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Synthesis and Biological Activity of Novel 1,3-Benzoxazine Derivatives as K^+ Channel Openers

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A new series of 1,3-benzoxazine derivatives with a 2-pyridine 1-oxide group at C4 was designed to explore novel K^+ channel openers. Synthesis was carried out by using a palladium(0)-catalyzed carbon–carbon bond formation reaction of imino-triflates with organozinc reagents and *via* a new one-pot 1,3-benzoxazine skeleton formation reaction of benzoylpyridines. The compounds were tested for vasorelaxant activity in tetraethylammonium chloride (TEA) and $BaCl_2$-induced and high KCl-induced contraction of rat aorta to identify potential K^+ channel openers, and also for oral hypotensive effects in spontaneously hypertensive rats. An electron-withdrawing group with the proper shape at C6 and a methyl or halogeno group at C7 of the 1,3-benzoxazine nucleus were required for the development of optimal vasorelaxant and hypotensive activity. In particular, 2-(6-bromo-7-chloro-2,2-dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-oxide (7l) showed more potent vasorelaxant activity ($EC_{50}=0.14\,\mu M$) against TEA and $BaCl_2$-induced contraction and longer-lasting hypotensive effects than cromakalim (1).

Key words 4-(2-pyridyl)-2*H*-1,3-benzoxazine; K^+ channel opener; hypotensive effect

K^+ channel openers are thought to exert their smooth muscle relaxant activity through hyperpolarization of the cell membrane as a result of opening K^+ channels.[1–3] Therefore, they have therapeutic potential for the treatment of conditions such as hypertension, angina pectoris, asthma, and urinary incontinence.[4] There are several structural types of K^+ channel openers[5] represented by cromakalim (**1**), nicorandil (**2**), pinacidil (**3**), minoxidil sulfate (**4**), diazoxide (**5**), and aprikalim (**6**). In particular, the discovery of cromakalim, a specific K^+ channel opener with highly potent antihypertensive activity, has stimulated extensive efforts to synthesize superior agents. There have been numerous reports on modification of substituents at various positions of the benzopyran ring,[6] but few reports on modification of the benzopyran nucleus itself.[7] In the course of our studies on new hypotensive K^+ channel openers, we considered replacing the benzopyran ring with other [6,6]-fused rings. Key features for the antihypertensive activity of **1** include a geminal dimethyl group at C2, a cyclic amide containing a 2-oxo function at C4, and a strong electron-withdrawing group at C6.[6] Both X-ray and NMR studies[8,9] have indicated that the cyclic amide ring of **1** favors an orthogonal relationship with the plane of the benzopyran ring. The lactam ring of **1** was replaced by other heterocyclic rings containing an oxo function such as pyridone,[10] pyridine *N*-oxide[11] or indolone,[12] for which the same relative orientation would be expected. Based on this background, we have designed novel 2*H*-1,3-benzoxazine derivatives **7** having a geminal dimethyl group at C2, a pyridine *N*-

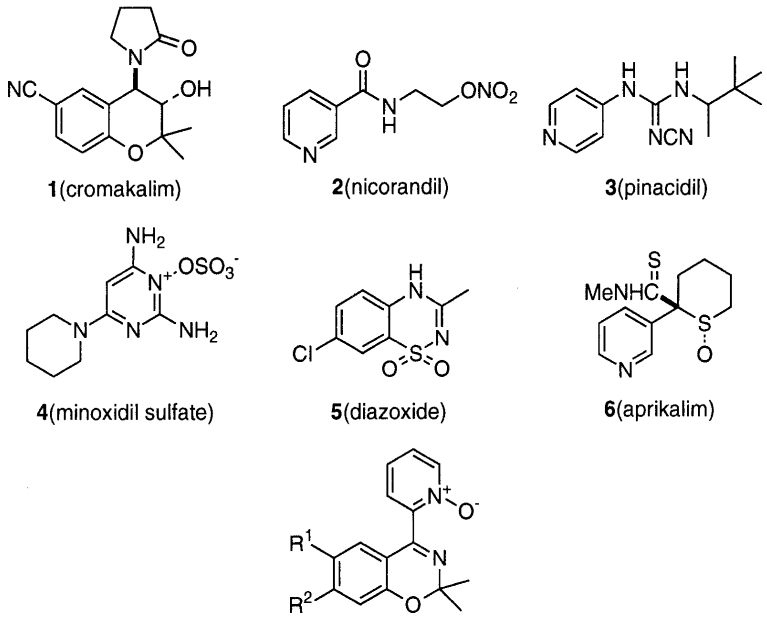

Chart 1

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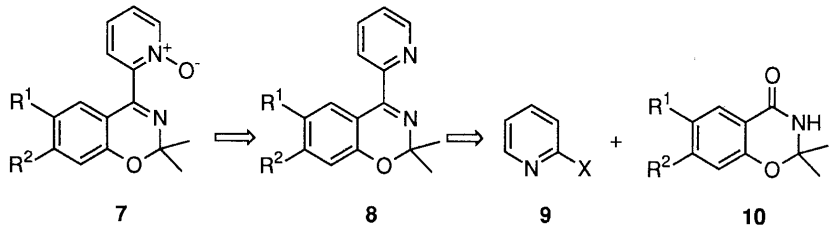


Chart 2

oxide moiety at C4, an electron-withdrawing group at C6, and a less bulky group at C7. This 1,3-benzoxazine nucleus has no chiral center, and its nitrogen atom may exert an electrostatic effect corresponding to the C3 hydroxy group of **1**. In addition, considering the stability of the 1,3-benzoxazine system, we have chosen the pyridine *N*-oxide group as the C4 substituent. In this paper, we describe the synthesis and biological activity of a novel series of 1,3-benzoxazine K^+ channel openers.

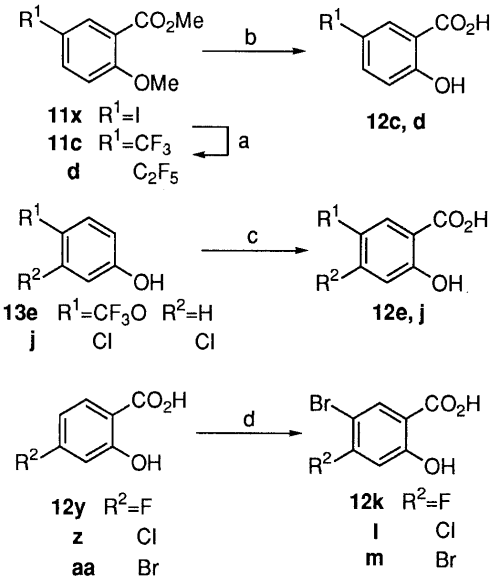
Chemistry

The synthetic route to the target compounds **7** outlined in Chart 2, which was characterized by a cross coupling reaction of pyridine reagents **9** with 2*H*-1,3-benzoxazin-4-ones **10**, was initially investigated. Intermediates **10** were synthesized by acetonidation of salicylamides **15** prepared from the corresponding salicylic acids **12**. 5-Perfluorosalicylic acids **12c** and **12d** were prepared by perfluoroalkylation of the 5-iodosalicylic acid derivative **11x**[13] followed by demethylation. *o*-Carboxylation of the phenols **13e** and **13j** by means of the Kolbe–Schmitt reaction gave salicylic acids **12e** and **12j**. Bromination of **12y**, **12z** and **12aa** gave 5-bromosalicylic acids **12k—m** (Chart 3).

Acetylation and subsequent conversion to acid chlorides of the salicylic acids **12**, followed by treatment with NH_4OH, gave salicylamides **15**. 5-Methoxycarbonylsalicylamide (**15p**) was prepared by regioselective hydrolysis and subsequent amidation and esterification of the diester **14p**. 5-Benzoylsalicylamide (**15q**) was prepared by the Friedel–Crafts reaction of the salicylamide **15u**. Treatment of the salicylamides **15** with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH gave the 2*H*-1,3-benzoxazin-4-ones **10** in good yield (Chart 5, Table 1).

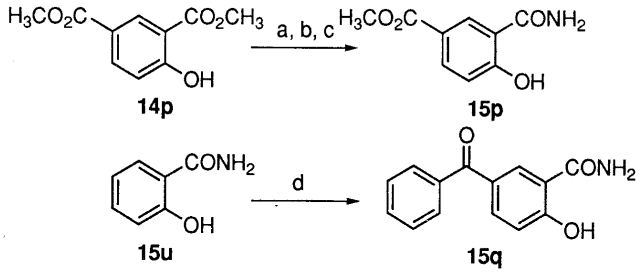
6-Cyano-2,2-dimethyl-2*H*-1,3-benzoxazin-4-one (**10f**) was prepared by cyanation of the corresponding 6-bromo derivative **10b** with CuCN, and the 6-trimethylsilylethynyl derivative **10t** was prepared by palladium(0)-catalyzed trimethylsilylethynylation of the corresponding 6-iodo derivative **10x**.[14]

Few 1,3-benzoxazine compounds with a 4-substituent linked by a carbon–carbon bond have been synthesized. Reaction of an organometallic compound with imino ether or imino halide is generally used to form a carbon–carbon bond at an imino carbon. However, this was difficult in the case of the 6-cyano derivative **10f**, whose cyano group might inhibit the reaction of the imine moiety. Thus, a new carbon–carbon bond formation reaction at C4 of 1,3-benzoxazine, the cross-coupling reaction in the presence of a palladium(0) catalyst,[15] was investigated. In this reaction, the use of an organometallic



reagent: (a) CF_3CO_2Na or $C_2F_5CO_2Na$, CuI; (b) BBr_3; (c) CO_2, K_2CO_3, 190 °C; (d) Br_2, AcONa.

Chart 3

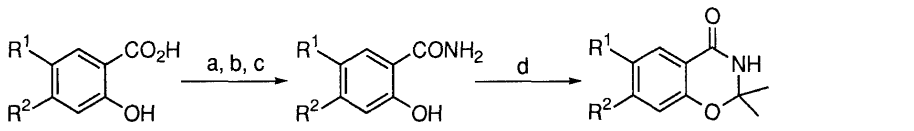


reagent: (a) $AlCl_3$, $(CH_3)_2S$; (b) NH_4OH; (c) CH_3OH, H_2SO_4; (d) PhCOCl, $AlCl_3$.

Chart 4

compound with low reactivity to the cyano group was thought to be appropriate, so 2-pyridylzinc chloride **18** prepared from 2-lithiopyridine by metal exchange at 0 °C *in situ* was employed. Since the imine moiety was expected to be highly reactive, imino triflates **16**, which were thought to be the most reactive, were used. Thus, reaction of **16** and **18** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) at room temperature afforded the desired compounds **8** in good yield (Chart 6, Table 2).

The 6-trifluoromethyl derivative **8c** was also prepared *via* an alternative short synthetic route. The benzonitrile



12a R^1=Cl R^2=H; **b** Br H; **s** CH_3 H; **v** H CH_3; **w** H C_2H_5O; **x** I H; **c-e, j-m**

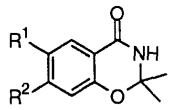
15a-e, j-m, s, v-x: **g** R^1=CH_3CO R^2=H; **p** CH_3OCO H; **q** PhCO H; **u** H H

10a-e, g, j-m, p, q, s, u-x: **b** R^1=Br R^2=H (e); **f** CN H (e); **t** $Me_3SiC{\equiv}C$ H (f); **x** I H (f)

reagent: (a) Ac_2O; (b) $(COCl)_2$, DMF; (c) NH_4OH; (d) 2,2-dimethoxypropane, TsOH; (e) CuCN; (f) $Me_3SiC{\equiv}CH$, $Pd(OAc)_2$, Ph_3P, Et_3N.

Chart 5

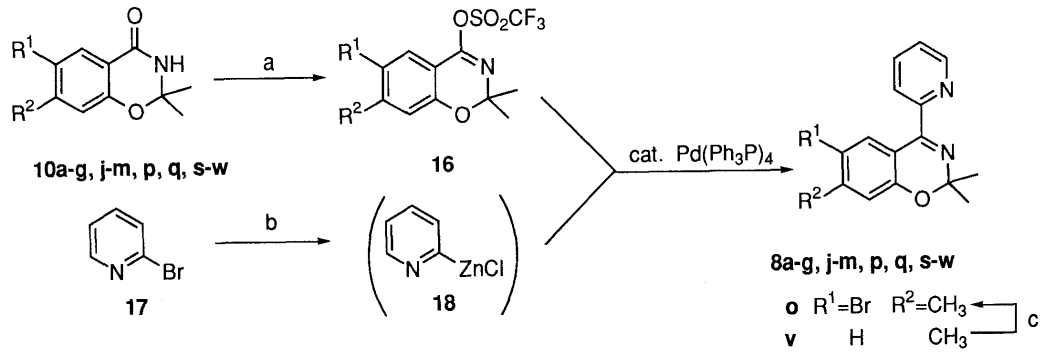
Table 1. 2,2-Dimethyl-2*H*-1,3-benzoxazin-4-ones **10**



Compd.	R^1	R^2	Yield[a]	mp (°C)	^{1}H-NMR ($CDCl_3$[b])
10a	Cl	H	43	153.5—154.5	1.66 (6H, s), 6.88 (1H, d, J=8.8 Hz), 7.00—7.30 (1H, br s), 7.40 (1H, dd, J=8.8, 2.6 Hz), 7.90 (1H, d, J=2.6 Hz)
10b	Br	H	52	177—179	1.65 (6H, s), 6.83 (1H, d, J=8.6 Hz), 7.20—7.35 (1H, br s), 7.54 (1H, dd, J=8.6, 2.6 Hz), 8.04 (1H, d, J=2.6 Hz)
10c	CF_3	H	42	171—172.5	1.69 (6H, s), 7.04 (1H, d, J=8.4 Hz), 7.14—7.38 (1H, br s), 7.66—7.75 (1H, m), 8.22—8.24 (1H, m)
10d	C_2F_5	H	47	165—167	1.70 (6H, s), 7.05 (1H, d, J=8.6 Hz), 7.26—7.40 (1H, br s), 7.66 (1H, dd, J=8.6, 2.2 Hz), 8.19 (1H, d, J=2.2 Hz)
10e	CF_3O	H	49	125—128	1.67 (6H, s), 6.95 (1H, d, J=8.8 Hz), 7.06—7.18 (1H, br s), 7.27—7.34 (1H, m), 7.78—7.80 (1H, m)
10f[c]	CN	H	57	208—212	1.70 (6H, s), 7.02 (1H, d, J=8.4 Hz), 7.71 (1H, dd, J=8.4, 2.2 Hz), 7.94—8.08 (1H, br s), 8.25 (1H, d, J=2.2 Hz)
10g	CH_3CO	H	36[d]	161.5—162.5	1.70 (6H, s), 2.62 (3H, s), 7.01 (1H, d, J=8.6 Hz), 7.16—7.36 (1H, br s), 8.14 (1H, dd, J=8.6, 2.2 Hz), 8.52 (1H, d, J=2.2 Hz)
10j	Cl	Cl	49	229—231	1.66 (6H, s), 7.07 (1H, s), 7.18—7.28 (1H, br s), 7.98 (1H, s)
10k	Br	F	51	207—210	1.67 (6H, s), 6.73 (1H, d, J=8.8 Hz), 7.50—7.60 (1H, br s), 8.12 (1H, d, J=7.8 Hz)
10l	Br	Cl	58	230—233	1.55 (6H, s), 7.37 (1H, s), 7.98 (1H, s), 8.90—8.98 (1H, br s)
10m	Br	Br	57	247—251	1.54 (6H, s), 7.48 (1H, s), 7.95 (1H, s), 8.90—8.98 (1H, br s)
10p	CH_3OCO	H	62[d]	188—192	1.65 (6H, s), 3.90 (3H, s), 6.96 (1H, d, J=8.6 Hz), 7.70—7.80 (1H, br s), 8.12 (1H, dd, J=8.6, 2.2 Hz), 8.60 (1H, d, J=2.2 Hz)
10q	PhCO	H	93[d]	232—234	1.70 (6H, s), 6.72—6.80 (1H, br s), 7.05 (1H, d, J=8.6 Hz), 7.45—7.64 (3H, m), 7.77—7.80 (2H, m), 8.05 (1H, dd, J=8.6, 2.2 Hz), 8.38 (1H, d, J=2.2 Hz)
10s	CH_3	H	58	164—165	1.65 (6H, s), 2.33 (3H, s), 6.82 (1H, d, J=8.4 Hz), 7.25 (1H, dd, J=8.4, 2.2 Hz), 7.36—7.44 (1H, br s), 7.72 (1H, d, J=2.2 Hz)
10t	$TMSC{\equiv}C$	H	54[d]	194—195	0.23 (9H, s), 1.64 (6H, s), 6.60—6.90 (1H, br s), 6.86 (1H, d, J=8.4 Hz), 7.53 (1H, dd, J=8.4, 2.0 Hz), 8.05 (1H, d, J=2.0 Hz)
10u	H	H	96[d]	139—141	1.66 (6H, s), 6.58—6.78 (1H, br s), 6.93 (1H, dd, J=8.2, 1.0 Hz), 7.07 (1H, td, J=7.6, 1.0 Hz), 7.42—7.50 (1H, m), 7.93 (1H, dd, J=7.6, 1.6 Hz)
10v	H	CH_3	88	168—171	1.64 (6H, s), 2.36 (3H, s), 6.66—6.76 (2H, m), 6.86—6.91 (1H, m), 7.80 (1H, d, J=8.0 Hz)
10w	H	C_2H_5O	80	168—169	1.32 (3H, t, J=7.0 Hz), 1.51 (6H, s), 4.06 (2H, q, J=7.0 Hz), 6.47 (1H, d, J=2.2 Hz), 6.62 (1H, dd, J=8.6, 2.2 Hz), 7.64 (1H, d, J=8.6 Hz), 8.38—8.46 (1H, br s)
10x	I	H	45	148—149	1.65 (6H, s), 6.71 (1H, d, J=8.8 Hz), 7.72 (1H, dd, J=8.8, 2.2 Hz), 8.22 (1H, d, J=2.2 Hz)

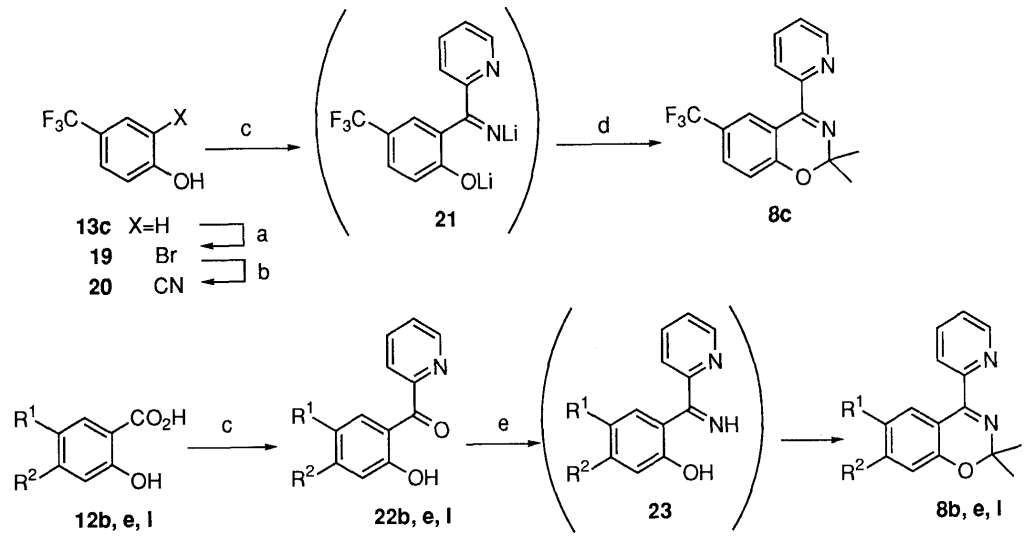
a) From the corresponding salicylic acids **12**, unless otherwise indicated. *b*) **10l**, **m**, **v** and **w** were measured in DMSO-d_6. *c*) IR (KBr) cm^{-1}: 2230. *d*) From the corresponding salicylamides **15**.

20 was treated with 2-lithiopyridine to give the imine intermediate **21**. Compound **21** was then reacted with NH_4OAc and 2,2-dimethoxypropane to afford **8c** in good yield (Chart 7, Table 2). This result suggested that 4-(2-pyridyl)-2*H*-1,3-benzoxazines **8** could also be obtained by cyclization of 2-(2-hydroxybenzoyl)pyridines **22** prepared by coupling of salicylic acids **12** and 2-lithiopyridine. Treatment of benzoylpyridines **22** with excess ammonia



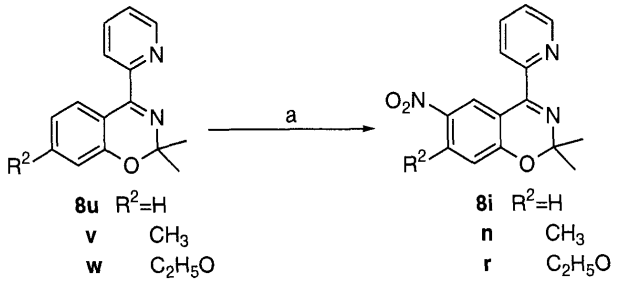
reagent: (a) $(CF_3SO_2)_2O$, 2,6-lutidine; (b) 1) nBuLi, 2) $ZnCl_2$; (c) Br_2.

Chart 6



reagent: (a) Br_2; (b) CuCN; (c) 2-lithiopyridine; (d) NH_4OAc, 2,2-dimethoxypropane; (e) NH_3, acetone, NH_4Cl, $CaSO_4$, 80 °C.

Chart 7



reagent: (a) HNO_3, H_2SO_4, AcOH.

Chart 8

and acetone in the presence of NH_4Cl as a catalyst and Drierite ($CaSO_4$) as a dehydrating agent in a sealed tube at 80 °C gave the desired **8** in good yields (Chart 7, Table 2). Monitoring of the reaction by TLC suggested that the benzoylpyridines **22** were quickly converted to the corresponding imines **23** in the early stage and that the imines **23** were cyclized slowly to afford 1,3-benzoxazines **8**. This new one-pot 1,3-benzoxazine skeleton formation reaction should be a convenient and useful method for the synthesis of 2,2-dimethyl-4-substituted-2*H*-1,3-benzoxazine derivatives.

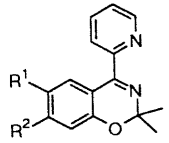
Bromination of the 7-methyl derivative **8v** gave the 6-bromo-7-methyl derivative **8o** (Chart 6). Nitration of the 7-unsubstituted (**8u**), methyl (**8v**) and ethoxy (**8w**) derivatives gave the corresponding 6-nitro derivatives **8i**, **n**, **r**, respectively (Chart 8).

Finally, 4-(2-pyridyl)-2*H*-1,3-benzoxazines **8** were oxidized with *m*CPBA at −20 °C to afford 2-(2,2-dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-oxides **7**, the target compounds, in moderate yields (Chart 9, Table 3). The di-*N*-oxide **24** was isolated as a by-product in the oxidation of **8b**. Deprotection of the 6-trimethylsilylethynyl derivative **7t** with K_2CO_3 gave the 6-ethynyl derivative **7h** (Chart 9).

Results and Discussion

The compounds were initially evaluated for vasorelaxant activity on 30 mM tetraethylammonium chloride (TEA) and 0.3 mM $BaCl_2$-induced contraction of rat aorta. Next, similar experiments using 80 mM KCl instead of

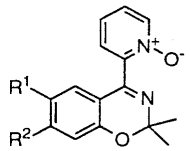
Table 2. 2,2-Dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazines **8**



Compd.	R^1	R^2	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$)
8a	Cl	H	47	87—87.5	$C_{15}H_{13}ClN_2O$	66.06 (66.27	4.80 4.83	10.27 10.21)	1.67 (6H, s), 6.83 (1H, d, J=8.6 Hz), 7.31 (1H, dd, J=8.6, 2.6 Hz), 7.38—7.44 (1H, m), 7.72 (1H, d, J=2.4 Hz), 7.76—7.90 (2H, m), 8.71 (1H, dt, J=4.6, 1.4 Hz)
8b	Br	H	31, 52[b]	94—95	$C_{15}H_{13}BrN_2O$	56.48 (56.28	4.17 4.26	8.78 8.54)	1.67 (6H, s), 6.78 (1H, d, J=8.6 Hz), 7.35—7.50 (2H, m), 7.75—7.90 (3H, m), 8.72 (1H, dt, J=5.0, 1.4 Hz)
8c	CF_3	H	42, 62[c]	59—59.5	$C_{16}H_{13}F_3N_2O$	62.74 (62.68	4.28 4.04	9.15 9.12)	1.70 (6H, s), 6.96 (1H, d, J=8.8 Hz), 7.38—7.48 (1H, m), 7.57—7.63 (1H, m), 7.83—7.91 (2H, m), 8.05 (1H, d, J=1.6 Hz), 8.69—8.73 (1H, m)
8d	C_2F_5	H	64	Oil	$C_{17}H_{13}F_5N_2O$				1.71 (6H, s), 6.98 (1H, d, J=8.8 Hz), 7.34—7.47 (1H, m), 7.55—7.60 (1H, m), 7.83—7.87 (2H, m), 8.05 (1H, d, J=2.2 Hz), 8.69—8.73 (1H, m)
8e	CF_3O	H	84, 49[b]	Oil	$C_{16}H_{13}F_3N_2O_2$				1.68 (6H, s), 6.88 (1H, d, J=8.8 Hz), 7.19—7.26 (1H, m), 7.34—7.46 (1H, m), 7.69 (1H, d, J=2.8 Hz), 7.82—7.85 (2H, m), 8.68—8.72 (1H, m)
8f[d]	CN	H	27	142—144	$C_{16}H_{13}N_3O \cdot 0.25H_2O$	71.76 (71.69	5.08 4.77	15.69 15.46)	1.71 (6H, s), 6.94 (1H, d, J=8.4 Hz), 7.41—7.48 (1H, m), 7.62 (1H, dd, J=8.8, 4.0 Hz), 7.85—7.88 (2H, m), 8.25 (1H, d, J=2.2 Hz), 8.70—8.74 (1H, m)
8g	CH_3CO	H	33	97—98	$C_{17}H_{16}N_2O_2$	72.84 (72.59	5.75 5.79	9.99 9.78)	1.71 (6H, s), 2.52 (3H, s), 6.93 (1H, d, J=8.4 Hz), 7.39—7.46 (1H, m), 7.80—7.94 (2H, m), 8.01 (1H, dd, J=8.4, 2.2 Hz), 8.37 (1H, d, J=2.2 Hz), 8.73 (1H, dt, J=4.8, 1.2 Hz)
8i	NO_2	H	98[e]	105—108	$C_{15}H_{13}N_3O_3$	63.60 (63.52	4.63 4.71	14.83 14.55)	1.73 (6H, s), 6.97 (1H, d, J=9.0 Hz), 7.42—7.49 (1H, m), 7.81—7.92 (2H, m), 8.26 (1H, dd, J=9.0, 2.8 Hz), 8.72—8.75 (1H, m), 8.83 (1H, d, J=2.8 Hz)
8j	Cl	Cl	68	104—105	$C_{15}H_{12}Cl_2N_2O$	58.65 (58.38	3.94 3.74	9.12 9.14)	1.69 (6H, s), 7.01 (1H, s), 7.35—7.47 (1H, m), 7.82—7.86 (2H, m), 7.94 (1H, s), 8.68—8.72 (1H, m)
8k	Br	F	45	119—121	$C_{15}H_{12}BrFN_2O$	53.75 (53.56	3.61 3.35	8.36 8.27)	1.67 (6H, s), 6.68 (1H, d, J=9.2 Hz), 7.37—7.45 (1H, m), 7.79—7.90 (2H, m), 8.03 (1H, d, J=8.0 Hz), 8.68—8.73 (1H, m)
8l	Br	Cl	49, 50[b]	100—103	$C_{15}H_{12}BrClN_2O$	51.24 (51.06	3.44 3.60	7.97 8.09)	1.67 (6H, s), 7.02 (1H, s), 7.37—7.45 (1H, m), 7.80—7.87 (2H, m), 8.07 (1H, s), 8.68—8.73 (1H, m)
8m	Br	Br	54	99—101	$C_{15}H_{12}Br_2N_2O$	45.49 (45.23	3.05 3.09	7.07 6.95)	1.67 (6H, s), 7.20 (1H, s), 7.37—7.47 (1H, m), 7.80—7.88 (2H, m), 8.07 (1H, s), 8.68—8.74 (1H, m)
8n	NO_2	CH_3	64[e]	139—143	$C_{16}H_{15}N_3O_3$	64.64 (64.26	5.09 5.09	14.13 13.96)	1.71 (6H, s), 2.64 (3H, s), 7.44 (1H, ddd, J=6.2, 4.8, 2.8 Hz), 7.80—7.93 (2H, m), 8.69 (1H, s), 8.70—8.75 (1H, m)
8o	Br	CH_3	72[e]	119—124	$C_{16}H_{15}BrN_2O$	56.49 (56.61	4.74 4.42	8.23 8.21)	1.66 (6H, s), 2.37 (3H, s), 6.79 (1H, s), 7.39 (1H, ddd, J=6.6, 4.8, 2.2 Hz), 7.76—7.89 (3H, m), 8.68—8.74 (1H, m)
8p	CH_3OCO	H	52	104—106	$C_{17}H_{16}N_2O_3$	68.91 (68.67	5.44 5.52	9.45 9.24)	1.70 (6H, s), 3.86 (3H, s), 6.92 (1H, d, J=8.4 Hz), 7.39—7.45 (1H, m), 7.76—7.90 (2H, m), 8.06 (1H, dd, J=8.4, 2.0 Hz), 8.34 (1H, d, J=2.0 Hz), 8.71—8.76 (1H, m)
8q	PhCO	H	51	176—179	$C_{22}H_{18}N_2O_2$	77.17 (77.35	5.30 5.31	8.18 8.20)	1.72 (6H, s), 6.96 (1H, d, J=8.6 Hz), 7.33—7.63 (4H, m), 7.78—7.86 (4H, m), 7.89 (1H, dd, J=8.6, 2.0 Hz), 8.26 (1H, d, J=2.0 Hz), 8.62—8.67 (1H, m)
8r	NO_2	C_2H_5O	32[e]	134—139	$C_{17}H_{17}N_3O_4$	61.63 (61.74	5.32 5.21	12.66 12.64)	1.51 (3H, t, J=7.0 Hz), 1.70 (6H, s), 4.20 (2H, q, J=7.0 Hz), 6.49 (1H, s), 7.38—7.47 (1H, m), 7.79—7.90 (2H, m), 8.62 (1H, s), 8.68—8.75 (1H, m)
8s	CH_3	H	49	71—73	$C_{16}H_{16}N_2O \cdot 0.4H_2O$	74.05 (74.10	6.56 6.36	10.72 10.76)	1.67 (6H, s), 2.25 (3H, s), 6.79 (1H, d, J=8.0 Hz), 7.14—7.20 (1H, m), 7.31—7.42 (2H, m), 7.72—7.87 (2H, m), 8.70—8.74 (1H, m)
8t	$TMSC{\equiv}C$	H	37	88.5—89.5	$C_{20}H_{22}N_2OSi \cdot 0.5H_2O$	69.93 (69.81	6.75 6.47	8.16 7.81)	0.21 (9H, s), 1.67 (6H, s), 6.82 (1H, d, J=8.6 Hz), 7.25—7.50 (2H, m), 7.70—7.90 (3H, m), 8.73—8.76 (1H, m)
8u	H	H	39	78—80	$C_{15}H_{14}N_2O$	75.61 (75.26	5.92 5.64	11.76 11.94)	1.69 (6H, s), 6.87—6.95 (2H, m), 7.32—7.42 (2H, m), 7.57 (1H, dd, J=7.6, 1.8 Hz), 7.75—7.87 (2H, m), 8.69—8.72 (1H, m)
8v	H	CH_3	66	64—66	$C_{16}H_{16}N_2O$	76.16 (76.32	6.39 6.16	11.10 11.25)	1.67 (6H, s), 2.33 (3H, s), 6.71 (1H, br s), 6.72 (1H, d, J=8.4 Hz), 7.33—7.39 (1H, m), 7.42 (1H, d, J=8.4 Hz), 7.71—7.87 (2H, m), 8.68—8.72 (1H, m)
8w	H	C_2H_5O	61	Oil	$C_{17}H_{18}N_2O_2$				1.42 (3H, t, J=7.0 Hz), 1.68 (6H, s), 4.05 (2H, q, J=7.0 Hz), 6.39—6.49 (2H, m), 7.32—7.42 (1H, m), 7.51 (1H, d, J=8.4 Hz), 7.72—7.87 (2H, m), 8.67—8.73 (1H, m)

a) From the corresponding 1,3-benzoxazin-4-ones **10**, unless otherwise indicated. *b*) From the corresponding 2-hydroxyphenyl 2-pyridyl ketones **22**. *c*) From **20**. *d*) IR (KBr) cm^{-1}: 2230. *e*) From the corresponding 4-(2-pyridyl)-2*H*-1,3-benzoxazines **8**.

Table 3. 2-(2,2-Dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-Oxides **7**



Compd.	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$)
7a	Cl	H	22	157.5—158.5	$C_{15}H_{13}ClN_2O_2$	62.40 (62.13)	4.54 4.56	9.70 9.48)	1.70 (6H, s), 6.81 (1H, d, J=8.6 Hz), 6.92 (1H, d, J=2.4 Hz), 7.20—7.50 (4H, m), 8.29 (1H, dd, J=5.0, 2.2 Hz)
7b	Br	H	19	152—153	$C_{15}H_{13}BrN_2O_2$	54.07 (53.85	3.93 3.89	8.41 8.37)	1.70 (6H, s), 6.77 (1H, d, J=8.8 Hz), 7.05 (1H, d, J=2.4 Hz), 7.36—7.46 (4H, m), 8.27—8.31 (1H, m)
7c	CF_3	H	11	91.5—92.5	$C_{16}H_{13}F_3N_2O_2 \cdot 0.5H_2O$	58.01 (58.25	4.26 3.96	8.46 8.33)	1.72 (6H, s), 6.94 (1H, d, J=8.4 Hz), 7.17 (1H, d, J=2.2 Hz), 7.32—7.48 (3H, m), 7.54—7.60 (1H, m), 8.27—8.31 (1H, m)
7d	C_2F_5	H	29	135—137	$C_{17}H_{13}F_5N_2O_2 \cdot 0.2H_2O$	54.32 (54.24	3.59 3.41	7.45 7.44)	1.73 (6H, s), 6.96 (1H, d, J=8.4 Hz), 7.13 (1H, d, J=2.2 Hz), 7.32—7.48 (3H, m), 7.53 (1H, dd, J=8.4, 2.2 Hz), 8.27—8.30 (1H, m)
7e	CF_3O	H	22	105—107	$C_{16}H_{13}F_3N_2O_3$	56.81 (56.55	3.87 3.72	8.28 8.34)	1.71 (6H, s), 6.81 (1H, d, J=2.6 Hz), 6.87 (1H, d, J=8.8 Hz), 7.17—7.23 (1H, m), 7.30—7.48 (3H, m), 8.26—8.30 (1H, m)
7f[a]	CN	H	35	153—154	$C_{16}H_{13}N_3O_2 \cdot 0.25H_2O$	67.97 (67.72	4.59 4.79	14.69 14.81)	1.73 (6H, s), 6.93 (1H, d, J=8.6 Hz), 7.25—7.27 (1H, m), 7.38—7.50 (3H, m), 7.58 (1H, dd, J=8.6, 2.0 Hz), 8.29—8.32 (1H, m)
7g	CH_3CO	H	17	117.5—118.5	$C_{17}H_{16}N_2O_3$	68.91 (68.61	5.44 5.58	9.45 9.30)	1.73 (6H, s), 6.93 (1H, d, J=8.6 Hz), 7.25—7.27 (1H, m), 7.38—7.50 (3H, m), 7.58 (1H, dd, J=8.6, 2.0 Hz), 8.29—8.32 (1H, m)
7h	HC≡C	H	81[b]	162—163	$C_{17}H_{14}N_2O_2 \cdot 0.2H_2O$	72.42 (72.70	5.15 5.12	9.94 9.70)	1.71 (6H, s), 2.93 (1H, s), 6.82 (1H, d, J=8.4 Hz), 7.07 (1H, d, J=2.0 Hz), 7.35—7.50 (4H, m), 8.27—8.31 (1H, m)
7i	NO_2	H	31	220—221 (dec.)	$C_{15}H_{13}N_3O_4$	60.20 (60.00	4.38 4.53	14.04 13.75)	1.75 (6H, s), 6.95 (1H, d, J=9.0 Hz), 7.36—7.52 (3H, m), 7.83 (1H, d, J=2.8 Hz), 8.20—8.33 (2H, m)
7j	Cl	Cl	32	156—157	$C_{15}H_{12}Cl_2N_2O_2$	55.75 (55.49	3.74 3.72	8.67 8.56)	1.69 (6H, s), 6.99 (1H, s), 7.02 (1H, s), 7.35—7.47 (3H, m), 8.25—8.30 (1H, m)
7k	Br	F	29	186—187	$C_{15}H_{12}BrFN_2O_2$	51.30 (51.17	3.44 3.27	7.98 7.87)	1.70 (6H, s), 6.67 (1H, d, J=9.2 Hz), 7.14 (1H, d, J=7.4 Hz), 7.36—7.47 (3H, m), 8.26—8.31 (1H, m)
7l	Br	Cl	30	184—186	$C_{15}H_{12}BrClN_2O_2$	49.01 (48.98	3.29 3.28	7.62 7.51)	1.69 (6H, s), 7.01 (1H, s), 7.16 (1H, s), 7.32—7.48 (3H, m), 8.25—8.31 (1H, m)
7m	Br	Br	16	199—202	$C_{15}H_{12}Br_2N_2O_2$	43.72 (43.88	2.94 3.31	6.80 6.42)	1.69 (6H, s), 7.16 (1H, s), 7.19 (1H, s), 7.32—7.48 (3H, m), 8.25—8.32 (1H, m)
7n	NO_2	CH_3	24	198—202	$C_{16}H_{15}N_3O_4$	61.34 (61.24	4.83 4.45	13.41 13.10)	1.73 (6H, s), 2.62 (3H, s), 6.78 (1H, s), 7.34—7.52 (3H, m), 7.71 (1H, s), 8.26—8.32 (1H, s)
7o	Br	CH_3	11	224—232	$C_{16}H_{15}BrN_2O_2 \cdot 0.25H_2O$	54.64 (54.54	4.44 4.24	7.96 7.80)	1.68 (6H, s), 2.34 (3H, s), 6.77 (1H, s), 7.06 (1H, s), 7.30—7.48 (3H, m), 8.24—8.32 (1H, m)
7p	CH_3OCO	H	41	139—144	$C_{17}H_{16}N_2O_4 \cdot 0.25H_2O$	64.45 (64.18	5.25 5.06	8.84 8.52)	1.72 (6H, s), 3.81 (3H, s), 6.90 (1H, d, J=8.4 Hz), 7.36—7.52 (3H, m), 7.59 (1H, d, J=2.0 Hz), 8.02 (1H, dd, J=8.4, 2.0 Hz), 8.27—8.34 (1H, m)
7q	PhCO	H	31	158—162	$C_{22}H_{18}N_2O_3$	73.73 (73.62	5.06 4.91	7.82 7.92)	1.75 (6H, s), 6.93 (1H, d, J=8.6 Hz), 7.32—7.60 (7H, m), 7.73—7.87 (3H, m), 8.21—8.27 (1H, m)
7r	NO_2	C_2H_5O	15	129—134	$C_{17}H_{17}N_3O_5$	59.47 (59.12	4.99 4.84	12.24 12.02)	1.50 (3H, t, J=7.0 Hz), 1.73 (6H, s), 4.19 (2H, q, J=7.0 Hz), 6.47 (1H, s), 7.33—7.50 (3H, m), 7.63 (1H, s), 8.26—8.32 (1H, m)
7s	CH_3	H	7	188—190	$C_{16}H_{16}N_2O_2$	71.62 (71.21	6.01 6.06	10.44 10.32)	1.69 (6H, s), 2.19 (3H, s), 6.72—6.78 (2H, m), 7.12—7.17 (1H, m), 7.34—7.43 (3H, m), 8.27—8.31 (1H, m)
7t	TMSC≡C	H	10	91—92	$C_{20}H_{22}N_2O_2Si \cdot 1.2H_2O$	64.56 (64.35	6.61 6.31	7.52 7.30)	0.19 (9H, s), 1.70 (6H, s), 6.80 (1H, d, J=8.4 Hz), 7.04 (1H, d, J=2.0 Hz), 7.30—7.80 (4H, m), 8.28—8.32 (1H, m)

a) IR (KBr) cm^{-1}: 2230. *b*) From **7t**.

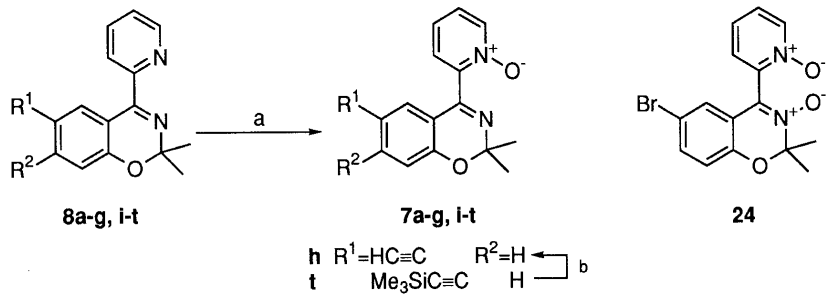


Chart 9

30 mM TEA and 0.3 mM $BaCl_2$ were performed to identify potential K^+ channel openers. Cromakalim **1** and pinacidil **3** relaxed TEA and $BaCl_2$-induced contraction with EC_{50} values of 1.8 and 5.2 μM, respectively. However, these K^+ channel openers did not relax rat aorta precontracted with 80 mM KCl at the approximate EC_{50} concentrations for TEA and $BaCl_2$-induced contraction. Ca^{2+} channel blockers such as nifedipine and diltiazem relaxed both TEA and $BaCl_2$- and 80 mM KCl-induced contraction. Thus, we defined the "K ratio" as the ratio of vasorelaxation for 80 mM KCl-induced contraction to that for TEA and $BaCl_2$-induced contraction to distinguish K^+ channel openers from other vasorelaxant agents. The K ratio of K^+ channel openers ought to be nearly 0, while those of other compounds should be larger. In fact, the K^+ channel openers **1** and **3** showed K ratios of 0.16 and 0.08, and nifedipine and diltiazem showed values of 0.99 and 0.72, respectively. Therefore, we tentatively considered a compound with a value of the K ratio below 0.5 as a K^+ channel opener. Further detailed studies of the screening system for K^+ channel openers will be reported elsewhere.

The vasorelaxant activities of the compounds synthesized are summarized in Table 4 as EC_{50} values and K ratio values. The 6-substituted derivatives **7a—i** showed potent vasorelaxant activity. The compounds whose K ratios were below 0.10 at concentrations near EC_{50} were considered to be K^+ channel openers. The 6-bromo (**7b**, $EC_{50}=1.7$ μM), trifluoromethyl (**7c**, $EC_{50}=1.3$ μM), trifluoromethoxy (**7e**, $EC_{50}=1.0$ μM), and nitro derivatives (**7i**, $EC_{50}=0.33$ μM) showed highly potent activity, and were more potent than **1**. On the other hand, compound **7f** with a 6-cyano group exhibited 2.5 times less potent activity ($EC_{50}=4.5$ μM) in comparison with the corresponding benzopyran derivative **1**. Introduction of an electron-donating group such as a methyl group at C6 (**7s**) resulted in a decrease of activity ($EC_{50}>10$ μM). These results indicated that an electron-withdrawing group at C6 was necessary for good vasorelaxant activity in the 1,3-benzoxazine series as well as the benzopyran series. They also indicated that 1,3-benzoxazine derivatives did not always need a strong electron-withdrawing group at C6 for the development of optimal activity, whereas benzopyran derivatives did: suitable groups in highly potent 1,3-benzoxazine derivatives were bromo, trifluoromethyl, and trifluoromethoxy, which have weaker electron-withdrawing activity than a cyano group. In addition, compound **7q** with the strongly electron-withdrawing benzoyl group showed decreased activity ($EC_{50}>10$ μM), whereas compound **7h** with the weakly electron-withdrawing ethynyl group showed vasorelaxant activity ($EC_{50}=10$ μM). A benzoyl group is bulkier than the electron-withdrawing groups described above, while an ethynyl group is compact, and the shapes of ethynyl and cyano groups are similar. Furthermore, 6-trifluoromethyl and trifluoromethoxy compounds (**7c** and **7e**) were about 3-fold more active than the 6-pentafluoroethyl compound **7d** ($EC_{50}=3.3$ μM). From these results, an electron-withdrawing group with a proper size or shape at C6 is required for optimal vasorelaxant activity among 1,3-benzoxazine derivatives.

It is noteworthy that introduction of an appropriate group at C7 in addition to the C6 electron-withdrawing group enhanced the activity. 6-Bromo-7-halogeno, *i.e.* 7-fluoro (**7k**, $EC_{50}=0.80$ μM), 7-chloro (**7l**, $EC_{50}=0.14$

Table 4. Vasorelaxant Activities and Hypotensive Effects of **7**

Compd.	Relaxation of rat aorta EC_{50}[a] (μM)	K ratio[b]	Max fall in BP[c] (%)
7a	2.3	0	38
7b	1.7	0.01	32
7c	1.3	0.02	46
7d	3.3	0.10	25
7e	1.0	0	47
7f	4.5	0	39
7g	9.7	0	22
7h	10	0	58[d]
7i	0.33	0	61
7j	2.4	0.05	36
7k	0.80	0	55
7l	0.14	0.07	41
7m	0.96	0.08	22
7n	1.6	0	56[d]
7o	0.65	0	26[d]
7p	>10	NT[e]	NT
7q	>10	NT	NT
7r	>10	NT	NT
7s	>10	NT	NT
24	>10	NT	NT
Cromakalim	1.8	0.16	45

a) Drug concentration required to relax the 30 mM TEA and 0.3 mM $BaCl_2$-induced contraction in rat aorta by 50%. *b*) Ratio of vasorelaxation for 80 mM KCl-induced contraction to that for TEA and $BaCl_2$-induced contraction. *c*) Hypotensive effects in conscious SHRs (male) by oral administration (1.0 mg/kg). Systolic blood pressure was measured for 24 h after administration and the values are expressed as means of maximum percentage fall in BP ($n=2$—4 for **7a—k** and **m—o**, $n=9$ for **7l**, and $n=8$ for cromakalim). *d*) Dose of compound: 10 mg/kg. *e*) Not tested.

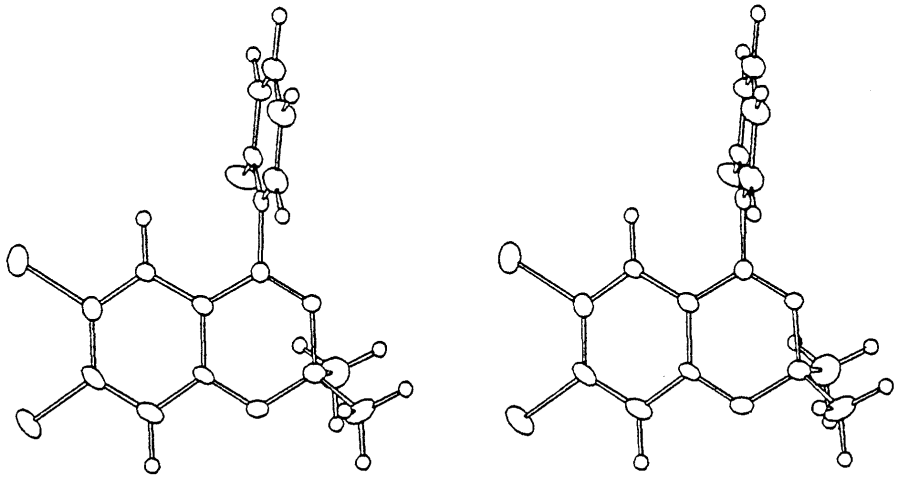


Fig. 1. Stereoview of **7l**

μM), and 7-bromo (**7m**, $EC_{50}=0.96\,\mu$M) derivatives were more active than the corresponding 6-bromo derivative **7b**. Halogen substituents at C7 increased potency in the order of bromo, fluoro, and chloro. Interestingly, the 6-bromo-7-methyl derivative **7o** ($EC_{50}=0.65\,\mu$M) was more potent than the 6-bromo derivative **7b**. However, the 6-nitro-7-ethoxy derivative **7r** ($EC_{50}>10\,\mu$M) showed significantly reduced activity compared with the highly active 6-nitro derivative **7i**. Among these 6,7-disubstituted benzoxazines, the 6-bromo-7-chloro derivative **7l** showed the most potent vasorelaxant activity. These results suggested that an important factor for optimal vasorelaxant activity was a proper size or lipophilicity, rather than the electron-withdrawing nature of the 7-substituent.

The X-ray crystal structure of **7l** is shown in Fig. 1. As expected, the pyridine *N*-oxide ring was orthogonal to the plane of 2*H*-1,3-benzoxazine nucleus. This result suggested that the structural requirements of benzopyran K^+ channel openers for biological activity[16] could also apply to our 1,3-benzoxazine derivatives.

Oxidation of the nitrogen in the benzoxazine nucleus might change the conformation, which included an orthogonal relationship of the pyridine *N*-oxide ring with the benzoxazine ring. The di-*N*-oxide **24** was less active ($EC_{50}>10\,\mu$M).

Compounds **7** were also examined for oral hypotensive effects in conscious spontaneously hypertensive rats (SHRs). The results are listed in Table 4 as means of maximum percentage fall in blood pressure. The hypotensive potencies of benzoxazine compounds which exhibited more potent vasorelaxant activity than **1** were comparable to that of **1**. On the other hand, the profiles of benzoxazine compounds, especially 6,7-dihalogenated derivatives, were better than **1**. To give a typical example, the time courses of changes in blood pressure and heart rate after oral administration of **7l** are shown in Fig. 2, along with those of **1** for comparison.[17] Cromakalim (**1**) evoked a rapid decrease in blood pressure and subsequent significant reflex tachycardia soon after oral administration, while compound **7l** reduced blood pressure with slow onset of action, and evoked less reflex tachycardia. In addition, the hypotensive effects induced by **7l** lasted much longer than those of **1**.

Table 5. Summary of Crystal Data and Intensity Data Collection for **7l**

Formula	$C_{15}H_{12}BrClN_2O_2$
Formula weight	367.63
Crystal color, habit	Colorless, prism
Approx. crystal dimensions (mm)	$0.9\times0.3\times0.2$
Crystal system	Orthorhombic
Space group	P_{bca}
a (Å)	10.942 (3)
b (Å)	33.130 (4)
c (Å)	8.262 (3)
V (Å^3)	2995 (1)
Z	8
Calculated density (g/cm^3)	1.631
Absorption coef. (cm^{-1})	58.11
Temperature (°C)	22
Radiation	Cu-K_α (1.5418 Å)
2θ range of reflections for cell determination (°)	41—50
Scan mode	2θ–ω
Scan speed (°/min)	32
2θ range of data collection (°)	3—120
Number of unique reflections	2617
Number of reflections used for refinement ($F\geq3\sigma F$)	2130
R,[a] R_w[b]	0.063, 0.070

a) $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. b) $R_w=[\Sigma w||F_o|-|F_c||^2/w\Sigma|F_o|^2]^{1/2}$ where $w=1.0$.

In summary, the search for new K^+ channel openers with [6,6]-fused rings other than benzopyran has led to new 1,3-benzoxazine derivatives synthesized by using a new and convenient one-pot 1,3-benzoxazine skeleton formation reaction, as well as a palladium(0)-catalyzed cross-coupling reaction. The results of SAR study of the 1,3-benzoxazine derivatives **7** suggested that an electron-withdrawing group at C6 with a proper size or shape is essential for the optimal vasorelaxant activity, and that introduction of a halogen or methyl group at the 7-position increases the activity. 2-(6-Bromo-7-chloro-2,2-dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-oxide (**7l**) showed the most potent vasorelaxant activity, and induced a long-lasting hypotensive effect superior to that of cromakalim.

Experimental

All melting points were determined on a Yanagimoto micro melting

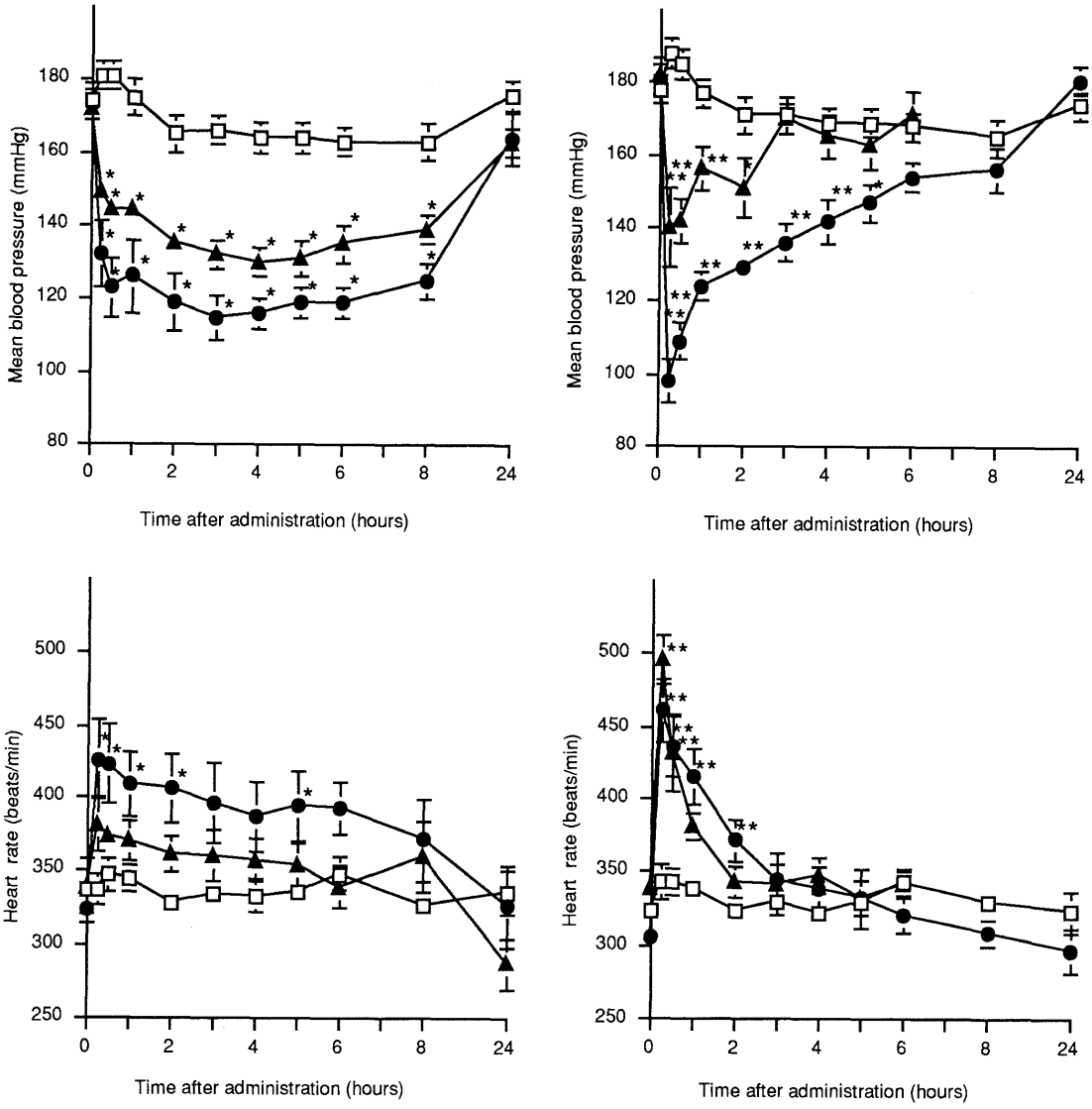


Fig. 2. Effects of Oral Administration of **7l** (Left) and **1** (Right) on Mean Blood Pressure (Top) and Heart Rate (Bottom) in Conscious SHRs, $n=7$—9

—□—, vehicle; —▲—, 0.3 mg/kg, *p.o.*; —●—, 1.0 mg/kg, *p.o.* $*p<0.05$ and $**p<0.01$, significantly different from the vehicle group (Dunnett's test).

point apparatus, and are uncorrected. The IR spectra were recorded on a Hitachi 215 grating infrared spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard, and coupling constants (J) are given in hertz. High-resolution MS were measured on a JEOL JMS-AX505W mass spectrometer. Column chromatography was performed using silica gel (Wakogel C-300 or Merck Kieselgel 60, 70—230 mesh). When necessary, both tetrahydrofuran (THF) and 1,4-dioxane were distilled from sodium metal/benzophenone ketyl. Solutions in organic solvents were dried over anhydrous $MgSO_4$.

5-Trifluoromethylsalicylic Acid (12c) A mixture of methyl 5-iodo-2-methoxybenzoate (**11x**, 36.0 g, 0.123 mol), sodium trifluoroacetate (67.1 g, 0.494 mol), cuprous iodide (75.0 g, 0.394 mol), *N*,*N*-dimethylformamide (DMF, 300 ml), and toluene (100 ml) was stirred under an argon atmosphere at 140 °C for 1.5 h and then at 160 °C for 5 h. After cooling, the precipitate was filtered off, and the filtrate was evaporated *in vacuo*. The residue was partitioned between EtOAc and water. The resulting precipitate was filtered off through a pad of Celite, and the organic layer was washed with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc) to give methyl 5-trifluoromethyl-2-methoxybenzoate (**11c**, 24.4 g) as an oil.

Compound **11c** (24.4 g) was dissolved in CH_2Cl_2 (300 ml), then a solution of boron tribromide (92.6 g, 0.370 mol) in CH_2Cl_2 (50 ml) was added dropwise at −78 °C for 30 min. The mixture was warmed to room temperature, stirred for 2 h, then poured into ice-cooled water, and the organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was washed successively with cyclohexane and hexane to give **12c** (4.90 g, 19%), mp 138—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.90—4.70 (1H, br s), 7.13 (1H, d, $J=8.6$ Hz), 7.76 (1H, dd, $J=8.6$, 2.2 Hz), 8.22 (1H, br s), 10.75 (1H, br s).

Compound **12d** was obtained in 24% yield by a similar method to that used for **12c**, mp 119.5—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.00—4.40 (1H, br s), 7.14 (1H, d, $J=8.8$ Hz), 7.72 (1H, br dd, $J=8.6$, 2.2 Hz), 8.18 (1H, br d, $J=2.2$ Hz), 10.77 (1H, s).

4,5-Dichlorosalicylic Acid (12j) A mixture of 3,4-dichlorophenol (**13j**, 5.00 g, 30.7 mmol), K_2CO_3 (10.6 g, 76.7 mmol), and dry ice (12.0 g, 273 mmol) was heated in a sealed tube at 190 °C for 4 h. Water was added and the whole was washed with Et_2O. The aqueous layer was acidified with saturated $KHSO_4$, and extracted with EtOAc. The extract was dried and evaporated *in vacuo*. The residue was recrystallized from EtOH to give **12j** (3.90 g, 61%), mp 177—180 °C (sublime). ^{1}H-NMR (DMSO-d_6) δ: 7.28 (1H, s), 7.89 (1H, s).

Compound **12e** was obtained in 83% yield by a similar method to that used for **12j**, mp 128—129 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.08 (1H, d, $J=9.0$ Hz), 7.54 (1H, dd, $J=9.0$, 2.8 Hz), 7.68 (1H, d, $J=2.8$ Hz).

5-Bromo-4-chlorosalicylic Acid (12l) A solution of bromine (55.7 g, 0.348 mol) in MeOH (560 ml) was added dropwise to a solution of 4-chlorosalicylic acid (**12z**, 60.0 g, 0.348 mol) and sodium acetate (120 g, 1.46 mol) in MeOH (2.1 l) at −70 °C for 1.5 h, and the mixture was warmed to room temperature. After evaporation of the solvent *in vacuo*,

water (2 l) was added to the residue, and the mixture was acidified with HCl. The resulting precipitate was collected by filtration, washed successively with water and EtOAc, and dried over P_2O_5 under reduced pressure to give **12l** (34.1 g, 39%), mp 208—213 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.30 (1H, s), 8.02 (1H, s).

Compounds **12k** and **12m** were obtained by a similar method to that used for **12l**, in 50% and 59% yields, respectively. **12k**: mp 203—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.05 (1H, d, J=10.4 Hz), 8.01 (1H, d, J=8.4 Hz). **12m**: mp 227—232 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.42 (1H, s), 7.99 (1H, s).

5-Methoxycarbonylsalicylamide (15p) Dimethyl sulfide (38 ml, 522 mmol) was added to a mixture of dimethyl 4-hydroxyisophthalate (**14p**, 6.05 g, 28.8 mmol), $AlCl_3$ (15.4 g, 11.5 mmol), and CH_2Cl_2 (180 ml) at −30 °C. The mixture was warmed to room temperature, stirred for 2 h, then poured into ice-cooled water and extracted with EtOAc. The extract was dried and evaporated *in vacuo*. The residue was washed with CH_2Cl_2 to give crude methyl 4-carboxysalicylate (3.46 g) as a solid.

The crude salicylate (3.46 g) was added to a 30% NH_4OH solution at room temperature, and the mixture was stirred for 24 h. After evaporation of the solvent *in vacuo*, the residue was acidified with 1 N HCl, and extracted with EtOAc. The extract was dried and evaporated *in vacuo*. The residue was washed with isopropyl ether to give crude 4-carboxysalicylamide (1.40 g) as a solid.

A mixture of the crude salicylamide (1.40 g), H_2SO_4 (0.3 ml), and MeOH (100 ml) was refluxed for 16 h, then concentrated *in vacuo*, and the residue was extracted with EtOAc. The extract was washed with H_2O (500 ml), dried, and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2–MeOH) to give **15p** (1.00 g, 17.8%), mp 230 °C (sublime). ^{1}H-NMR (DMSO-d_6) δ: 3.84 (3H, s), 6.99 (1H, d, J=8.8 Hz), 7.98 (1H, dd, J=8.8, 2.0 Hz), 7.97—8.10 (1H, br s), 8.55 (1H, d, J=2.0 Hz), 8.60—8.72 (1H, br s).

5-Benzoylsalicylamide (15q) $AlCl_3$ (34.7 g, 260 mmol) was added to a mixture of salicylamide **15u** (13.7 g, 100 mmol), benzoyl chloride (28.1 g, 200 mmol), and nitrobenzene (140 ml) at −40 °C. The reaction mixture was warmed to room temperature, stirred for 14 h, then poured into ice-cooled water and extracted with EtOAc. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was crystallized from isopropyl ether to give **15q** (15.8 g, 66%), mp 220—222 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.03 (1H, d, J=8.6 Hz), 7.51—7.83 (6H, m), 7.97—8.08 (1H, br s), 8.39 (1H, d, J=2.0 Hz), 8.56—8.66 (1H, br s).

6-Bromo-2,2-dimethyl-2*H*-1,3-benzoxazin-4-one (10b) A mixture of 5-bromosalicylic acid (**12b**, 50.0 g, 0.230 mol) and acetic anhydride (100 ml) was refluxed for 30 min. After cooling, the solvent was removed under reduced pressure. The residue was taken up in water (100 ml), and the mixture was stirred at room temperature for 30 min, then extracted with EtOAc. The extract was washed with brine, dried, and evaporated *in vacuo* to give crude 2-acetoxy-5-bromobenzoic acid as an oil.

A mixture of the crude benzoic acid, DMF (0.50 ml, 6.46 mmol), and THF (200 ml) was treated dropwise with oxalyl chloride (50.0 ml, 0.576 mol) at room temperature for 30 min, and the mixture was stirred for 1 h. The solvent was evaporated *in vacuo* to give crude 2-acetoxy-5-bromobenzoyl chloride as an oil.

A mixture of the crude benzoyl chloride and THF (100 ml) was added dropwise to ice-cooled concentrated NH_4OH (100 ml) over 15 min, and the whole was stirred at room temperature for 2 h. The solvent was evaporated *in vacuo*, and the residue was diluted with water (300 ml) and adjusted to pH 2 with 6 N HCl. The precipitate was collected by filtration, washed with ice-cooled water (150 ml × 2), and dried over P_2O_5 at 60 °C for 8 h under reduced pressure to give 5-bromosalicylamide (**15b**, 53.6 g) as a solid.

A mixture of **15b** (53.6 g), acetone (300 ml), 2,2-dimethoxypropane (100 ml), and *p*-toluenesulfonic acid monohydrate (5.00 g, 26.3 mmol) was refluxed for 24 h. The solvent was evaporated *in vacuo*, and the residue was diluted with EtOAc (600 ml). The EtOAc was washed in turn with 10% aqueous Na_2CO_3 (100 ml × 2) and brine, dried, and evaporated *in vacuo*. The residue was crystallized from a mixture of isopropyl ether (100 ml) and hexane (100 ml) to give 6-bromo-2,2-dimethyl-2*H*-1,3-benzoxazin-4-one (**10b**, 30.5 g, 52%).

Compounds **10a**, **c**—**e**, **g**, **j**—**m**, **p**, **q**, **s**, **u**, and **v**—**x** were obtained by a similar method to that used for **10b** (**10g**, **p**, **q**, and **u** were prepared from the corresponding salicylamides **15g**, **p**, **q**, and **u**, respectively). The yields, melting points, and ^{1}H-NMR data of these compounds are listed in Table 1.

6-Cyano-2,2-dimethyl-2*H*-1,3-benzoxazin-4-one (10f) A mixture of **10b** (1.00 g, 3.90 mmol), cuprous cyanide (0.42 g, 4.69 mmol), and DMF (5.0 ml) was refluxed under an argon atmosphere for 4 h. The reaction mixture was poured into a solution of ferric chloride hexahydrate (4.00 g, 14.8 mmol) and concentrated HCl (1.0 ml) in water (12 ml), and stirred at room temperature for 30 min followed by extraction with EtOAc (60 ml). The extract was washed successively with diluted HCl, saturated $NaHCO_3$, and brine, dried, and evaporated *in vacuo*. The residue was washed with isopropyl ether to give **10f** (0.45 g, 57%). The melting point and ^{1}H-NMR data of this compound are listed in Table 1.

2,2-Dimethyl-6-trimethylsilylethynyl-2*H*-1,3-benzoxazin-4-one (10t) A mixture of **10x** (7.00 g, 23.1 mmol), trimethylsilylacetylene (11.1 g, 113 mmol), palladium(II) acetate (490 mg, 2.18 mmol), triphenylphosphine (1.20 g, 4.57 mmol), and triethylamine (70 ml) was stirred at 60 °C for 2 h under an argon atmosphere. After cooling, the precipitate was filtered off, and the filtrate was evaporated *in vacuo*. The residue was diluted with EtOAc, washed successively with saturated $NaHCO_3$ and brine, and dried. After evaporation of the solvent *in vacuo*, the residue was crystallized from EtOAc to give **10t** (3.40 g, 54%). The melting point and ^{1}H-NMR data of this compound are listed in Table 1.

6-Bromo-2,2-dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (8b) Trifluoromethanesulfonic anhydride (100 g, 0.354 mol) was added dropwise to a mixture of 6-bromo-2,2-dimethyl-2*H*-1,3-benzoxazin-4-one (**10b**, 60.0 g, 0.234 mol) and CH_2Cl_2 (300 ml) under an argon atmosphere at −78 °C, and the mixture was stirred for 15 min. Then 2,6-lutidine (41.5 ml, 0.354 mol) was added dropwise at −78 °C, and the whole was warmed to 0 °C then stirred for 20 min. The mixture was poured into water (500 ml) and extracted with EtOAc (1.5 l). The extract was washed successively with aqueous $KHSO_4$ (400 ml × 2), $NaHCO_3$ (400 ml × 2), and brine (400 ml), dried, and evaporated *in vacuo* to give crude 6-bromo-4-trifluoromethylsulfonyloxy-2,2-dimethyl-2*H*-1,3-benzoxazine (**16b**, 140 g) as an oil, which was used in the next step without further purification.

A 1.6 M *n*-BuLi hexane solution (300 ml, 0.480 mol) was added dropwise to a solution of 2-bromopyridine (73.6 g, 0.466 mol) in dry THF (840 ml) under an argon atmosphere at −78 °C, and the mixture was stirred for 30 min. To this mixture was added a mixture of $ZnCl_2$ (70.0 g, 0.514 mol) and dry THF (330 ml) at −78 °C. The whole was warmed to 0 °C and stirred for 20 min, then tetrakis(triphenylphosphine)palladium(0) (13.4 g, 0.012 mol) and crude **16b** (140 g) were added. The reaction mixture was warmed to room temperature and stirred for 14 h, then saturated $NaHCO_3$ (1 l) was added, and the precipitate was filtered off through a pad of Celite. The Celite pad was washed with EtOAc (200 ml × 2). The mother liquid was extracted with EtOAc (1 l). The extract was washed with brine (500 ml), dried, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc) to give 6-bromo-2,2-dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (**8b**, 23.3 g, 31%) as yellow crystals.

Compounds **8a**, **c**—**g**, **j**—**m**, **p**, **q**, and **s**—**w** were obtained by a similar method to that used for **8b**. The yields, melting points, elemental analysis, and ^{1}H-NMR data of these compounds are listed in Table 2.

2-Cyano-4-trifluoromethylphenol (20) Bromine (15.9 ml, 0.308 mol) was added dropwise to a solution of 4-trifluoromethylphenol (**13c**, 50.0 g, 0.308 mol) in CH_2Cl_2 (300 ml) at room temperature, and the mixture was stirred for 38 h. It was washed successively with aqueous Na_2SO_3 and brine, dried, and evaporated *in vacuo* to give crude 2-bromo-4-trifluoromethylphenol (**19**, 75.8 g) as an oil.

A mixture of crude **19** (75.8 g), cuprous cyanide (27.6 g, 0.308 mol), and DMF (250 ml) was refluxed under an argon atmosphere for 2 h, then poured into a solution of ferric chloride hexahydrate (138 g, 0.509 mol) and concentrated HCl (35.0 ml) in water (400 ml). The whole was stirred at room temperature for 30 min, followed by extraction with EtOAc (1.2 l). The extract was washed successively with diluted HCl, saturated $NaHCO_3$, and brine, then dried and evaporated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc) to give **20** (34.6 g, 60%), mp 149.5—151 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.19 (1H, d, J=8.8 Hz), 7.85 (1H, dd, J=8.8, 2.0 Hz), 8.11 (1H, d, J=2.0 Hz). IR (KBr): 2230 cm^{-1}.

6-Trifluoromethyl-2,2-dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (8c) from 20 A 1.6 M *n*-BuLi hexane solution (2.10 ml, 3.30 mmol) was added dropwise to a solution of 2-bromopyridine (474 mg, 3.00 mmol) in dry THF (5.0 ml) under an argon atmosphere at −78 °C, and the mixture was stirred for 30 min. Then a solution of **20** (187 mg, 1.00 mmol) in dry THF (5 ml) was added under the same conditions. The mixture was stirred for 1 h at −78 °C, quenched with acetic acid (180 mg,

3.00 mmol) and concentrated *in vacuo*. The residue was taken up in NH_4OAc (2.00 g, 25.9 mmol) and 2,2-dimethoxypropane (5.00 ml, 40.7 mmol), and the whole was refluxed for 3 h, then concentrated *in vacuo* and diluted with EtOAc. The EtOAc solution was washed successively with saturated $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc) to give **8c** (190 mg, 62%).

2-(5-Bromo-4-chloro-2-hydroxybenzoyl)pyridine (22l) A 1.6 M *n*-BuLi hexane solution (24.4 ml, 39.0 mmol) was added dropwise to a solution of 2-bromopyridine (6.32 g, 40.0 mmol) in dry THF (49 ml) under an argon atmosphere at −78 °C, and the mixture was stirred at −78 °C for 10 min. Then a solution of 5-bromo-4-chlorosalicylic acid (**12l**, 2.34 g, 9.31 mmol) in dry 1,4-dioxane (12 ml) was added dropwise at −78 °C. The reaction mixture was stirred at 0 °C for 10 min, then MeOH (6 ml) and water (100 ml) were added, and the whole was extracted with EtOAc. The extract was washed successively with saturated NH_4Cl and brine, dried, and concentrated *in vacuo*. The residue was purified by column chlomatography (CH_2Cl_2) to give **22l** (1.48 g, 51%) as yellow crystals, mp 124—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.21 (1H, s), 7.56—7.65 (1H, m), 7.95—8.14 (2H, m), 8.62 (1H, s), 8.72—8.79 (1H, m). *Anal.* Calcd for $C_{12}H_7BrClNO_2$: C, 46.11; H, 2.26; N, 4.48. Found: C, 45.95; H, 2.28; N, 4.64.

Compounds **22b** and **22e** were obtained by a similar method to that used for **22l** in 42% and 40% yields, respectively. **22b**: mp 71—73 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.97 (1H, d, J=9.0 Hz), 7.53—7.61 (2H, m), 7.93—8.06 (2H, m), 8.38 (1H, d, J=2.2 Hz), 8.74—8.78 (1H, m), 12.63 (1H, s). *Anal.* Calcd for $C_{12}H_8BrNO_2$: C, 51.83; H, 2.90; N, 5.04. Found: C, 51.75; H, 2.92; N, 5.17. **22e**: an oil. ^{1}H-NMR ($CDCl_3$) δ: 7.07 (1H, d, J=9.2 Hz), 7.36—7.42 (1H, m), 7.55—7.62 (1H, m), 7.94—8.10 (2H, m), 8.25 (1H, d, J=3.0 Hz), 8.73—8.76 (1H, m). HRMS Calcd for $C_{13}H_8F_3NO_3$: 283.0456. Found: 283.0461.

6-Bromo-7-chloro-2,2-dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (8l) One-Pot 1,3-Benzoxazine Skeleton Formation Reaction A mixture of **22l** (1.20 g, 3.84 mmol), saturated NH_3 in acetone (15.0 ml, containing *ca.* 23 mmol of NH_3), NH_4Cl (1.20 g, 22.4 mmol), and $CaSO_4$ (2.40 g, 17.6 mmol) was stirred in a sealed tube at 80 °C for 5.5 h. The precipitate was filtered off, and the filtrate was partitioned between EtOAc and saturated NH_4Cl. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (hexane–isopropyl ether) to give **8l** (669 mg, 50%) as light yellow crystals.

2,2-Dimethyl-6-nitro-4-(2-pyridyl)-2*H*-1,3-benzoxazine (8i) Sulfuric acid (3.0 ml) and nitric acid (0.20 ml) were added to a mixture of **8u** (500 mg, 2.10 mmol) and acetic acid (1.0 ml) at 0 °C, and the mixture was stirred for 10 min. It was poured into an ice-cooled mixture of 5 N NaOH (50 ml) and saturated $NaHCO_3$ (20 ml), and the whole was extracted with EtOAc. The extract was washed successively with saturated $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The residue was crystallized from hexane to give **8i** (580 mg, 98%).

Compounds **8n** and **r** were obtained by a similar method to that used for **8i** in 64% and 32% yields, respectively. The melting points, elemental analysis, and ^{1}H-NMR data of these compounds are listed in Table 2.

6-Bromo-2,2,7-trimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (8o) A solution of bromine (320 mg, 2.00 mmol) in EtOAc (3 ml) was added dropwise to a mixture of **8v** (500 mg, 1.98 mmol), sodium acetate (419 mg, 5.00 mmol), and EtOAc (10 ml) at −40 °C. The mixture was stirred at the same temperature for 15 min, and then poured into ice-cooled 1 N NaOH, followed by extraction with EtOAc. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc) to give **8o** (471 mg, 72%). The melting point and ^{1}H-NMR data of this compound are listed in Table 2.

2-(2,2-Dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-Oxides 7a—g and 7i—t. General Procedure 70% *m*-Chloroperbenzoic acid (32.6 g, 132 mmol) was added portionwise to a solution of 6-bromo-2,2-dimethyl-4-(2-pyridyl)-2*H*-1,3-benzoxazine (**8b**, 23.3 g, 73.6 mmol) in CH_2Cl_2 (720 ml) at −20 °C, and the mixture was stirred at −20 °C for 24 h. The reaction was quenched with aqueous Na_2SO_3, and the organic layer was washed successively with aqueous Na_2CO_3 and brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc then EtOAc–MeCN). The first eluate was concentrated *in vacuo*, and the product was recrystallized from EtOAc to give 2-(6-bromo-2,2-dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-oxide (**7b**, 4.54 g, 19%) as colorless crystals. The second eluate was concentrated *in vacuo*, and the product was washed with Et_2O to give the di-*N*-oxide **24** (231 mg, 1%), mp 138.5—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, s), 1.87 (3H, s), 6.85 (1H, d, J=2.2 Hz), 6.93 (1H, d, J=8.6 Hz), 7.32—7.44 (4H, m), 8.32—8.36 (1H, m). *Anal.* Calcd for $C_{15}H_{13}BrN_2O_3$: C, 51.60; H, 3.75; N, 8.02. Found: C, 51.42; H, 3.85; N, 7.93.

The yields, melting points, elemental analysis, and ^{1}H-NMR data of **7a**—**t** are listed in Table 3.

2-(6-Ethynyl-2,2-dimethyl-2*H*-1,3-benzoxazin-4-yl)pyridine 1-Oxide (7h) A mixture of **7t** (110 mg, 0.31 mmol), K_2CO_3 (9.64 mg, 0.0698 mmol), and MeOH (1.1 ml) was stirred at room temperature for 1 h. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (EtOAc–MeCN) to give **7h** (70.8 mg, 81%). The melting point, elemental analysis, and ^{1}H-NMR data of this compound are listed in Table 3.

Single-Crystal X-Ray Analysis of 7l Crystals of **7l** were grown from EtOAc. Data were collected on a Rigaku AFC5R diffractometer and corrected for Lorentz and polarization factors. Absorption correction was not applied. The structure was solved by direct methods with the aid of TEXSAN[18] and refined by CRYLSQ in the XTAL package.[19] The parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model in which the distances from the bonded carbon atoms were fixed at 1.09 Å. Thermal parameters of hydrogen atoms were taken from their bonded atoms as Uiso and fixed through the next several cycles of refinement. Crystal data and conditions are summarized in Table 5.

***In Vitro* Experiments: Rat Aorta Preparation** Male Wistar rats (300—350 g) were anesthetized with pentobarbital (60 mg/kg, i.p.), and the thoracic aorta was rapidly removed. The aorta was freed from connective tissue, and cut into pieces 2—3 mm in length to make ring preparations which were mounted for isometric recording with 1 g resting tension in a 20 ml organ bath containing modified Krebs solution (36 °C, pH 7.4, 95% O_2–5% CO_2). The composition of the Krebs solution was (mM) 113.1 NaCl, 4.6 KCl, 1.2 $CaCl_2$, 1.2 $MgCl_2$, 3.5 NaH_2PO_4, 21.9 $NaHCO_3$ and 10 dextrose. The preparations were equilibrated for 60 min, and 60 mM KCl was applied to obtain the standard contraction for a normalization. Contractions were measured isometrically by a force transducer (FD pick up, Nihon-Kohden) with output to a pen recorder (Nihon Denki San-ei), and measurements were performed from the charts.

Screening System for K^+ Channel Openers TEA (30 mM) and $BaCl_2$ (0.3 mM) were added to the solution to induce sustained contraction of rat aorta for screening. After obtaining a sustained contraction (15 min later), a screening compound was added cumulatively (3, 10 and 30 μM). Similar experiments using 80 mM KCl instead of TEA and $BaCl_2$ were performed.

Blood Pressure Measurement in SHR SHRs (250—300 g) were anesthetized with pentobarbital (60 mg/kg, i.p.) and polyethylene tubing was placed in the left femoral artery for blood pressure measurement. One day after the operation, the tubing was connected to a pressure transducer (Spectramed) and the measured blood pressure was recorded with a pen-recorder (Nihon-Denki-San-ei). Agents were suspended in 1% arabic solution and administered orally in a volume of 2 ml/kg.

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