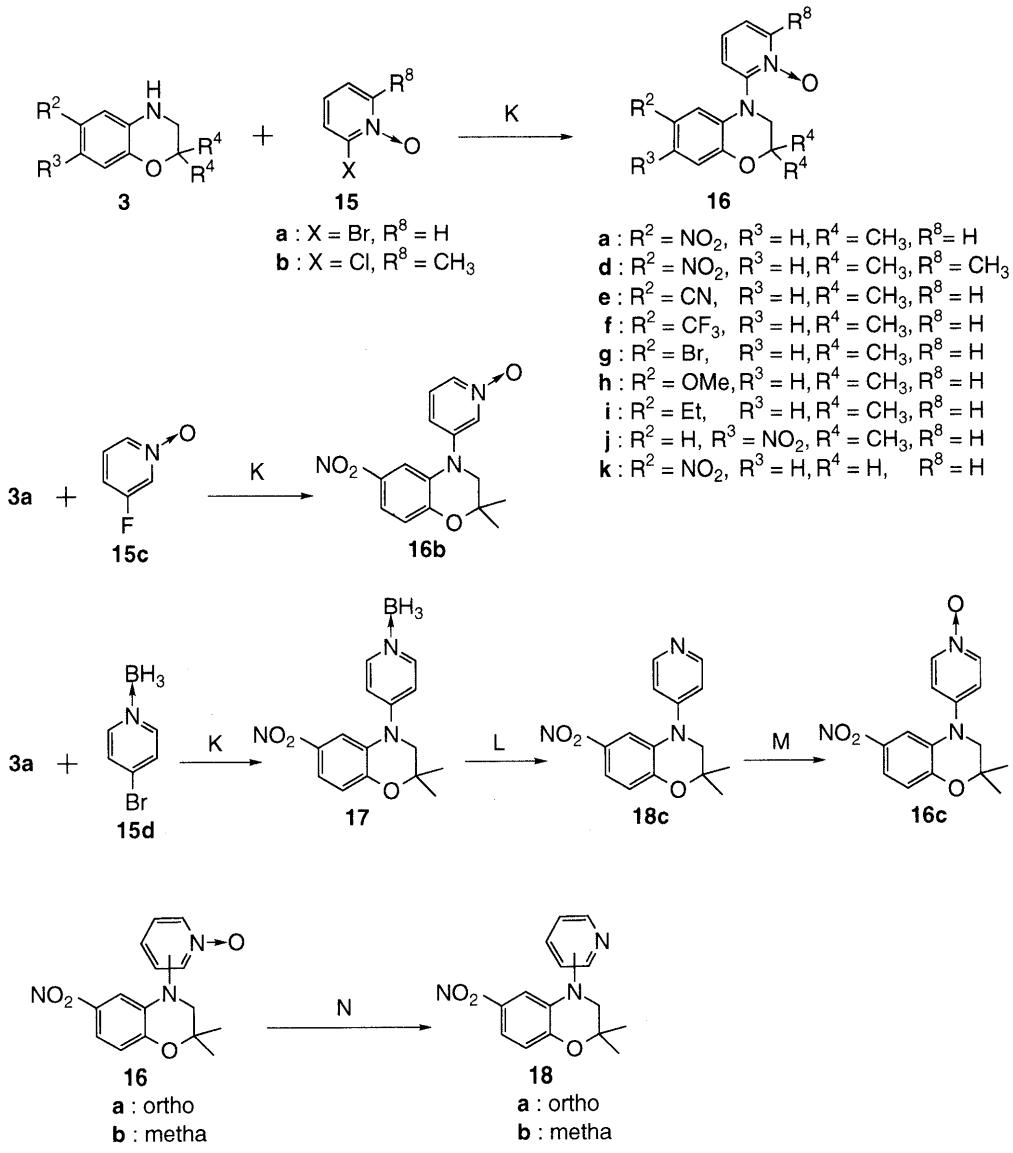


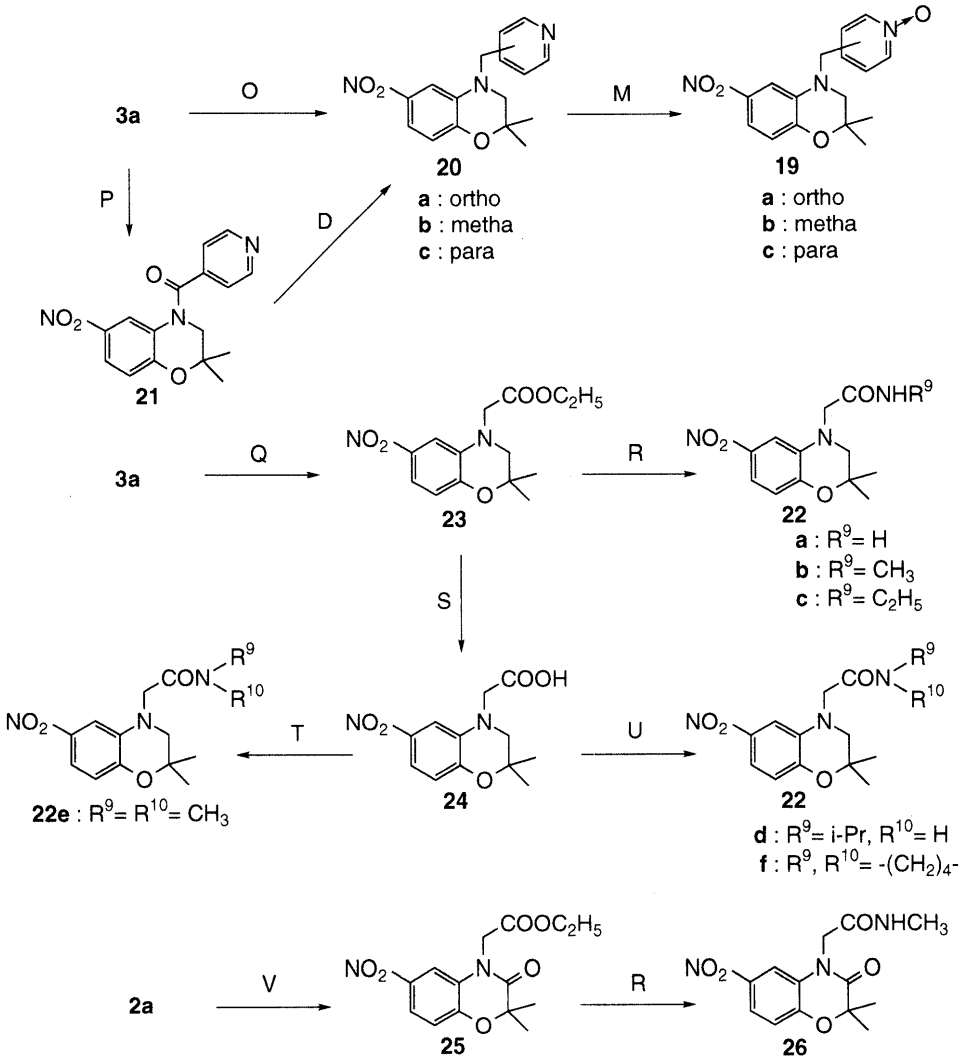
Chart 3

hydroxide, methylamine, or ethylamine respectively. Other amides (**22d**—**f**) were prepared *via* the acid halide or activated ester derived from the carboxylic acid (**24**).

Results and Discussion

The potassium channel-activating effects of the compounds were evaluated *in vitro* in terms of inhibitory effect (IC_{50}) on 3,4-diaminopyridine-induced rhythmic contraction in isolated dog coronary artery,[14] and *in vivo* hypotensive activity (maximum fall in mean blood pressure, %) in anesthetized dogs (Table 1).

Compound **7a**, with the same lactam ring as cromakalim at the 4 position of 3,4-dihydro-2*H*-1,4-benzoxazine, showed approximately equivalent activity to cromakalim and it was concluded that 3,4-dihydro-2*H*-1,4-benzoxazine is a promising skeleton for potassium channel activators. Replacement of the cyano group at the 6 position with a nitro group strengthened the activity (**7b**). Replacement of the 5-membered lactam of **7b** with a 6-membered lactam afforded **7c** with similar potent activity. The cyclopentanone derivatives (**9a, b**) and the γ-butyrolactone derivative (**10**) showed less activity than lactam derivatives (**7a, b**). Modification of the carbonyl group to a hydroxyl group (**11a, b**) resulted in a reduction in potency. Introduction of a double bond into the cyclopentanone afforded 5-oxocyclopentene derivatives (**12a, b**) with retention of high activity. Replacement of the 5-membered ring of **12a** by a 6-membered ring afforded **13a** with reduced activity. Introduction of a methyl group in the α position of the carbonyl group of **12a** resulted in a reduction in potency. Modification of the carbonyl group of **12a** to oxime afforded **14** with reduced activity. The 2-pyridine *N*-oxide derivative (**16a**) was approximately 10 times *in vitro* and 3 times *in vivo* more potent than cromakalim. Introduction of a methyl group at the α position of the *N*-oxide afforded **16d** with reduced activity. Regioisomers of **16a**, *i.e.*, the 3-derivative (**16b**) and 4-derivative (**16c**), showed a drastic reduction in potency. Pyridyl derivatives (**18a, c**) showed



O) 2- or 3-picolyl chloride, Et_3N / DMF P) Isonicotinoyl chloride, NaH / DMF
Q) $BrCH_2COOC_2H_5$, NaH / DMF R) R^9NH_2 / H_2O or MeOH S) aq. NaOH T) i) $SOCl_2$, Py / $CHCl_3$ ii) HNR^9R^{10}, Et_3N / $CHCl_3$ U) HOBT, DCC, HNR^9R^{10} / CH_2Cl_2
V) $BrCH_2COOC_2H_5$, K_2CO_3 / DMF

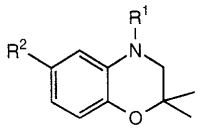
Chart 4

weak activity, with the exception of the 3-pyridyl derivative (**18b**), which was comparable in activity to cromakalim. In order to investigate the best position of the pyridine ring, picoline *N*-oxide derivatives (**19a—c**) and picolyl derivatives (**20a—c**) were prepared, but all were less potent than **16a**. As for an acyclic substituent at the 4 position, the acetonyl derivative (**9c**) showed strong activity. The phenacyl derivative (**9d**) showed reduced activity. Of the acetamide derivatives, *N*-unsubstituted acetamide (**22a**) and *N*-methyl acetamide (**22b**) showed comparable activity to cromakalim, but large *N*-alkyl-substituents (**22c, d**) resulted in reduced activity. Interestingly, *N,N*-dimethyl acetamide (**22e**) was much more active than *N*-monomethyl acetamide (**22b**). *N,N*-Tetramethylene acetamide (**22f**) was less active than *N,N*-dimethyl acetamide (**22e**). The ester derivative **23** showed weak activity, but the acetylamino derivative **27** showed strong activity. As for modification at the 3 position of 3,4-dihydro-2*H*-1,4-benzoxazine, introduction of a carbonyl group provided oxazinone derivatives (**8c, 26**) with much lowered potency as compared with **9c**, **22b** respectively (Table 2).

Modification of the substituent at the 6-position of **16a** provided the cyano derivative (**16e**), trifluoromethyl derivative (**16f**), bromo derivative (**16g**), methoxy derivative (**16h**) and ethyl derivative (**16i**) (Table 3); the activities of these compounds showed a linear correlation with the σ_m values of the substituents at the 6 position of the 3,4-dihydro-2*H*-1,4-benzoxazine (Fig. 3). A shift of the nitro group of **16a** from position 6 to position 7 afforded **16j** with dramatically reduced activity. This result showed that an electron-withdrawing group at the 6 position was requisite for optimum activity. As for modification at the 2 position, deletion of the *gem*-dimethyl group gave **16k** with much reduced activity, and this result was consistent with the case of the benzopyran derivatives.[2)]

The oral hypotensive effects of several representative compounds in conscious spontaneously hypertensive rats

Table 1. 4-Substituted-3,4-dihydro-2*H*-1,4-benzoxazines



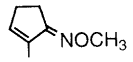
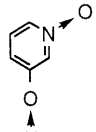
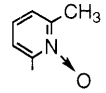
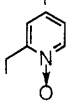
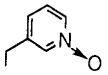
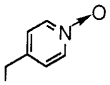
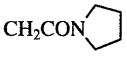
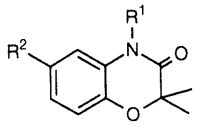
Compd.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	Recryst[c] solvent	Formula[d]	*In vitro* IC_{50}[e] (μM)	*In vivo* Dose (i.v.) (μg/kg)	*In vivo* Max fall in MBP[f] (%)
Cromakalim								0.39	10	28
7a		CN	B	34	149—150	O	$C_{15}H_{17}N_3O_2$	0.16	10	27
7b		NO_2	B	36	141—143	O	$C_{14}H_{17}N_3O_4$	0.049	3 10	20 43
7c		NO_2	B	60	166—168	E	$C_{15}H_{19}N_3O_4$	0.024	30 100	16 48
9a		CN	E	52	172—175	E	$C_{16}H_{18}N_2O_2$	0.73	100	29
9b		NO_2	E	60	118—119	DH	$C_{15}H_{18}N_2O_4$	0.24	30 100	15 42
10		CN	G	8	144—146	O	$C_{15}H_{16}N_2O_3$	0.51	100 300	12 35
11a		CN	F	49	95—97	EH	$C_{16}H_{20}N_2O_2$	1.8	300	15
11b		NO_2	D	62	87—88	H	$C_{15}H_{20}N_2O_4$	8.1	300	17
12a		CN	H	50	124—126	OH	$C_{16}H_{16}N_2O_2$	0.13	10 30	8 31
12b		NO_2	H	50	96—98	O	$C_{15}H_{16}N_2O_4$	0.010	10 30	9 28
13a		CN	J	61	166—170	O	$C_{17}H_{18}N_2O_2$	0.66	1000	21
13b		CN	J	56	106—108	O	$C_{17}H_{18}N_2O_2$	0.29	300	26
14		CN	I	78	138—141	OH	$C_{17}H_{19}N_3O_2$	0.58	300	25
16a		NO_2	K	55	224—226	CO	$C_{15}H_{15}N_3O_4$	0.014	3 10	21 49
16b		NO_2	K	50	198—199	CE	$C_{15}H_{15}N_3O_4$	>10	30	24
16c		NO_2	M	84	202—204	E	$C_{15}H_{15}N_3O_4$	>10	300	24
16d		NO_2	K	33	161—163	E	$C_{16}H_{17}N_3O_4$	0.045	10 30	18 39
18a		NO_2	N	48	108—109	O	$C_{15}H_{15}N_3O_3$	3.1	100	23
18b		NO_2	N	82	124—126	ED	$C_{15}H_{15}N_3O_3$	0.052	10	23
18c		NO_2	L	95	168—170	CD	$C_{15}H_{15}N_3O_3 \cdot 0.5H_2O$	3.2	300	21
19a		NO_2	M	58	139—140	OD	$C_{16}H_{17}N_3O_4$	1.5	30	25
19b		NO_2	M	57	122—123	ED	$C_{16}H_{17}N_3O_4$	2.8	100	21

Table 1. (continued)

Compd.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	Recryst[c] solvent	Formula[d]	*In vitro* IC_{50}[e] (μM)	*In vivo* Dose (i.v.) (μg/kg)	*In vivo* Max fall in MBP[f] (%)
19c		NO_2	M	86	166—168	CD	$C_{16}H_{17}N_3O_4 \cdot 0.25H_2O$	3.0	30	20
20a		NO_2	O	23	174—178	O	$C_{16}H_{17}N_3O_4 \cdot HCl$	1.2	100	15
20b		NO_2	O	25	186—189	O	$C_{16}H_{17}N_3O_3 \cdot HCl$	0.42	30	15
20c		NO_2	D	80	143—145	CD	$C_{16}H_{17}N_3O_3$	0.37	30	20
9c	CH_2COCH_3	NO_2	E	66	98—99	DH	$C_{13}H_{16}N_2O_4$	0.069	10	23
9d	CH_2COPh	NO_2	E	72	125—128	DH	$C_{18}H_{18}N_2O_4$	0.73	300	26
22a	CH_2CONH_2	NO_2	R	48	183—184	EH	$C_{12}H_{15}N_3O_4$	0.17	30	29
22b	$CH_2CONHMe$	NO_2	R	90	127—128	EH	$C_{13}H_{17}N_3O_4$	0.17	10	17
									30	37
22c	$CH_2CONHEt$	NO_2	R	48	115—116	EH	$C_{14}H_{19}N_3O_4$	0.43	100	19
22d	$CH_2CONHiPr$	NO_2	U	62	156—157	EH	$C_{15}H_{21}N_3O_4$	2.4	1000	18
22e	CH_2CONMe_2	NO_2	T	41	179—180	EH	$C_{14}H_{19}N_3O_4$	0.016	10	21
22f		NO_2	U	66	165—166	EH	$C_{16}H_{21}N_3O_4$	0.14	100	8
									300	46
23	CH_2COOEt	NO_2	Q	72	95—96	EH	$C_{14}H_{18}N_2O_5$	2.1	300	18
27	$NHCOCH_3$	Br	B′	60	167—168	OD	$C_{12}H_{15}BrN_2O_2$	0.18	30	30

a) Refers to general method of synthesis as shown in Charts 2—4 and detailed in the experimental section. *b*) Yields are based on the final step of the indicated synthetic method and are not optimized. *c*) C=$CHCl_3$, D=Et_2O, E=EtOAc, H=*n*-hexane, O=EtOH, T=acetone. *d*) All C, H, N analyses were within ±0.4% of the theoretical values. *e*) Drug concentration required to inhibit 3,4-diaminopyridine-induced rhythmic contraction in dog coronary artery by 50% (n=3—6). *f*) Blood pressure was measured in groups of 3—5 anesthetized dogs.

Table 2. 4-Substituted-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines



Compd.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	Recryst[c] solvent	Formula[d]	*In vitro* IC_{50}[e] (μM)	*In vivo* Dose (i.v.) (μg/kg)	*In vivo* Max fall in MBP[f] (%)
8c	CH_2COCH_3	NO_2	C	67	136—137	E	$C_{13}H_{14}N_2O_5$	>10	1000	3
26	$CH_2CONHMe$	NO_2	R	28	212—214	EH	$C_{13}H_{15}N_3O_5$	1.8	300	23

a—*f*) See footnotes to Table 1.

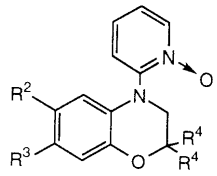
(SHR) were examined. Cyclopentene derivatives (**12a, b**) showed only weak hypotensive effects, but pyridine *N*-oxide derivatives (**16a, e**) showed more potent hypotensive effects than cromakalim (Table 4). It is supposed that the difference in the oral potency between **12a, b** and **16a, e** was attributable to the stability of the structure, because the former had an unstable enamine moiety, the latter had a stable pyridine structure. In terms of the inhibitory effect on spontaneous rhythmic contraction in the rat isolated portal vein,[15] **16a** was approximately 10 times more potent than cromakalim (IC_{50}: **16a**, 0.014 μM; cromakalim, 0.13 μM) and this inhibitory effect was competitively antagonized by glibenclamide. These test data indicated that **16a** is an ATP-dependent potassium channel activator.[16]

We conclude that the 3,4-dihydro-2*H*-1,4-benzoxazine derivatives described here represent a potent new class of potassium channel activators. Compound **16a** (YM934), the optimal compound in this series, was selected as a candidate for clinical testing.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus without correction. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX90Q or FX100 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra (MS) were determined with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Elemental analyses were within ± 0.4% of the calculated values. HPLC was carried out using a Hitachi L-6000 pump, L-4000 UV-detector and D-2500 recorder. Silica gel F_{254}

Table 3. Pyridine *N*-Oxide Derivatives



Compd.	R^2	R^3	R^4	Method[a]	Yield[b] (%)	mp (°C)	Recryst[c] solvent	Formula[d]	*In vitro* IC_{50}[e] (μM)	*In vivo* Dose (i.v.) (μg/kg)	*In vivo* Max fall in MBP[f] (%)
16e	CN	H	Me	K	33	175—177	O	$C_{16}H_{15}N_3O_2$	0.13	3	10
										10	42
16f	CF_3	H	Me	K	24	144—147	E	$C_{16}H_{15}F_3N_2O_2 \cdot HCl$	0.19	30	21
16g	Br	H	Me	K	34	149—151	O	$C_{15}H_{15}BrN_2O_2$	0.12	30	21
16h	OMe	H	Me	K	16	143—144	OE	$C_{16}H_{18}N_2O_3$	3.5	100	24
16i	Et	H	Me	K	23	160—163	E	$C_{17}H_{20}N_2O_2 \cdot HCl \cdot 0.1H_2O$	3.5	300	25
16j	H	NO_2	Me	K	31	146—148	A	$C_{15}H_{15}N_3O_4 \cdot HCl \cdot 0.25H_2O$	>10	300	15
16k	NO_2	H	H	K	51	139—141	CD	$C_{13}H_{11}N_3O_4 \cdot 0.1H_2O$	1.3	30	24

a—*f*) See footnotes to Table 1.

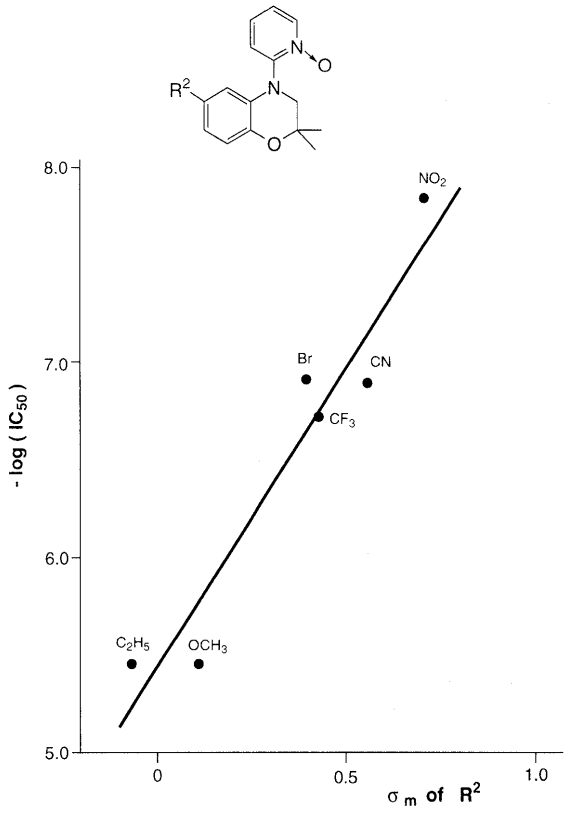


Fig. 3. Correlation between σ_m of R^2 and Calculated IC_{50} *in Vitro*

The relevant equation is $-\log(IC_{50}$ in M$)=3.11\sigma_m+5.44$ ($n=6$, $r=0.954$, $p<0.01$).

(Merck) thin-layer chromatography (TLC) plates were used. Column chromatography was performed on 100-200 mesh silica gel from Wako. Anhydrous $MgSO_4$ or Na_2SO_4 were used as the drying agent for organic extraction. All solvent evaporation was performed under vacuum. Yields were not optimized.

Method I. 3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazine (3a)

a) i) 2-Bromoisobutyryl bromide (2.47 ml, 20 mmol) and Et_3N (2.0 g, 20 mmol) were added dropwise to a solution of 2-amino-5-nitrophenol (3.08 g, 20 mmol) in THF (30 ml) with ice cooling. The mixture was poured into ice water and extracted with ethyl acetate (AcOEt). The organic layer was washed with water, dried, and evaporated to give 2-(2-bromoisobutyrylamino)-5-nitrophenol, which was crystallized from AcOEt (4.94 g, 82%).

ii) Potassium carbonate (0.23 g, 1.7 mmol) was added to a solution of the above phenol (1.0 g, 3.3 mmol) in DMF (10 ml), and the solution was stirred overnight at 50 °C, then poured into ice water. The precipitate was collected by filtration and washed with water. The crude product was recrystallized from ethanol to give **2a** (0.51 g, 70%): mp 209—210 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (6H, s), 7.02 (1H, d), 7.78 (1H, dd), 7.89 (1H, br s). *Anal.* Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.59; H, 4.52; N, 12.65.

b) Compound **2b** was prepared following the procedure described in the ref. 9.

Compound **2c** was prepared according to Newbery and Phillips.[8]

c) Compound **2a** (9.0 g, 43 mmol) was added to 100 ml of a 1.0 M solution of borane–THF complex in THF with ice cooling. The mixture was refluxed for 2 h, then carefully diluted with 12 ml of methanol (MeOH) and the whole was refluxed for 1 h. Concentrated hydrochloric acid (12 ml) was then added and refluxing was continued for 1 h. The mixture was concentrated and the resulting solid was pulverized in diethyl ether and collected by filtration. The solid was suspended in a dilute aqueous solution of sodium hydroxide and then extracted with AcOEt. The organic layer was washed with water and dried. Evaporation of the solvent gave a solid (7.7 g, 93%), which was recrystallized from CH_2Cl_2–hexane to give **3a**: mp 151—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, s), 3.15 (2H, d), 6.78 (1H, d), 7.50 (1H, d), 7.59 (1H, dd). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.59; H, 5.88; N, 13.48.

Compounds **3b**, **c** were prepared in a similar way.

3b: mp 110—112 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, s), 3.16 (2H, d), 4.61 (1H, br s), 6.40—6.55 (1H, m), 7.59—7.79 (2H, m). *Anal.* Calcd for

Table 4. Hypotensive Effects in SHR

Compound	Dose (mg/kg, *p.o.*)	MBP[a] Δ%
16a	0.03	−25
16e	0.3	−40
Cromakalim	0.3	−35

a) Mean blood pressure was measured in groups of 8 SH rats.

$C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.42; H, 5.70; N, 13.50.

3c: mp 116—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.41—3.49 (2H, m), 4.27—4.36 (2H, m), 6.78 (2H, d), 7.44 (1H, d),7.54 (1H, dd). *Anal.* Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.25; H, 4.49; N, 15.62.

Method II. 3,4-Dihydro-2,2-dimethyl-6-trifluoromethyl-2*H*-1,4-benzoxazine (3d) d) A solution of 2-bromoisobutyraldehyde (8.8 g, 58 mmol) in DMF (23 ml) was added dropwise to a mixture of 2-nitro-4-trifluoromethylphenol (10 g, 48 mmol), anhydrous potassium carbonate (8.0 g, 80 mmol) and DMF (30 ml), and the mixture was stirred at room temperature for 4 d, then poured into ice water and extracted with toluene. The organic layer was washed with 0.5 N aqueous sodium hydroxide solution and water, and dried. The solvent was distilled off and the residue was chromatographed with AcOEt–hexane (3 : 1, v/v). The product was crystallized from hexane to give 2-(2-nitro-4-trifluoromethylphenoxy)isobutyraldehyde (**5d**) (4.4 g, 33%).

e) The above aldehyde (4.4 g) was dissolved in ethanol (40 ml). After addition of a catalytic amount of Raney nickel, the mixture was hydrogenated at atmospheric pressure, then filtered, and the filtrate was concentrated. The residue was chromatographed with benzene–hexane (2 : 3, v/v) to give **3d** (2.3 g, 63%), which was crystallized from hexane: mp 81—82 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (6H, s), 3.10 (2H, s), 3.3—4.4 (1H, br s), 6.7—7.1 (3H, m). *Anal.* Calcd for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; F, 24.65; N, 6.06. Found: C, 57.10; H, 5.31; F, 24.62; N, 6.00.

Compounds **3e—g** were prepared in a similar way.

3e: mp 65—67 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, s), 3.05 (2H, d), 6.51—6.77 (3H, m). *Anal.* Calcd for $C_{10}H_{12}BrNO$: C, 49.61; H, 5.00; N, 5.79; Br, 33.00. Found: C, 49.63; H, 4.94; Br, 32.84; N, 5.63.

3f: mp 56—58 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, s), 3.04 (2H, s), 3.69 (3H, s), 3.84 (1H, br s), 6.12—6.25 (2H, m), 6.57—6.70 (1H, m). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.65; H, 8.05; N, 7.19.

3g: Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t), 1.33 (6H, s), 2.51 (2H, q), 3.07 (2H, s), 3.75 (1H, br s), 6.46—6.74 (3H, m). *Anal.* Calcd for $C_{12}H_{17}NO \cdot 0.25H_2O$: C, 73.62; H, 9.01; N, 7.15. Found: C, 73.53; H, 8.85; N, 7.16.

6-Cyano-3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzoxazine (3h) f) A mixture of **3e** (480 mg, 2.0 mmol), cuprous cyanide (206 mg, 2.3 mmol) and DMF (5 ml) was stirred at 130 °C for 4 h and at 150 °C for a further 5 h. The mixture was diluted with ethylenediamine (0.5 ml) and water (10 ml) and then extracted with benzene. The organic layer was washed with water and dried and the solvent was distilled off. The residue was chromatographed with AcOEt–hexane (10 : 1, v/v) to give **3h** (160 mg, 43%): mp 102—103.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, s), 1.5—2.5 (1H, s), 3.12 (2H, s), 6.77 (1H, d), 6.86 (1H, d), 6.97 (1H, dd). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.09; H, 6.49; N, 14.84.

3,4-Dihydro-2,2-dimethyl-6-nitro-4-(2-oxo-1-pyrrolidinyl)-2*H*-1,4-benzoxazine (7b) A) i) Compound **3a** (3.0 g) was dissolved in a mixture of MeOH (34 ml) and acetic acid (2.07 ml). A solution of sodium nitrite (2.0 g) in water (6.6 ml) was then added dropwise and the mixture was stirred overnight. The mixture was neutralized with aqueous sodium hydroxide solution, concentrated and extracted with chloroform ($CHCl_3$). The organic layer was washed with brine, dried and filtered. The filtrate was concentrated to give 3,4-dihydro-2,2-dimethyl-6-nitro-4-nitroso-2*H*-1,4-benzoxazine (3.2 g, 94%).

ii) This nitroso compound (2.3 g, 9.7 mmol) was dissolved in MeOH (69 ml) and then the solution was cooled to 0 °C. After addition of a solution of sodium hydroxide (1.16 g, 29.0 mmol) in water (8.1 ml), formamidinesulfinic acid (3.13 g, 29.0 mmol) was gradually added. The mixture was stirred overnight and concentrated. The residue was chromatographed with AcOEt–hexane (1 : 9, v/v) to give 4-amino-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazine (**6b**) (0.4 g, 18%), which was crystallized from ether–hexane: mp 83—85 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, s), 3.18 (2H, s), 6.77 (1H, d), 7.66 (1H, dd), 8.06 (1H, d). *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.75; H, 5.80; N, 18.93.

B) A solution of **6b** (0.35 g, 1.6 mmol) in 4 ml of methylene chloride (CH_2Cl_2) was cooled to 0 °C, then Et_3N (0.16 g, 1.6 mmol) was added, followed by the dropwise addition of a solution of 4-chlorobutyryl chloride (0.18 ml, 1.6 mmol) in CH_2Cl_2 (1.4 ml). After having been stirred for 30 min, the mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was crystallized from ether to give crude 4-chloro-*N*-(3,4-dihydro-2,2-dimetyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)butyrylamide (0.43 g, 82%). The above amide (0.41 g, 1.3 mmol) was dissolved in DMF (8 ml) and the solution was cooled to 0 °C. Potassium *tert*-butoxide (0.14 g, 1.3 mmol) was then added. The mixture was stirred for 1 h, diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from ether and then recrystallized from ethanol to give **7b** (0.16 g, 44%): mp 141—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.49 (3H, s), 2.1—2.7 (4H, m), 3.15 (1H, d), 3.4—3.8 (3H, m), 6.84 (1H, d), 7.46 (1H, d), 7.70 (1H, dd). *Anal.* Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.61; H, 5.89; N, 14.40.

Compounds **7a**, **c**, **27** were prepared in a similar way.

7a: mp 149—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, s), 1.45 (3H, s), 2.1—2.6 (4H, m), 3.11 (1H, d), 3.4—3.7 (3H, m), 6.74—6.84 (2H, m), 7.04 (1H, dd). *Anal.* Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.29; H, 6.08; N, 15.51.

7c: mp 166—168 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, s), 1.40 (3H, s), 1.7—2.1 (2H, m), 2.4—2.6 (4H, m), 3.3—3.7 (4H, m), 6.92 (1H, d), 7.28 (1H, d), 7.59 (1H, dd). *Anal.* Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.89; H, 6.32; N, 13.73.

27: mp 167—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.45 (6H, m), 2.06, 2.12 (3H, s × 2), 3.16, 3.30 (2H, s × 2), 6.56—6.97 (3H, m). *Anal.* Calcd for $C_{12}H_{15}BrN_2O_2$: C, 48.18; H, 5.05; Br, 26.71; N, 9.36. Found: C, 48.14; H, 5.01; Br, 26.51; N, 9.29.

3,4-Dihydro-2,2-dimethyl-6-nitro-4-(2-oxocyclopentyl)-2*H*-1,4-benzoxazine (9b) C) A solution of **2a** (3.0 g, 13.5 mmol) in THF (50 ml) was cooled to 0 °C, then sodium hydride (60% in oil, 0.60 g, 15.0 mmol) was added and the mixture was stirred for 30 min. 2-Chlorocyclohexanone (2.0 ml, 20 mmol) was added and the mixture was stirred at room temperature for 2 h. After addition of MeOH (50 ml), the mixture was concentrated and extracted with AcOEt. The organic solution was washed with brine and dried. The solvent was removed by evaporation, and the residue was chromatographed with $CHCl_3$–hexane (1 : 1 → 1 : 0, v/v) to give 3,4-dihydro-2,2-dimethyl-6-nitro-3-oxo-4-(2-oxocyclopentyl)-2*H*-1,4-benzoxazine (**8b**), which was crystallized from Et_2O–hexane (2.7 g, 67%): mp 141—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s), 1.59 (3H, s), 1.80—2.96 (6H, m), 4.07—4.45 (1H, m), 7.08 (1H, d), 7.79 (1H, d), 7.96 (1H, dd). *Anal.* Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.12; H, 5.25; N, 9.15.

Compound **8c** was prepared in a similar way: mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) δ:1.59 (6H, s), 2.34 (3H, s), 4.77 (2H, s), 7.07 (1H, d), 7.47 (1H, d), 7.94 (1H, dd). *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.11; H, 5.03; N, 10.04.

D) Compound **8b** (2.0 g, 6.6 mmol) was added to 40 ml (40 mmol) of a 1.0 M solution of borane–THF complex in THF at 0—10 °C. The solution was stirred under reflux for 2 h, then carefully diluted with MeOH (50 ml) and stirring was continued for 30 min. Concentrated hydrochloric acid (10 ml) was added and the mixture stirred for 30 min, then concentrated. The residue was suspended in a 5% aqueous solution of sodium hydroxide and extracted with AcOEt. The organic layer was washed with water and dried. The solution was concentrated and the residue was chromatographed with $CHCl_3$–hexane (8 : 2 → 10 : 0, v/v). The less polar fractions were combined and concentrated to give *cis*-3,4-dihydro-2,2-dimethyl-4-(2-hydroxycyclopentyl)-6-nitro-2*H*-1,4-benzoxazine (**11b**) (1.2 g, 62%): mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) d: 1.32 (3H, s), 1.39 (3H, s), 1.60—1.77 (2H, m), 1.85—2.05 (2H, m), 2.07—2.18 (2H, m), 3.24 (1H, d, J = 13 Hz), 3.29 (1H, d, J = 13 Hz), 3.79—3.84 (1H, m), 4.57 (1H, m), 6.80 (1H, d, J = 9 Hz), 7.59—7.61 (1H, m). *Anal.* Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.60; H, 7.00; N, 9.53.

The polar fractions were combined and concentrated to give *trans*-3,4-dihydro-2,2-dimethyl-4-(2-hydroxycyclopentyl)-6-nitro-2*H*-1,4-benzoxazine (0.06 g, 3%). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.37 (3H, s), 1.55—1.61 (1H, m), 1.65—1.76 (2H, m), 1.88—1.91 (1H, m), 2.01—2.10 (2H, m), 2.99 (1H, d, J = 13 Hz), 3.04 (1H, d, J = 13 Hz), 4.06—4.11 (1H, m), 4.25 (1H, m), 6.78 (1H, d, J = 9 Hz), 7.58 (1H, dd, J = 9, 3 Hz),7.75 (1H, d, J = 3 Hz).

E) Dry dimethyl sulfoxide (0.33 ml, 4.65 mmol) was slowly added to a solution of oxalyl chloride (0.2 ml, 2.29 mmol) in dry CH_2Cl_2 (3 ml) at −50 to −60 °C and the mixture was stirred at the same temperature for 5 min. Then a solution of **11b** (0.6 g, 1.97 mmol) in dry CH_2Cl_2 (3 ml) was added over a period of 5 min and the mixture was stirred for 15 min. Et_3N (0.7 ml, 5.02 mmol) was added, and the whole was diluted with

water (20 ml) and extracted with CH_2Cl_2. The organic layer was washed with brine and dried. The solution was concentrated and the residue was chromatographed with $CHCl_3$–hexane (2 : 8, v/v) to give **9b** (0.36 g, 60%): mp 118—119 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, s), 1.41 (3H, s), 1.75—2.60 (6H, m), 2.83 (1H, d), 2.99 (1H, d), 4.22—4.44 (1H, m), 6.79 (1H, d), 7.51 (1H, d), 7.61 (1H, dd). *Anal.* Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.84; H, 6.38; N, 9.52.

Compounds **9a**, **c**, **d** were prepared in a similar way.

9a: mp 171—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.36 (3H, s), 1.7—2.6 (6H, m), 2.86 (2H, dd, J=3.5, 11.5 Hz), 4.0—4.3 (1H, br s), 6.74 (1H, d, J=8.5 Hz), 6.80 (1H, d, J=2.5 Hz), 6.94 (1H, dd, J=2.5, 8.5 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.01; H, 6.82; N, 10.29.

9c: mp 98—99 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, s), 2.24 (3H, s), 3.18 (2H, s), 4.17 (2H, s), 6.80 (1H, d), 7.23 (1H, d), 7.60 (1H, dd). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.92; H, 6.21; N, 10.52.

9d: mp 125—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (6H, s), 3.24 (2H, s), 4.84 (2H, s), 6.82 (1H, d), 7.28 (1H, d), 7.50—7.65 (4H, m), 7.93—8.04 (2H, m). *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.16; H, 5.62; N, 8.47.

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-hydroxycyclopentyl)-2*H*-1,4-benzoxazine (11a)** F) Compound **3h** (1.0 g, 5.3 mmol) was dissolved in DMF (20 ml) followed by addition of sodium hydride (60% in oil, 0.24 g, 5.5 mmol). The mixture was stirred at 70 °C for 1 h, and after cooling to room temperature, cyclopentene oxide (0.5 ml, 5.8 mmol) was added. The mixture was stirred at 70 °C for 3 h, allowed to cool, diluted with water and extracted with AcOEt. The extract was washed with water and dried. The filtrate was concentrated and the residue was chromatographed with AcOEt–hexane (1 : 8→1 : 4, v/v) to give **11a** (0.71 g, 49%): mp 95—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.34 (3H, s), 1.67—1.73 (2H, m), 1.87—1.91 (2H, m), 1.99—2.05 (2H, m), 2.96 (1H, d, J=10 Hz), 2.99 (1H, d, J=10 Hz), 3.98—3.99 (1H, m), 4.22 (1H, m), 6.76 (1H, d, J=9 Hz), 6.92 (1H, dd, J=9, 3 Hz), 7.10 (1H, d, J=3 Hz). *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.40; H, 7.46; N, 10.23.

6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxo-3-oxolanyl)-2*H*-1,4-benzoxazine (10) G) α-Bromo-γ-butyrolactone (7.9 g, 48 mmol) was added to a solution of **3h** (1.0 g, 5.3 mmol) and Et_3N (1.77 g, 17.6 mmol), and the mixture was stirred at 120 °C for 3 h, then poured into water and extracted with AcOEt. The organic layer was dried and evaporated. The residue was chromatographed with AcOEt–hexane (1 : 8→1 : 2, v/v) to give **10** (0.11 g, 8%): mp 144—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, s), 1.41 (3H, s), 2.2—2.7 (2H, m), 2.99 (2H, d), 4.2—4.8 (3H, m), 6.82 (1H, d), 6.89 (1H, d), 7.05 (1H, dd). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.03; H, 5.93; N, 10.21.

6-Cyano-3,4-dihydro-2,2-dimethyl-4-(5-oxo-1-cyclopentene-1-yl)-2*H*-1,4-benzoxazine (12a) H) Carbon tetrachloride (20 ml), *N*-bromosuccinimide (5.34 g, 30 mmol) and a catalytic amount of dibenzoyl peroxide were added to cyclopentanone (2.53 g, 30 mmol). The mixture was refluxed for 3 h, then cooled and filtered and the filtrate was concentrated. The residue and Et_3N (2.43 g, 24 mmol) were added to a solution of **3h** (0.38 g, 2 mmol) in THF (5 ml) and the mixture was stirred at room temperature overnight, then concentrated, diluted with water, and extracted with AcOEt. The organic layer was dried and concentrated. The residue was chromatographed with AcOEt–hexane (1 : 10→1 : 4, v/v) to give **12a** (0.3g, 50%): mp 124—126 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 2.50—2.77 (4H, m), 3.42 (2H, s), 6.84 (1H, d), 7.01—7.14 (2H, m), 7.21 (1H, t). *Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.52; H, 5.99; N, 10.30.

Compound **12b** was prepared in a similar way: mp 96—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (6H, s), 2.51—2.59 (2H, m), 2.64—2.75 (2H, m), 3.44 (2H, s), 6.83 (1H, dd), 7.24 (1H, t), 7.61—7.22 (2H, m). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.11; H, 5.64; N, 9.43.

6-Cyano-3,4-dihydro-4-(5-methoxyimino-1-cyclopenten-1-yl)-2,2-dimethyl-2*H*-1,4-benzoxazine (14) I) Compound **12a** (0.3 g, 1 mmol) was dissolved in 3 ml of pyridine, followed by addition of *O*-methylhydroxylamine hydrochloride (0.26 g, 3 mmol). The mixture was stirred overnight and the solvent was evaporated off. The residue was poured into water and extracted with AcOEt. The extract was washed with water, dried, and concentrated to give **14** (0.26 g, 88%): mp 138—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 2.4—2.8 (4H, m), 3.38 (2H, s), 3.84 (3H, s), 6.26 (1H, t), 6.78 (1H, d), 6.98 (1H, dd), 7.14 (1H, d). *Anal.* Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.40; H, 6.60; N, 13.95.

6-Cyano-3,4-dihydro-2,2-dimethyl-4-(6-oxo-1-cyclohexen-1-yl)-2*H*-1,4-benzoxazine (13a) J) Compound **3h** (0.5 g, 2.7 mmol), cyclohexene-1,2-dione (0.33 g, 2.9 mmol) and a catalytic amount of *p*-toluenesulfonic acid were dissolved in 15 ml of toluene. Using a Dean–Stark trap, the solution was refluxed for 4 h. After cooling, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and concentrated. The residue was chromatographed with AcOEt–hexane (1 : 5, v/v) to give **13a** (0.5 g, 61%): mp 166—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, s), 2.0—2.2 (2H, m), 2.5—2.7 (4H, m), 2.20 (2H, s), 6.60 (1H, d), 6.76 (1H, d), 6.8—7.0 (2H, m). *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.36; H, 6.38; N, 9.83.

Compound **13b** was synthesized in a similar way: mp 106—108 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d), 1.34 (6H, s), 2.1—3.1 (3H, m), 3.43 (2H, s), 6.84 (1H, d), 7.0—7.2 (3H, m). *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.49; H, 6.50; N, 9.88.

2-(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine 1-Oxide (16a) K) Compound **3a** (2.66 g, 12.7 mmol) was dissolved in DMF (10 ml) followed by addition of sodium hydride (60% in oil, 1.02 g, 25.4 mmol) and the mixture was stirred for 30 min. 2-Bromopyridine *N*-oxide hydrochloride (2.77 g, 12.7 mmol) was added with ice-cooling. The whole was stirred at room temperature for 2 h, then poured into water and extracted with AcOEt. The organic layer was concentrated and the residue was chromatographed with $CHCl_3$ to give **16a** (2.0 g, 50%): mp 224—226 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, s), 3.69 (2H, s), 6.94 (1H, d), 7.05—7.41 (3H, m), 7.49 (1H, d), 7.77 (1H, dd), 8.31 (1H, ddd). *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.73; H, 5.20; N, 13.80.

Compounds **16d—k**, **16b**, **17** were prepared in a similar way. (In some cases heating was required.)

16d: mp 161—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, s), 2.57 (3H, s), 3.65 (2H, s), 6.89 (1H, d), 7.13—7.28 (3H, m), 7.40 (1H, d), 7.70 (1H, dd). *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.97; H, 5.48; N, 13.21.

16e: mp 175—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 3.67 (2H, s), 6.86—7.33 (6H, m), 8.26—8.33 (1H, m). *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.20; H, 5.38; N, 14.88.

16f: mp 144—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, s), 3.97 (2H, s), 7.03 (1H, d), 7.2—7.5 (3H, m), 7.64 (1H, dd), 7.8—8.1 (1H, m), 8.76 (1H, dd), 11.85 (1H, br s). *Anal.* Calcd for $C_{16}H_{15}F_3N_2O_2 \cdot HCl$: C, 53.27; H, 4.47; Cl, 9.83; F, 15.80; N, 7.77. Found: C, 53.08; H, 4.38; Cl, 9.86; F, 15.67; N, 7.68.

16g: mp 149—151 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, s), 3.65 (2H, s), 6.72 (1H, d), 6.80—7.40 (5H, m), 8.19—8.28 (1H, m). *Anal.* Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; Br, 23.84; N, 8.36. Found: C, 53.74; H, 4.49; Br, 23.83; N, 8.39.

16h: mp 143—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 3.66 (3H, s), 3.71 (2H, s), 6.36—6.54 (2H, m), 6.77—7.47 (4H, m), 8.23—8.30 (1H, m). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.07; H, 6.35; N, 9.69.

16i: mp 160—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t), 1.28 (6H, s), 2.42 (2H, q), 3.60 (2H, br s), 6.51 (1H, s), 6.71—6.78 (2H, m), 7.29—7.33 (1H, m), 7.60—7.62 (2H, m), 8.45—8.46 (1H, m). *Anal.* Calcd for $C_{17}H_{20}N_2O_2 \cdot HCl \cdot 0.1H_2O$: C, 63.29; H, 6.62; Cl, 10.99; N, 8.68. Found: C, 63.13; H, 6.63; Cl, 11.00; N, 8.66.

16j: mp 146—148 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (6H, s), 3.70 (2H, s), 6.45 (1H, m), 7.3—7.8 (5H, m), 8.46 (1H, dd), 9.49 (1H, br s). *Anal.* Calcd for $C_{15}H_{15}N_3O_4 \cdot HCl \cdot 0.25H_2O$: C, 52.64; H, 4.86; Cl, 10.36; N, 12.28. Found: C, 52.63; H, 4.68; Cl, 10.42; N, 12.25.

16k: mp 139—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (2H, t), 4.44 (2H, t), 7.02 (1H, d), 7.2—7.4 (3H, m), 7.52 (1H, d), 7.78 (1H, dd), 8.36 (1H, d). *Anal.* Calcd for $C_{13}H_{11}N_3O_4 \cdot 0.1H_2O$: C, 56.77; H, 4.10; N, 15.28. Found: C, 56.74; H, 4.10; N, 15.17.

16b: mp 198—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (6H, s), 3.50 (2H, s), 6.96 (1H, d), 7.20—7.40 (2H, m), 7.81 (1H, dd), 7.90—8.30 (3H, m). *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.52; H, 5.02; N, 13.80.

17: mp 189 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.90 (9H, m), 3.64 (2H, s), 7.04 (1H, d), 7.12—7.26 (2H, m), 7.96 (1H, dd), 8.23 (1H, d), 8.28—8.45 (2H, m). *Anal.* Calcd for $C_{15}H_{18}BN_3O_3$: C, 60.23; H, 6.07; N, 14.05. Found: C, 60.08; H, 6.20; N, 14.02.

3,4-Dihydro-2,2-dimethyl-6-nitro-4-(4-pyridyl)-2*H*-1,4-benzoxazine (18c) L) A 1 N hydrochloric acid solution (46.8 ml, 46 mmol) was added

to a solution of **17** (0.7 g, 2.3 mmol) in THF (40 ml), and the mixture was stirred at 60 °C for 2 h, concentrated, made alkaline with an aqueous solution of hydroxide, and extracted with $CHCl_3$. The organic solution was washed with brine, dried, and evaporated to give **18c** (0.64 g, 95%): mp 168—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, s), 3.57 (2H, s), 6.97 (1H, d), 7.07—7.20 (2H, m), 7.84 (1H, dd), 8.20 (1H, d), 8.40—8.60 (2H, m). *Anal.* Calcd for $C_{15}H_{15}N_3O_3 \cdot 0.5H_2O$: C, 61.22; H, 5.48; N, 14.28. Found: C, 60.86; H, 5.21; N, 14.19.

4-(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)pyridine 1-Oxide (16c) M) *m*-Chloroperbenzoic acid (0.29 g, 1.5 mmol) was added to a solution of **18c** (0.35 g, 1.2 mmol) in CH_2Cl_2 (4.5 ml) at 0 °C and the mixture was stirred at room temperature for 18 h, then diluted with aqueous sodium hydrogen carbonate solution and concentrated. The residue was chromatographed with MeOH–$CHCl_3$ (1 : 20, v/v) to give **16c** (0.31 g, 84%): mp 202—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (6H, s), 3.56 (2H, s), 6.99 (1H, d), 7.05—7.35 (2H, m), 7.86 (1H, dd), 8.07 (1H, d), 8.10—8.35 (2H, m). *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.69; H, 5.00; N, 13.99.

Compounds **19a—c** were prepared in a similar way.

19a: mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, s), 3.27 (2H, s), 4.78 (2H, s), 6.83 (1H, d), 7.12—7.34 (4H, m), 7.61 (1H, dd), 8.24—8.42 (1H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.69; H, 5.47; N, 13.18.

19b: mp 122—123 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 3.15 (2H, s), 4.53 (2H, s), 6.85 (1H, d), 7.16—7.40 (2H, m), 7.47 (1H, d), 7.66 (1H, dd), 8.03—8.35 (2H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.66; H, 5.33; N, 13.30.

19c: mp 166—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, s), 3.14 (2H, s), 4.53 (2H, s), 6.85 (1H, d), 7.23—7.30 (2H, m), 7.44 (1H, d), 7.65 (1H, dd), 8.19—8.27 (2H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_4 \cdot 0.25H_2O$: C, 60.09; H, 5.52; N, 13.14. Found: C, 60.10; H, 5.38; N, 13.04.

3,4-Dihydro-2,2-dimethyl-6-nitro-4-(2-pyridyl)-2*H*-1,4-benzoxazine (18a) N) Phosphorus trichloride (0.67 ml, 6.1 mmol) was dropped into a solution of **16a** (0.8 g, 2.7 mmol) in AcOEt (7 ml), and the mixture was stirred at 70 °C for 10 min, then poured into ice water, made alkaline with sodium hydroxide, and extracted with $CHCl_3$. The organic solution was washed with brine, dried, and evaporated to give **18a** (0.37 g, 48%): mp 108—109 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (6H, s), 3.85 (2H, s), 6.85—6.99 (2H, m), 7.20—7.35 (1H, m), 7.57—7.65 (1H, m), 7.82 (1H, dd), 8.33—8.43 (2H, m). *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.05; H, 5.23; N, 14.58.

Compound **18b** was prepared in a similar way: mp 124—126 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, s), 3.51 (2H, s), 6.93 (1H, d), 7.25—7.58 (1H, m), 7.58—7.87 (4H, m), 8.20—8.90 (1H, m). *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.14; H, 5.26; N, 14.61.

O) Compounds **20a, b** were prepared in an analogous way to procedure *G*.

20a: mp 174—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.34 (6H, s), 3.37 (2H, s), 5.04 (2H, s), 6.84—6.96 (1H, m), 7.48—7.61 (2H, m), 7.72—7.91 (2H, m), 8.28—8.46 (1H, m), 8.80—8.90 (1H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_3 \cdot HCl$: C, 57.23; H, 5.40; N, 12.51; Cl, 10.56. Found: C, 57.36; H, 5.39; N, 12.59; Cl, 10.77.

20b: mp 186—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33 (6H, s), 3.29 (2H, s), 4.84 (2H, s), 6.84—6.93 (1H, m), 7.48—7.59 (2H, m), 7.99 (1H, dd, J=8, 5 Hz), 8.36—8.50 (1H, m), 8.77—8.89 (1H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_3 \cdot HCl$: C, 57.23; H, 5.40; N, 12.51; Cl, 10.56. Found: C, 57.09; H, 5.35; N, 12.64; Cl, 10.74.

P) Compound **21** was prepared in an analogous way to procedure C: mp 170—172 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.30 (6H, s), 3.69 (2H, s), 7.13 (1H, d), 7.56 (2H, dd), 7.99 (1H, dd), 8.58 (1H, m), 8.75 (1H, dd). *Anal.* Calcd for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.19; H, 4.85; N, 13.46.

Compound **20c** was prepared from **21** in the same way as **11**: mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, s), 3.15 (2H, s), 4.55 (2H, s), 6.84 (1H, d), 7.23—7.33 (2H, m), 7.45 (1H, d), 7.63 (1H, dd), 8.57—8.64 (2H, m). *Anal.* Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.07; H, 5.74; N, 14.01.

Q) Compound **23** was prepared in an analogous way to procedure C: mp 95—96 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t), 1.36 (6H, s), 3.21 (2H, s), 4.10 (2H, s), 4.20 (2H, q), 6.77 (1H, d), 7.37 (1H, d), 7.59 (1H, dd). *Anal.* Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.16; H, 6.15; N, 9.43.

2-(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)-*N*-methylacetamide (22b) R) A solution of methylamine in MeOH (40%, 5 ml) was added to **23** (1.0 g, 3.4 mmol). The mixture was stirred at 100 °C for 1 h, then concentrated to give **22b** (0.87 g, 90%): mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 2.86 (3H, d), 3.18 (2H, s), 3.93 (2H, s), 6.82 (1H, d), 7.42 (1H, d), 7.66 (1H, dd). *Anal.* Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 55.93; H, 6.11; N, 15.16.

Compounds **22a, c**, **26** were prepared in a similar way.

22a: mp 183—184 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 3.20 (2H, s), 3.93 (2H, s), 6.81 (1H, d), 7.44 (1H, d), 7.64 (1H, dd). *Anal.* Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.34; H, 5.68; N, 15.84.

22c: mp 115—116 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t), 1.40 (6H, s), 3.19 (2H, s), 3.34 (2H, m), 3.91 (2H, s), 6.82 (1H, d), 7.44 (1H, d), 7.66 (1H, dd). *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.24; H, 6.57; N, 14.34.

26: mp 212—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (6H, s), 2.86 (3H, d), 4.54 (2H, s), 5.86 (1H, br s), 7.06 (1H, d), 7.86—7.98 (2H, m). *Anal.* Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33. Found: C, 53.06; H, 5.10; N, 14.35.

(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)acetic Acid (24) S) A mixture of **23** (1.0 g, 3.4 mmol), sodium hydroxide (1.2 g, 30 mmol) and water (5 ml) was stirred at 100 °C for 30 min, then washed with AcOEt, acidified with concentrated hydrochloric acid, and extracted with AcOEt. The organic solution was dried and concentrated to give **24**, which was crystallized from AcOEt–hexane (0.86 g, 95%): mp 162—164 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (6H, s), 3.24 (2H, s), 4.22 (2H, s), 6.83 (1H, d), 7.34 (1H, d), 7.50 (1H, dd), 12.84 (1H, br s). *Anal.* Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.95; H, 5.22; N, 10.58.

2-(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)-*N*,*N*-dimethylacetamide (22e) T) Compound **24** (1.0 g, 3.7 mmol) and thionyl chloride (1.3 g, 11 mmol) were dissolved in $CHCl_3$ (6 ml), followed by addition of 2 drops of pyridine. The mixture was refluxed for 5 h and concentrated. The crude acid chloride was dissolved in $CHCl_3$ (5 ml) and then added dropwise to a solution of dimethylamine hydrochloride (0.93 g, 11 mmol) and Et_3N (1.2 g, 11 mmol) in $CHCl_3$ (20 ml) under ice-cooling. The mixture was stirred at room temperature for 4 h and concentrated. The residue was chromatographed with AcOEt–hexane (1 : 3→3 : 1, v/v) to give **22e** (0.46 g, 41%): mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, s), 2.99 (3H, s), 3.12 (3H, s), 3.23 (2H, s), 4.18 (2H, s), 6.79 (1H, d), 7.31 (1H, d), 7.60 (1H, dd). *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.76; H, 6.48; N, 14.28.

2-(3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzoxazin-4-yl)-*N*-isopropylacetamide (22d) U) Compound **24** (0.53 g, 2 mmol), dicyclohexylcarbodiimide (0.45 g, 2.2 mmol), and 1-hydroxybenzotriazole (0.41 g, 3 mmol) were dissolved in CH_2Cl_2 (10 ml), then isopropylamine (0.12 g, 2 mmol) was added and the mixture was stirred for 2 h. The precipitate was filtered off and the filtrate was washed with potassium carbonate solution, concentrated, and chromatographed with AcOEt–hexane (1 : 4, v/v) to give **22d** (0.38 g, 62%): mp 156—157 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (6H, d), 1.40 (6H, s), 3.17 (2H, s), 3.86 (2H, s), 4.09 (1H, m), 6.81 (1H, d), 7.43 (1H, d), 7.65 (1H, dd). *Anal.* Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.58; H, 6.96; N, 13.63.

Compound **22f** was prepared in a similar way: mp 165—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, s), 1.70—2.24 (4H, m), 3.27 (2H, s), 3.34—3.66 (4H, m), 4.08 (2H, s), 6.79 (1H, d), 7.33 (1H, d), 7.59 (1H, dd). *Anal.* Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.17; H, 6.68; N, 13.10.

V) Compound **25** was prepared in an analogous way to procedure C: mp 67—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t), 1.59 (6H, s), 4.28 (2H, q), 4.69 (2H, s), 7.08 (1H, d), 7.62 (1H, d), 7.97 (1H, dd). *Anal.* Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.49; H, 5.24; N, 9.06.

Biological Test. i) Effects on 3,4-Diaminopyridine-Induced Rhythmic Contractions[14] Mongrel dogs of either sex were anesthetized with pentobarbital (30 mg/kg i.v.) and killed by bleeding, then the heart was excised. The left coronary circumflex branch or the anterior-descending branch 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 contraction were recorded. The specimen was allowed to stabilize for 30 min, then rhythmic contractions were induced by addition of 3,4-diaminopyridine (10 mM).

When the amplitude and frequency of rhythmic contractions became substantially steady, 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 anesthesized with pentobarbital (30 mg/kg, i.v.). The experiment was performed under artificial respiration after tracheal intubation. After thoracotomy, blood pressure was measured. The mean blood pressure (MBP)-lowering in percent reduction (Δ%) is shown in Tables 1, 2, and 3.

iii) Hypotensive Effects in SHR (*p.o.*) 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, the blood pressure was measured without 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.

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