Chem. Pharm. Bull. 45(12) 1994—2004 (1997) Vol. 45, No. 12

# Synthesis and Biological Activity of Novel 2-(α-Alkoxyimino)benzylpyridine Derivatives as $K^+$ Channel Openers

Tsuyoshi MAEKAWA, Satoshi YAMAMOTO, Yumiko IGATA, Shota IKEDA,
Toshifumi WATANABE, and Mitsuru SHIRAISHI*

*Pharmaceutical Research Laboratories II, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.* Received May 30, 1997; accepted August 12, 1997

**The search for novel $K^+$ channel openers with a non-benzopyran skeleton, unlike cromakalim, led to the discovery of a new series of (*Z*)-2-(α-alkoxyimino)benzylpyridine derivatives. Synthesis was achieved by using a (*Z*)-dominant condensation reaction of benzoylpyridines with *O*-alkylhydroxylamines, followed by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation. The compounds were tested for their vasorelaxant activity in tetraethylammonium chloride (TEA) and $BaCl_2$- and high KCl-induced contraction of rat aorta to identify potential $K^+$ channel openers, and also for their effects on the coronary blood flow (CBF) after intracoronary injection in anesthetized dogs. A large number of the 2-(α-alkoxyimino)benzylpyridines strongly inhibited TEA and $BaCl_2$-induced contraction, had no effect on 80 mM KCl-induced contraction, and increased the CBF to more than 200% of the basal flow at 10—30 μg/dog. In particular, (*Z*)-2-[5-bromo-α-(*tert*-butoxyimino)-4-fluoro-2-hydroxybenzyl]-3-hydroxypyridine 1-oxide (7d) showed highly potent vasorelaxant activity ($EC_{50}=0.28\,\mu M$) comparable to that of levcromakalim ($EC_{50}=0.17\,\mu M$), and gave a significantly longer-lasting increase ($T_{1/2}=30$ min) in the CBF compared to levcromakalim, nicorandil, nitroglycerin, or diltiazem ($T_{1/2}=5.2$, 0.9, 0.4, and 2.2 min, respectively). It also exhibited a stable and long-lasting hypotensive effect (over 7 h) upon oral administration of 1 mg/kg in spontaneously hypertensive rats (SHRs).**

**Key words** (*Z*)-2-(α-alkoxyimino)benzylpyridine; $K^+$ channel opener; vasorelaxant activity; vasodilating effect; 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 been developed for the treatment of conditions such as hypertension, angina pectoris, asthma, and urinary incontinence.[4] There are several prototypes[5] in this class of compounds, represented by cromakalim (**1**), nicorandil (**2**), pinacidil (**3**), and aprikalim (**4**). In particular, the discovery of cromakalim,[6] a specific $K^+$ channel opener with highly potent hypotensive effects, provided a major impetus to $K^+$ channel opener research. There have been numerous reports[7] focused on the benzopyran structure of cromakalim (**1**). We previously reported a new series of 1,3-benzoxazine $K^+$ channel openers (**5**) in which the benzopyran ring was replaced with other [6,6]-fused rings.[8] As shown in our previous paper, the structural features of $K^+$ channel openers with [6,6]-fused ring systems, especially 1,3-benzoxazine derivatives **5**, can be summarized as follows. Less bulky electron-withdrawing groups at C6 and/or C7 and a heterocyclic ring with an α-oxo function such as pyridine *N*-oxide at C4 are essential for optimal activity. In addition, the heterocyclic ring should preferably have an orthogonal relationship with the plane of the [6,6]-fused ring. We therefore have designed novel 2-(α-alkoxyimino)benzylpyridines (**6** and **7**) with an electron-withdrawing group at C5 and/or C4 of the benzene ring and a bulky alkyl group as the oxime substituent. In this paper, we describe the synthesis and biological activity of a novel series of 2-(α-alkoxyimino)benzylpyridine derivatives as $K^+$ channel openers.

## Chemistry

The synthetic route to the target compounds **6** and **7** is outlined in Chart 2. As mentioned in the Results and Discussion section, the biologically active forms of

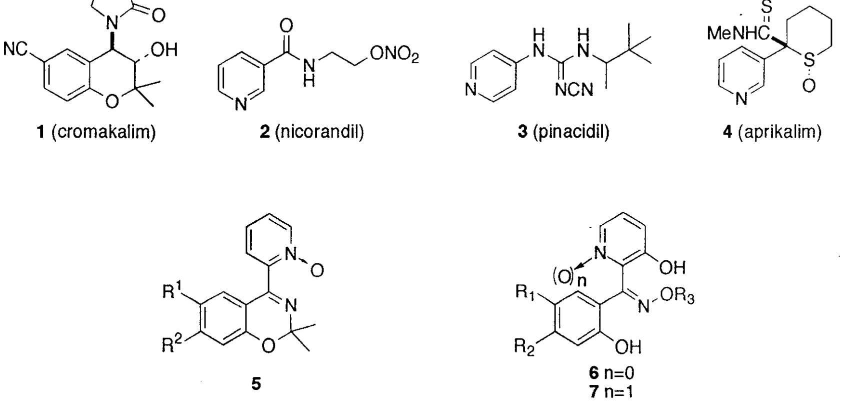


Chart 1

---

* To whom correspondence should be addressed.

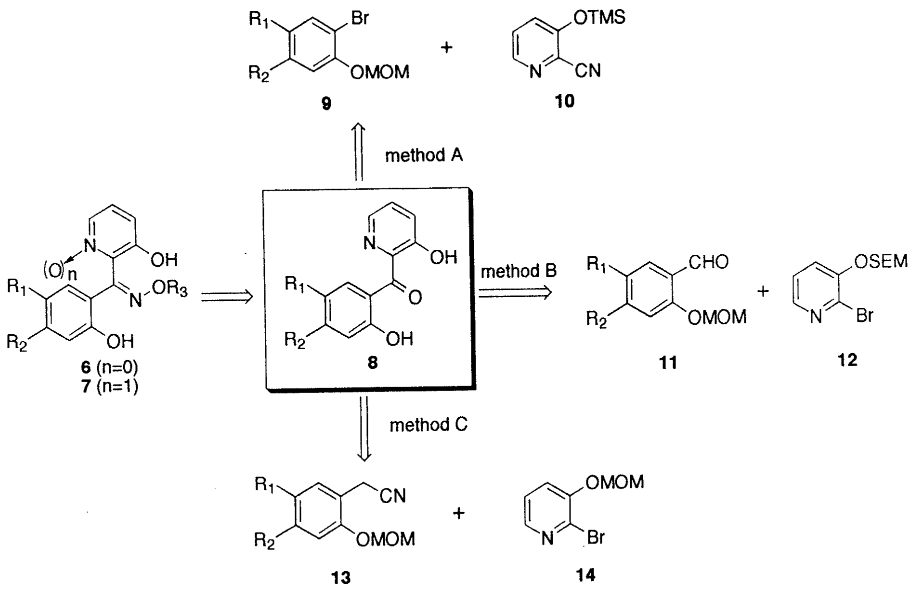
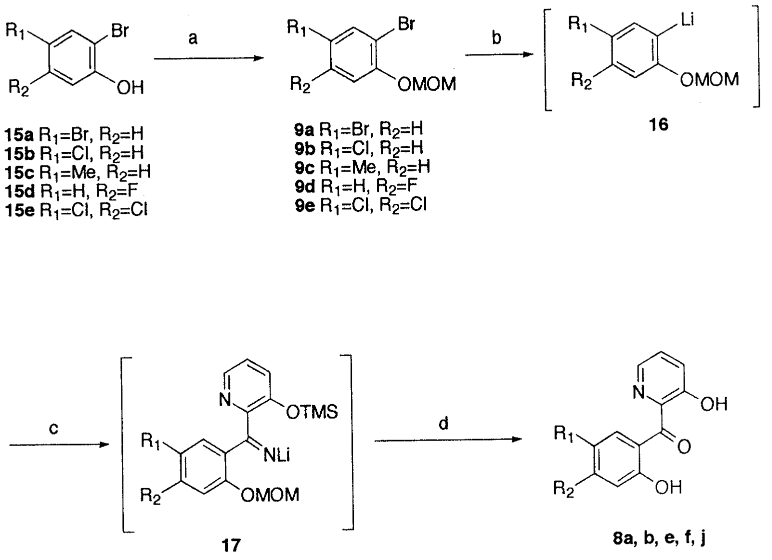


Chart 2

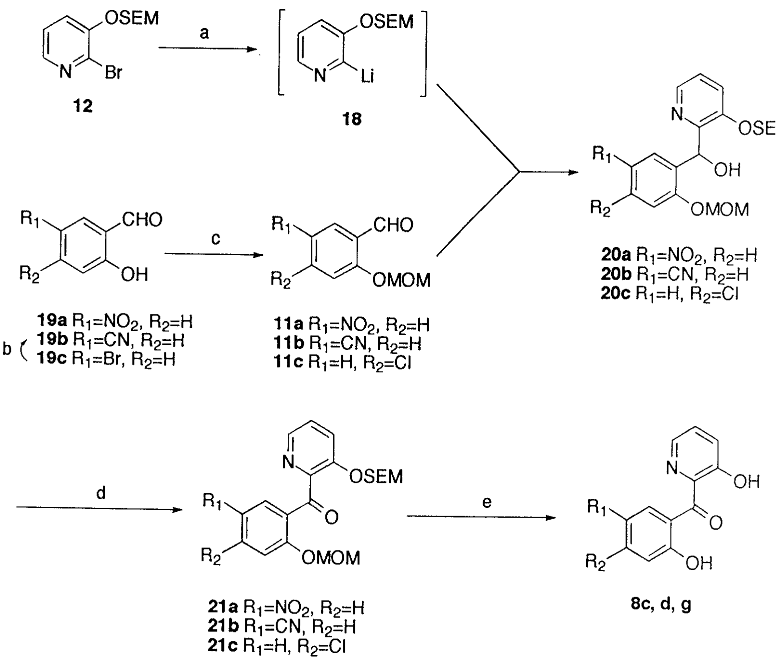


reagent: (a) MOMCl, DIPEA, $CH_2Cl_2$; (b) *n*-BuLi, $Et_2O$; (c) 2-cyano-3-trimethylsilyloxypyridine **10**, $Et_2O$; (d) *dil.* HCl, MeOH.

Chart 3 (Method A)

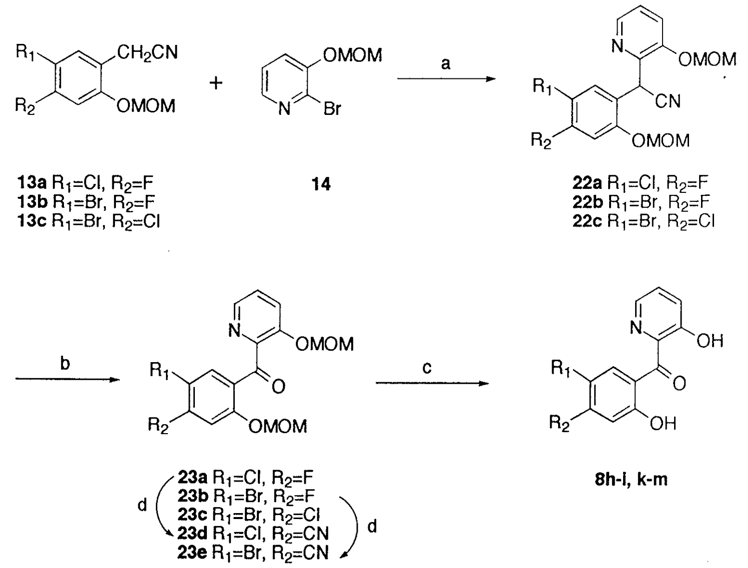
compounds **6** and **7** were the (*Z*)-isomers. The synthesis was characterized by a (*Z*)-dominant condensation of benzoylpyridines **8**, key intermediates, with *O*-alkylhydroxylamines, followed by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation. Intermediates **8** were mainly prepared by three methods. Method A involved treatment of 2-cyano-3-trimethylsilyloxypyridine (**10**)[9] with the phenyllithium derivatives **16** generated by halogen-metal exchange reaction of the corresponding bromobenzenes **9** with *n*-butyllithium, followed by acidic hydrolysis (Chart 3). The bromobenzene derivatives **9** were prepared by methoxymethylation of 2-bromophenols **15**. Conversion of the benzaldehydes **11** to the corresponding phenylpyridylmethanols **20** followed by activated $MnO_2$ oxidation and acidic hydrolysis provided the desired benzoylpyridines **8** (Method B; Chart 4). 2-Lithio-3-(2-trimethylsilylethoxymethoxy)pyridine **18**[10] utilized in Method B was obtained by treatment of 2-bromo-3-(2-trimethylsilylethoxymethoxy)pyridine (**12**) with *tert*-butyllithium in tetrahydrofuran (THF). Cyanation of 5-bromosalicylaldehyde **19c** with cuprous cyanide followed by methoxymethylation of its hydroxyl group gave the 5-cyano derivative **11b**. One of the starting materials, **11c**, was synthesized by methoxymethylation of the corresponding salicylic acid **24a**, $LiAlH_4$ reduction of the resulting ester **25a**, and subsequent activated $MnO_2$ oxidation (Chart 6).

The other synthetic route is illustrated in Chart 5 (Method C). Coupling reaction[11] of benzylcyanides **13** with 2-bromo-3-methoxymethoxypyridine (**14**) provided phenylpyridylacetonitriles **22**, which were converted to the corresponding ketone derivatives **23** by oxidative decyanation reaction[12] and subsequent deprotection of the hydroxyl groups to afford the desired key intermediates **8**. The benzylcyanides **13a**—**c** were prepared by cyana-



reagent: (a) *tert*-BuLi, THF; (b) CuCN, DMF; (c) MOMCl, $K_2CO_3$, DMF; (d) activated $MnO_2$, $CHCl_3$; (e) *dil.* $H_2SO_4$, acetone.

Chart 4 (Method B)

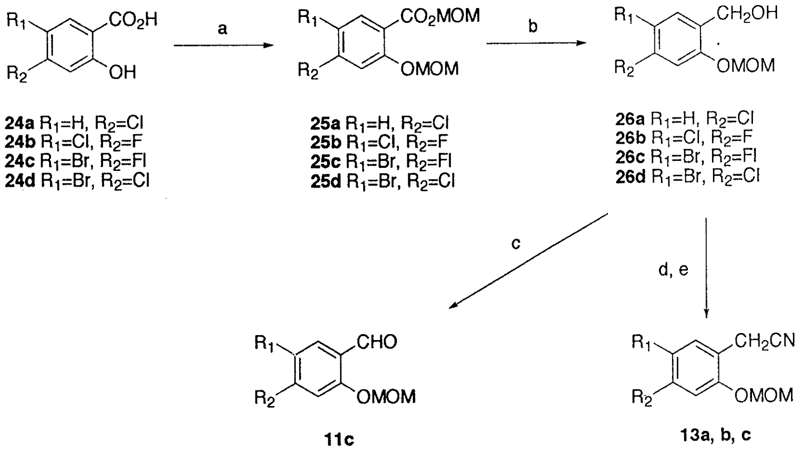


reagent: (a) TsNa, NaH, THF; (b) $O_2$, $K_2CO_3$, $H_2O$, DMSO; (c) *dil.* $H_2SO_4$, acetone; (d) KCN, DMSO.

Chart 5 (Method C)

tion of the benzylhalides derived from the corresponding benzylalcohols **26b**—**d** (Chart 6). Compounds **8l**, **m** with a cyano group at C4 on the benzene ring[13)] were prepared in high yield by treatment of the 4-fluorobenzoylpyridines **23a**, **b** with potassium cyanide in DMSO and subsequent acidic hydrolysis (Chart 5). These benzoylpyridines **8** synthesized by the above methods are summarized in Table 1.

Conversion of the benzoylpyridines **8** to 2-(α-alkoxyimino)benzylpyridine derivatives **6** is illustrated in Chart 7 and Table 2. Treatment of benzoylpyridines **8** with *O*-alkylhydroxylamines in the presence of triethylamine in ethanol under reflux gave both (*Z*)- and (*E*)-oximes **6**, and the yields of **6a**, the less polar isomer, and **6b** were 69% and 22%, respectively. With regard to the configuration of the oximes **6**, we supposed that the (*Z*)-isomer, **6a**, was less polar than **6b** on the basis of the spatial relationship between the pyridine ring and the oxime moiety. So, we examined the stereoselective condensation to the biologically active (*Z*)-oximes **6**. As a result of our exploration



reagent: (a) MOMCl, $K_2CO_3$, acetone; (b) LAH, $Et_2O$; (c) activated $MnO_2$, $CHCl_3$; (d) MsCl, TEA, $CH_2Cl_2$; (e) NaCN, NaI, DMSO.

Chart 6

Table 1. 2-(2-Hydroxybenzoyl)-3-hydroxypryridines **8**

| Compd. | $R_1$ | $R_2$ | Yield[a] (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|
| **8a** | Br | H | 68[a] | 143—145 | $C_{12}H_8BrNO_3$ | 49.01<br>(49.11 | 2.74<br>2.81 | 4.76<br>4.71) | 6.96 (1H, d, $J$=9.0 Hz), 7.54—7.61 (1H, m), 7.60 (2H, d, $J$=2.8 Hz), 8.28 (1H, t, $J$=2.8 Hz), 8.45 (1H, d, $J$=2.4 Hz), 12.56 (1H, s) |
| **8b** | Cl | H | 61[a] | 154—155 | $C_{12}H_8ClNO_3$ | 57.73<br>(57.60 | 3.23<br>3.21 | 5.61<br>5.67) | 7.01 (1H, d, $J$=9.0 Hz), 7.45 (1H, dd, $J$=9.0, 2.8 Hz), 7.60 (2H, d, $J$=2.8 Hz), 8.28 (1H, t, $J$=2.8 Hz), 8.32 (1H, d, $J$=2.8 Hz), 12.55 (1H, s) |
| **8c** | $NO_2$ | H | 79[b] | 216—220 | $C_{12}H_8N_2O_5$<br>$\cdot 1/8H_2O$ | 54.92<br>(54.95 | 3.07<br>3.04 | 10.67<br>11.07) | 6.99 (1H, d, $J$=9.0 Hz), 7.47 (1H, dd, $J$=8.6, 1.6 Hz), 7.54 (1H, dd, $J$=8.6, 4.0 Hz), 8.16 (1H, dd, $J$=4.0, 1.6 Hz), 8.23 (1H, dd, $J$=9.0, 2.8 Hz), 8.33 (1H, d, $J$=2.8 Hz) |
| **8d** | CN | H | 81[b] | 182—183 | $C_{13}H_8NO_3$<br>$\cdot 1/4H_2O$ | 63.81<br>(64.12 | 3.50<br>3.55 | 11.48<br>11.34) | 7.12 (1H, d, $J$=8.6 Hz), 7.66 (2H, d, $J$=3.0 Hz), 7.71 (1H, dd, $J$=8.6, 2.2 Hz), 8.29 (1H, t, $J$=3.0 Hz), 8.73 (1H, d, $J$=2.2 Hz), 12.53 (1H, s) |
| **8e** | $CH_3$ | H | 82[a] | 137—138 | $C_{13}H_{11}NO_3$ | 68.11<br>(67.78 | 4.84<br>4.84 | 6.11<br>5.97) | 2.33 (3H, s), 6.97 (1H, d, $J$=8.4 Hz), 7.34 (1H, dd, $J$=8.4, 3.0 Hz), 7.56 (2H, d, $J$=3.4 Hz), 8.08 (1H, d, $J$=3.0 Hz), 8.27 (1H, t, $J$=3.4 Hz), 12.62 (1H, s) |
| **8f** | H | F | 81[a] | 128.5—129 | $C_{12}H_8FNO_3$ | 61.81<br>(61.85 | 3.46<br>3.45 | 6.01<br>6.11) | 6.63—6.74 (2H, m), 7.58 (2H, d, $J$=2.8 Hz), 8.26 (1H, t, $J$=2.8 Hz), 8.45—8.53 (1H, m), 12.61 (1H, s) |
| **8g** | H | Cl | 74[b] | 108—109 | $C_{12}H_8ClNO_3$<br>$\cdot 1/2H_2O$ | 55.72<br>(56.12 | 3.51<br>3.22 | 5.42<br>5.20) | 6.93 (1H, dd, $J$=8.8, 2.2 Hz), 7.07 (1H, d, $J$=2.2 Hz), 7.59 (2H, d, $J$=3.0 Hz), 8.27 (1H, t, $J$=3.0 Hz), 8.33 (1H, d, $J$=8.8 Hz), 12.65 (1H, s) |
| **8h** | Cl | F | 96[c] | 194—195 | $C_{12}H_7ClFNO_3$ | 53.85<br>(53.54 | 2.64<br>2.62 | 5.23<br>5.33) | 6.82 (1H, d, $J$=10.6 Hz), 7.61 (2H, d, $J$=2.8 Hz), 8.26 (1H, t, $J$=2.8 Hz), 8.50 (1H, d, $J$=8.8 Hz), 12.63 (1H, s) |
| **8i** | Br | F | 93[c] | 205—209 | $C_{12}H_7BrFNO_3$ | 46.18<br>(46.38 | 2.26<br>2.01 | 4.49<br>4.58) | 6.80 (1H, d, $J$=10.0 Hz), 7.62 (2H, d, $J$=2.8 Hz), 8.26 (1H, t, $J$=2.8 Hz), 8.62 (1H, d, $J$=8.4 Hz), 12.64 (1H, s) |
| **8j** | Cl | Cl | 64[a] | 171—173 | $C_{12}H_7Cl_2NO_3$ | 50.73<br>(50.77 | 2.48<br>2.70 | 4.93<br>5.25) | 7.19 (1H, s), 7.63 (2H, d, $J$=3.0 Hz), 8.27 (1H, t, $J$=3.0 Hz), 8.43 (1H, s), 12.63 (1H, s) |
| **8k** | Br | Cl | 97[c] | 188—190 | $C_{12}H_7BrClNO_3$ | 43.87<br>(43.65 | 2.15<br>2.07 | 4.26<br>4.12) | 7.19 (1H, s), 7.63 (2H, d, $J$=3.0 Hz), 8.26 (1H, t, $J$=3.0 Hz), 8.56 (1H, s), 12.63 (1H, s) |
| **8l** | Cl | CN | 99[c] | 235—237 | $C_{13}H_7ClN_2O_3$ | 56.85<br>(56.55 | 2.57<br>2.43 | 10.20<br>10.01) | 7.40 (1H, s), 7.68 (2H, d, $J$=3.0 Hz), 8.29 (1H, t, $J$=3.0 Hz), 8.32 (1H, s), 12.45 (1H, s) |
| **8m** | Br | CN | 95[c] | 249—251 | $C_{13}H_7BrN_2O_3$<br>$\cdot 1/2H_2O$ | 47.59<br>(47.59 | 2.46<br>2.19 | 8.54<br>8.74) | 7.38 (1H, s), 7.67 (2H, d, $J$=2.8 Hz), 8.28 (1H, t, $J$=2.8 Hz), 8.45 (1H, s), 12.43 (1H, s) |

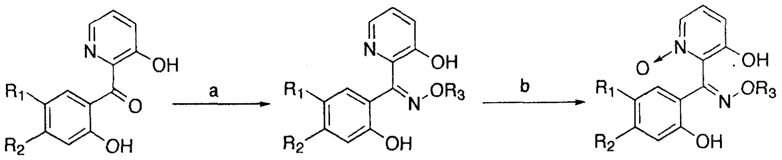
*a*) From the corresponding phenylbromides **9**. *b*) From the corresponding phenylpyridylmethanols **20**. *c*) From the corresponding phenylpyridylketones **23**.

focused mainly on a variety of amines and on reaction temperature, the stereoselective synthesis was carried out in the presence of pyrrolidine as a base at −25 °C to give the desired (*Z*)-2-(α-alkoxyimino)benzylpyridine derivatives **6a** in 78% yield. The reaction conditions described above were applied to other compounds with different

Table 2. (*Z*)-3-Hydroxy-2-(2-hydroxy-α-*tert*-butoxyiminobenzyl)pyridine **6**

| Compd. | $R_1$ | $R_2$ | $R_3$ | Yield[a,b] (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) | | | $^1$H-NMR ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N | |
| **6a** | Br | H | *tert*-Bu | 69, 78[c] | 218—219 | $C_{16}H_{17}BrN_2O_3$ | 52.62<br>(52.56 | 4.69<br>4.80 | 7.67<br>7.61) | 1.43 (9H, s), 6.91 (1H, d, *J*=8.6 Hz), 6.98 (1H, d, *J*=2.4 Hz), 7.30—7.50 (3H, m), 8.33 (1H, dd, *J*=4.0, 1.4 Hz) |
| **6b**[d] | Br | H | *tert*-Bu | 22, 7[c] | 151—152 | $C_{16}H_{17}BrN_2O_3$ | 52.62<br>(52.47 | 4.69<br>4.72 | 7.67<br>7.76) | 1.41 (9H, s), 6.99 (1H, d, *J*=9.6 Hz), 7.22—2.29 (1H, m), 7.40—7.45 (3H, m), 8.12 (1H, dd, *J*=4.4, 1.4 Hz), 9.45 (1H, s), 10.98 (1H, s) |
| **6c** | Br | H | iso-Pr | 68 | 192—194 | $C_{15}H_{15}BrN_2O_3$ | 51.30<br>(51.06 | 4.30<br>4.47 | 7.98<br>8.34) | 1.37 (6H, d, *J*=6.2 Hz), 4.61—4.73 (1H, m), 6.91 (1H, d, *J*=8.8 Hz), 7.01 (1H, d, *J*=2.4 Hz), 7.35 (1H, dd, *J*=8.8, 2.4 Hz), 7.40 (1H, dd, *J*=8.4, 4.2 Hz), 7.47 (1H, dd, *J*=8.4, 1.6 Hz), 8.35 (1H, dd, *J*=4.2, 1.6 Hz) |
| **6d** | Br | H | cyclo-Pent | 86[c] | 180—181 | $C_{17}H_{17}BrN_2O_3$ | 54.13<br>(54.18 | 4.54<br>4.56 | 7.43<br>7.29) | 1.58—1.69 (4H, m), 1.86—1.95 (4H, m), 4.94—5.03 (1H, m), 6.33 (1H, s), 6.89—6.99 (2H, m), 7.32—7.48 (3H, m), 8.34 (1H, dd, *J*=4.0, 1.8 Hz), 11.22 (1H, s) |
| **6e** | Br | H | Et | 77[c] | 190—192 | $C_{14}H_{13}BrN_2O_3$ | 49.87<br>(49.70 | 3.89<br>3.93 | 8.31<br>8.29) | 1.38 (3H, t, *J*=7.0 Hz), 4.40 (2H, q, *J*=7.0 Hz), 6.91 (1H, d, *J*=8.8 Hz), 6.98 (1H, d, *J*=2.6 Hz), 7.35 (1H, dd, *J*=8.8, 2.6 Hz), 7.39 (1H, dd, *J*=8.4, 4.2 Hz), 7.45 (1H, dd, *J*=8.4, 1.8 Hz), 8.34 (1H, dd, *J*=4.2, 1.8 Hz) |
| **6f** | Br | H | *n*-Bu | 61 | 152—153 | $C_{16}H_{17}BrN_2O_3$ | 52.62<br>(52.60 | 4.69<br>4.67 | 7.67<br>7.87) | 0.92 (3H, t, *J*=7.4 Hz), 1.27—1.42 (2H, m), 1.61—1.81 (2H, m), 4.34 (2H, t, *J*=6.6 Hz), 6.91 (1H, d, *J*=8.8 Hz), 6.98 (1H, d, *J*=2.2 Hz), 7.30—7.48 (3H, m), 8.34 (1H, dd, *J*=4.0, 1.4 Hz) |
| **6g** | Cl | H | *tert*-Bu | 80[c] | 212—213 | $C_{16}H_{17}ClN_2O_3$ | 59.91<br>(59.80 | 5.34<br>5.19 | 8.73<br>8.55) | 1.44 (9H, s), 6.42 (1H, s), 6.86 (1H, d, *J*=2.4 Hz), 6.96 (1H, d, *J*=8.6 Hz), 7.22 (1H, dd, *J*=8.6, 2.4 Hz), 7.40 (1H, dd, *J*=8.4, 4.2 Hz), 7.47 (1H, dd, *J*=8.4, 1.6 Hz), 8.36 (1H, dd, *J*=4.2, 1.6 Hz), 11.23 (1H, s) |
| **6h** | $NO_2$ | H | *tert*-Bu | 84 | 254—255 | $C_{16}H_{17}N_3O_5$ | 58.00<br>(57.89 | 5.17<br>5.07 | 12.68<br>12.85) | 1.47 (9H, s), 7.09 (1H, d, *J*=9.2 Hz), 7.45 (1H, dd, *J*=8.0, 4.0 Hz), 7.53 (1H, dd, *J*=8.0, 1.6 Hz), 7.97 (1H, d, *J*=2.6 Hz), 8.17 (1H, dd, *J*=9.2, 2.6 Hz), 8.36 (1H, dd, *J*=4.0, 1.6 Hz) |
| **6i** | CN | H | *tert*-Bu | 60 | 244—248 | $C_{17}H_{17}N_3O_3$<br>$\cdot 1/5H_2O$ | 64.64<br>(64.97 | 5.58<br>5.63 | 13.30<br>13.04) | 1.45 (9H, s), 6.48 (1H, s), 7.07 (1H, d, *J*=8.4 Hz), 7.29 (1H, d, *J*=2.2 Hz), 7.40—7.56 (3H, m), 8.35 (1H, dd, *J*=4.4, 1.8 Hz), 12.18 (1H, s) |
| **6j** | $CH_3$ | H | *tert*-Bu | 26 | 223—224.5 | $C_{17}H_{20}N_2O_3$ | 67.98<br>(67.83 | 6.71<br>6.75 | 9.33<br>9.16) | 1.43 (9H, s), 2.16 (3H, s), 6.44 (1H, s), 6.60 (1H, d, *J*=1.8 Hz), 6.93 (1H, d, *J*=8.4 Hz), 7.08 (1H, dd, *J*=8.4, 1.8 Hz), 7.36 (1H, dd, *J*=8.4, 4.2 Hz), 7.44 (1H, dd, *J*=8.4, 1.6 Hz), 8.35 (1H, dd, *J*=4.2, 1.6 Hz), 10.86 (1H, s) |
| **6k** | H | F | *tert*-Bu | 71 | 119—121 | $C_{16}H_{17}FN_2O_3$ | 63.15<br>(63.01 | 5.63<br>5.50 | 9.21<br>9.18) | 1.43 (9H, s), 6.39 (1H, s), 6.45—6.55 (1H, m), 6.72 (1H, dd, *J*=10.2, 2.4 Hz), 6.84 (1H, dd, *J*=8.8, 6.6 Hz), 7.37 (1H, dd, *J*=8.6, 4.4 Hz), 7.45 (1H, dd, *J*=8.6, 1.8 Hz), 8.35 (1H, dd, *J*=4.4, 1.8 Hz), 11.41 (1H, d, *J*=1.6 Hz) |
| **6l** | H | Cl | *tert*-Bu | 87[c] | 204—204.5 | $C_{16}H_{17}ClN_2O_3$<br>$\cdot 1/2H_2O$ | 58.27<br>(58.10 | 5.49<br>5.09 | 8.49<br>8.27) | 1.44 (9H, s), 6.40 (1H, s), 6.73—6.83 (2H, m), 7.01—7.05 (1H, m), 7.38 (1H, dd, *J*=8.4, 4.0 Hz), 7.45 (1H, dd, *J*=8.4, 1.8 Hz), 8.34 (1H, dd, *J*=4.0, 1.8 Hz), 11.31 (1H, s) |
| **6m** | Cl | F | *tert*-Bu | 53 | 191—191.5 | $C_{16}H_{16}ClFN_2O_3$ | 56.73<br>(56.54 | 4.76<br>4.83 | 8.27<br>7.99) | 1.44 (9H, s), 6.43 (1H, s), 6.82 (1H, d, *J*=10.6 Hz), 6.95 (1H, d, *J*=8.4 Hz), 7.41 (1H, dd, *J*=8.4, 4.4 Hz), 7.48 (1H, dd, *J*=8.4, 1.8 Hz), 8.35 (1H, dd, *J*=4.4, 1.8 Hz) |
| **6n** | Br | F | *tert*-Bu | 66, 86[c] | 139—143 | $C_{16}H_{16}BrFN_2O_3$<br>$\cdot 1/2H_2O$ | 49.00<br>(48.97 | 4.37<br>4.09 | 7.14<br>7.10) | 1.44 (9H, s), 6.46 (1H, s), 6.80 (1H, d, *J*=9.8 Hz), 7.08 (1H, d, *J*=8.0 Hz), 7.40 (1H, dd, *J*=8.6, 4.0 Hz), 7.47 (1H, dd, *J*=8.6, 1.6 Hz), 8.34 (1H, dd, *J*=4.2, 1.4 Hz), 11.67 (1H, s) |
| **6o**[d] | Br | F | *tert*-Bu | 25, 8[c] | 86—89 | $C_{16}H_{16}BrFN_2O_3$ | 50.15<br>(49.96 | 4.21<br>4.24 | 7.31<br>7.14) | 1.41 (9H, s), 6.88 (1H, d, *J*=9.8 Hz), 7.28 (1H, dd, *J*=8.0, 4.6 Hz), 7.45 (1H, dd, *J*=8.0, 1.4 Hz), 7.53 (1H, d, *J*=7.8 Hz), 8.11 (1H, dd, *J*=4.6, 1.4 Hz), 10.40 (1H, s), 10.95 (1H, s) |
| **6p** | Cl | Cl | *tert*-Bu | 58, 75[e] | 187—188.5 | $C_{16}H_{16}Cl_2N_2O_3$<br>$\cdot 1/2H_2O$ | 52.76<br>(52.88 | 4.70<br>4.49 | 7.69<br>7.83) | 1.43 (9H, s), 6.98 (1H, s), 7.13 (1H, s), 7.37—7.52 (2H, m), 8.31—8.33 (1H, m) |
| **6q** | Br | Cl | *tert*-Bu | 46 | 189—190 | $C_{16}H_{16}BrClN_2O_3$ | 48.08<br>(48.18 | 4.04<br>4.05 | 7.01<br>6.80) | 1.44 (9H, s), 6.52 (1H, s), 7.14 (2H, s), 7.40 (1H, dd, *J*=8.4, 4.4 Hz), 7.47 (1H, dd, *J*=8.4, 1.8 Hz), 8.33 (1H, dd, *J*=4.4, 1.8 Hz) |
| **6r** | Cl | CN | *tert*-Bu | 46 | 206—208 | $C_{17}H_{16}ClN_3O_3$<br>$\cdot 1/5H_2O$ | 58.44<br>(58.24 | 4.73<br>4.43 | 12.03<br>11.77) | 1.46 (9H, s), 6.55 (1H, s), 7.10 (1H, s), 7.31 (1H, s), 7.44 (1H, dd, *J*=8.4, 4.2 Hz), 7.51 (1H, dd, *J*=8.4, 1.8 Hz), 8.33 (1H, dd, *J*=4.2, 1.8 Hz), 11.99 (1H, s) |
| **6s** | Br | CN | *tert*-Bu | 58, 81[c] | 188.5—190 | $C_{17}H_{16}BrN_3O_3$ | 52.32<br>(52.16 | 4.13<br>4.14 | 10.77<br>10.75) | 1.45 (9H, s), 6.58 (1H, s), 7.25 (1H, s), 7.30 (1H, s), 7.44 (1H, dd, *J*=8.4, 4.0 Hz), 7.50 (1H, dd, *J*=8.4, 1.8 Hz), 8.32 (1H, dd, *J*=4.0, 1.8 Hz), 12.05 (1H, s) |

*a*) From the corresponding benzoylpyridines **8**. *b*) Carried out using triethylamine as a base in EtOH under reflux, unless otherwise indicated. *c*) Carried out using pyrrolidine as a base in EtOH at −25 °C. *d*) *E* isomer. *e*) Carried out using pyrrolidine as a base in EtOH under reflux.



**8** **6** **7**

reagent: (a) $R_3ONH_2 \cdot HCl$, base, EtOH; (b) *m*-CPBA, $CHCl_3$.

Chart 7

Table 3. (*Z*)-3-Hydroxy-2-(2-hydroxy-α-*tert*-butoxyiminobenzyl)pyridine 1-oxides **7**

| Compd. | $R_1$ | $R_2$ | Yield[a] (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) | | | $^1$H-NMR (DMSO-$d_6$) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | |
| **7a** | Br | H | 85 | 235 (dec.) | $C_{16}H_{17}BrN_2O_4$<br>$\cdot 1/4H_2O$ | 49.78<br>(49.84 | 4.57<br>4.35 | 7.26<br>7.22) | 1.25 (9H, s), 6.84 (1H, d, *J*=8.8 Hz), 6.98 (1H, d, *J*=8.4 Hz), 7.07 (1H, d, *J*=2.6 Hz), 7.30—7.42 (1H, m), 7.91 (1H, d, *J*=5.8 Hz), 11.27 (1H, s) |
| **7b** | Cl | H | 84 | 278—280 | $C_{16}H_{17}ClN_2O_4$ | 57.06<br>(57.03 | 5.09<br>5.15 | 8.32<br>8.41) | 1.26 (9H, s), 6.86—6.94 (2H, m), 7.02 (1H, d, *J*=8.6 Hz), 7.29 (1H, dd, *J*=8.8, 2.8 Hz), 7.37 (1H, dd, *J*=8.6, 6.6 Hz), 7.95 (1H, d, *J*=6.6 Hz), 10.94 (1H, s), 11.09 (1H, s) |
| **7c** | Cl | F | 92 | 253—256 | $C_{16}H_{16}ClFN_2O_4$ | 54.17<br>(54.09 | 4.55<br>4.54 | 7.90<br>7.91) | 1.25 (9H, s), 6.90 (1H, d(br.)), 7.04 (1H, d, *J*=8.4 Hz), 7.08—7.13 (1H, m), 7.33—7.41 (1H, m), 7.96 (1H, d, *J*=6.0 Hz), 8.28 (1H, s) |
| **7d** | Br | F | 95 | 245 (dec.) | $C_{16}H_{16}BrFN_2O_4$ | 48.14<br>(47.93 | 4.04<br>4.17 | 7.02<br>7.31) | 1.25 ((9H, s), 6.89 (1H, d, *J*=10.4 Hz), 7.05 (1H, d, *J*=8.6 Hz), 7.22 (1H, d, *J*=8.0 Hz), 7.38 (1H, dd, *J*=8.6, 6.4 Hz), 7.97 (1H, d, *J*=6.4 Hz), 11.02 (1H, s), 11.67 (1H, s) |
| **7e**[b] | Br | F | 62 | 234—235 | $C_{16}H_{16}BrFN_2O_4$ | 48.14<br>(48.14 | 4.04<br>4.06 | 7.02<br>7.00) | 1.25 ((9H, s), 6.79 (1H, d, *J*=10.6 Hz), 7.18 (1H, d, *J*=8.4 Hz), 7.38—7.47 (2H, m), 8.04 (1H, d, *J*=6.2 Hz), 11.21 (1H, s), 11.74 (1H, s) |
| **7f** | Cl | Cl | 79 | 255—256.5 | $C_{16}H_{16}Cl_2N_2O_4$ | 51.77<br>(51.83 | 4.34<br>4.35 | 7.55<br>7.66) | 1.25 (9H, s), 7.04 (1H, d, *J*=8.8 Hz), 7.13 (1H, s), 7.20 (1H, s), 7.38 (1H, dd, *J*=8.8, 6.6 Hz), 7.97 (1H, d, *J*=6.6 Hz), 10.98 (1H, s), 11.49 (1H, s) |
| **7g** | Br | Cl | 84 | 244—247 | $C_{16}H_{16}BrClN_2O_4$ | 46.23<br>(45.85 | 3.88<br>3.85 | 6.74<br>7.14) | 1.26 (9H, s), 7.04 (1H, d, *J*=8.6 Hz), 7.12 (1H, s), 7.32 (1H, s), 7.38 (1H, dd, *J*=8.6, 6.4 Hz), 7.96 (1H, d, *J*=6.4 Hz), 11.02 (1H, s), 11.48 (1H, s) |
| **7h** | Cl | CN | 96 | 296 (dec.) | $C_{17}H_{16}ClN_3O_4$<br>$\cdot 1/5H_2O$ | 55.88<br>(55.77 | 4.52<br>4.40 | 11.50<br>11.43) | 1.25 (9H, s), 7.01—7.07 (1H, m), 7.34—7.45 (3H, m), 7.94—7.97 (1H, m) |
| **7i** | Br | CN | 94 | 284 (dec.) | $C_{17}H_{16}BrN_3O_4$ | 50.26<br>(50.13 | 3.97<br>3.87 | 10.34<br>10.46) | 1.26 (9H, s), 7.04 (1H, d, *J*=8.6 Hz), 7.34—7.42 (2H, m), 7.50 (1H, s), 7.96 (1H, d, *J*=6.0 Hz), 7.96 (1H, d, *J*=6.4 Hz), 11.01 (1H, s), 11.64 (1H, s) |

*a*) From the corresponding 2-(α-*tert*-butoxyiminobenzyl)pyridines **6**. *b*) *E* isomer.

substituents at C4 and/or C5 on the benzene ring ($R_1$, $R_2$) and oxime substituents ($R_3$) to afford the corresponding (*Z*)-oximes in sufficient yields (**6a**, **b**, **d**, **e**, **g**, **l**, **n**, **o**, and **s**).

The obtained 2-(α-alkoxyimino)benzylpyridines **6** were oxidized with *m*-CPBA to afford the pyridine *N*-oxides **7** in high yields (Chart 7 and Table 3).

## 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 30 mM TEA and 0.3 mM $BaCl_2$ were performed to identify potential $K^+$ channel openers. As described in the previous report,[8] 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 results are listed in Table 4 as $EC_{50}$ values and K ratio values for vasorelaxant activities.

Firstly, the effects of an oxime moiety were examined. The (*Z*)-*tert*-butyloxime of the 5-bromo derivative **6a** ($EC_{50}=0.68\,\mu M$, K ratio = 0.08) showed potent vasorelaxant activity based on $K^+$ channel opener action, but the corresponding (*E*)-isomer **6b** ($EC_{50}=20\,\mu M$) was much less active. The (*Z*)-iso-propyloxime **6c** ($EC_{50}=0.71\,\mu M$) was as active as the *tert*-butyloxime **6a**. Replacement of the *tert*-butyl substituent with less bulky groups such as cyclo-pentyl **6d** ($EC_{50}=11\,\mu M$), ethyl **6e** ($EC_{50}=7.8\,\mu M$), and *n*-butyl **6f** ($EC_{50}=4.8\,\mu M$) reduced the potency.

The effects of substituents on the benzene ring at the 5-position were also determined with compounds whose oxime moiety was fixed as the *tert*-butyl group. Compounds with a halogeno group showed strong vasorelaxant effects (**6a** and **6g** ($EC_{50}=0.59\,\mu M$)). Compounds with

Table 4. Vasorelaxant Activities and CBF Effects of **6** and **7**

| Compd. | Relaxation of rat aorta | | CBF effects in dog[c] | |
|---|---|---|---|---|
| | EC$_{50}$[a] ($\mu$M) | K ratio[b] | % increase | $T_{1/2}$ (min) |
| **6a** | 0.68 | 0.08 | 224 | 1.5 |
| **6b** | 20 | NT[d] | NT | NT |
| **6c** | 0.71 | 0.06 | 90 | 0.8 |
| **6d** | 11 | NT | 43 | 0.7 |
| **6e** | 7.8 | 0.10 | 46 | — |
| **6f** | 4.8 | NT | 63 | — |
| **6g** | 0.59 | 0 | 170 | 1.6 |
| **6h** | 14 | NT | 120 | 2.1 |
| **6i** | 5.3 | 0.12 | 81 | — |
| **6j** | 19 | NT | 117 | 1.8 |
| **6k** | 3.0 | 0.02 | 50 | — |
| **6l** | 2.3 | 0 | 48 | 1.1 |
| **6m** | 0.29 | 0 | 272 | 5.1 |
| **6n** | 0.13 | 0 | 318 | 4.5 |
| **6p** | 0.28 | 0 | 269 | 3.0 |
| **6q** | 0.44 | 0 | 168 | 4.7 |
| **6r** | 0.070 | 0 | 274[e] | 4.4 |
| **6s** | 0.056 | 0.09 | 298[e] | 6.2 |
| **7a** | 2.3 | 0 | 78 | 2.4 |
| **7b** | 2.9 | 0 | 129 | 7.3 |
| **7c** | 0.58 | 0 | 202 | 47.7 |
| **7d** | 0.28 | 0 | 223 | 29.8 |
| **7e** | >30 | NT | NT | NT |
| **7f** | 0.55 | 0 | 241 | 44.6 |
| **7g** | 0.62 | 0.07 | 205 | 29.5 |
| **7h** | 0.55 | 0.04 | 265[e] | 34.3 |
| **7i** | 0.21 | 0 | 366[e] | 42.9 |
| Levcromakalim | 0.17 | 0.02 | 275[e] | 5.2 |
| Nicorandil | 13 | NT | 223[f] | 0.9 |
| Diltiazem | 0.20 | 0.72 | 167[f] | 2.2 |
| Nitroglycerin | NT | NT | 157[e] | 0.4 |

*a*) Drug concentration required to relax the 30 mM TEA and 0.3 mM $BaCl_2$-induced contration 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*) Dose of compound: 30 $\mu$g/dog, i.c. *d*) Not tested. *e*) Dose of compound: 10 $\mu$g/dog, i.c. *f*) Dose of compound: 100 $\mu$g/dog, i.c.

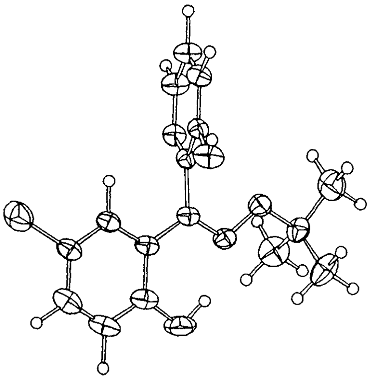


Fig. 1. Molecular Structure of **6a** as Determined by X-Ray Crystal Analysis

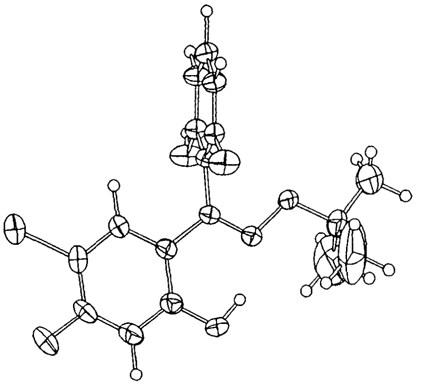


Fig. 2. Molecular Structure of **7d** as Determined by X-Ray Crystal Analysis

strong electron-withdrawing groups such as nitro and cyano groups showed decreased activity (**6h** (EC$_{50}$= 14 $\mu$M) and **6i** (EC$_{50}$=5.3 $\mu$M)). Introduction of electron-donating groups such as a methyl group also resulted in a decrease in activity (**6j** (EC$_{50}$=19 $\mu$M)). Thus, a halogeno group at C5 on the benzene ring was required for optimal vasorelaxant activity.

It is noteworthy that introduction of a halogeno or cyano group at C4 on the benzene ring in the 5-halogeno derivatives significantly enhanced the activity, despite the moderate activity of the 4-fluoro **6k** (EC$_{50}$=3.0 $\mu$M) or 4-chloro **6l** (EC$_{50}$=2.3 $\mu$M) derivative. In particular, 5-bromo-4-fluoro **6n** (EC$_{50}$=0.13 $\mu$M), 5-chloro-4-cyano **6r** (EC$_{50}$=0.070 $\mu$M), and 5-bromo-4-cyano **6s** (EC$_{50}$= 0.056 $\mu$M) derivatives showed greatly increased potency in comparison with the corresponding 5-halogeno derivatives (**6a** and **6g**). The corresponding 4,5-disubstituted benzylpyridine *N*-oxides (**7c**, **d**, and **f**—**i**) also showed potent vasorelaxant activity based on K$^+$ channel opener action (EC$_{50}$=0.21—0.62 $\mu$M, K ratio=0—0.04).

The prepared compounds were also tested for their effects on the coronary blood flow (CBF) upon intracoronary injection in anesthetized dogs. These results are summarized in Table 4 as means of maximum percentage increase and half-life periods ($T_{1/2}$ values) of the CBF effects. (*Z*)-3-Hydroxy-2-($\alpha$-*tert*-butoxyimino)-benzylpyridine derivatives **6a**, **g**, **m**, **n**, and **p**—**s**, which showed potent vasorelaxant activity, exhibited potent vasodilating effects. In particular, 5-halogeno-4-cyano derivatives (**6r**, **s**) increased the CBF to more than 250% of the basal flow at 10 $\mu$g/dog. In addition, conversion of the 4,5-disubstituted benzylpyridine derivatives, which showed highly potent vasodilating effects, to the corresponding pyridine *N*-oxides (**7**), especially 5-halogeno-4-cyano derivatives (**7h**, **i**), resulted in a significantly longer-lasting increase in the CBF as compared with levcromakalim ((3*S*,4*R*)-isomer of cromakalim **1**), nicorandil **2**, diltiazem, and nitroglycerin ($T_{1/2}$= 29.5—47.7 min).

The X-ray crystal structures of the 3-hydroxypyridine **6a** and the pyridine *N*-oxide **7d**, which showed potent K$^+$ channel opener activity, are illustrated in Figs. 1 and 2. Both pyridine rings were orthogonal to the plane of the benzene rings, as expected. These results suggested that the spatial orientation of benzopyran K$^+$ channel openers required for biological activity[14] could also apply to our (*Z*)-2-($\alpha$-*tert*-butoxyimino)benzylpyridine derivatives **6** and the corresponding pyridine *N*-oxides **7**, in spite of their quite different structural features.

Compound **7d** was also examined for oral hypotensive effects in conscious spontaneously hypertensive rats (SHRs). The time courses of changes in blood pressure and heart rate after oral administration of **7d** are shown in Fig. 3, along with those of levcromakalim for com-

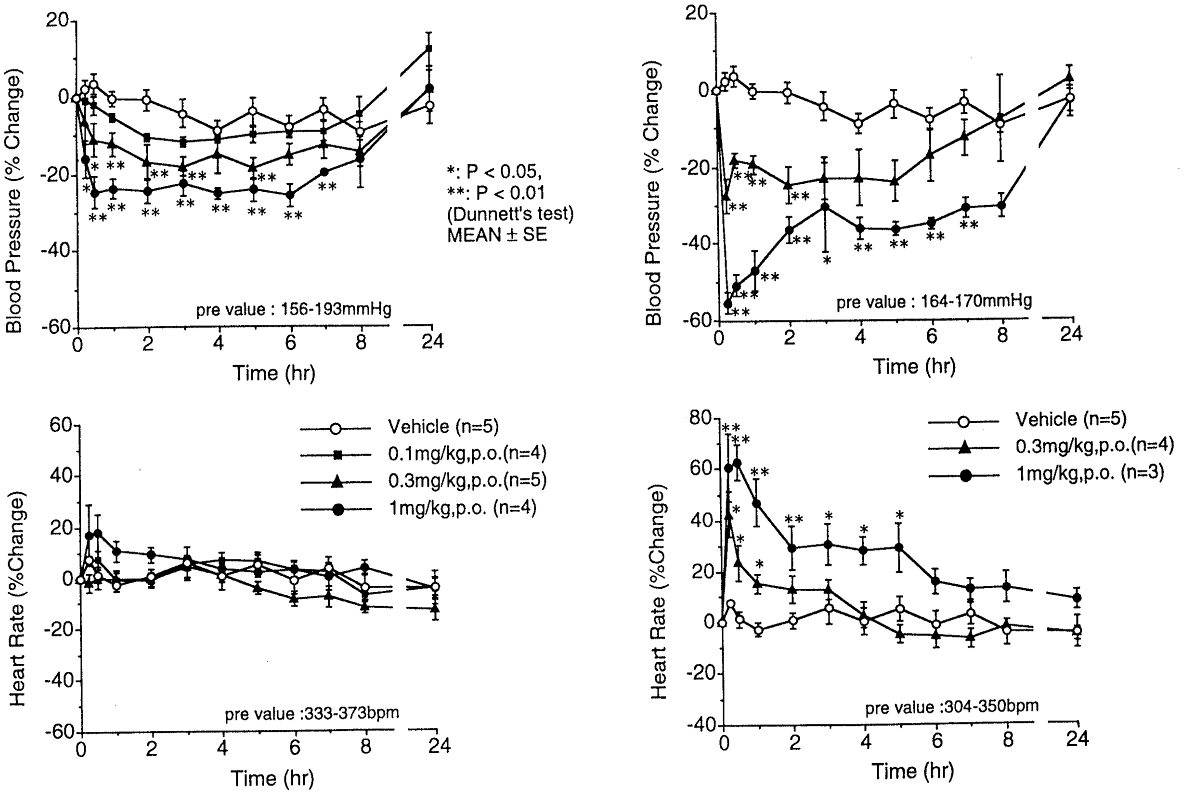


Fig. 3. Effects of Oral Administration of **7d** (Left) and Levcromakalim (Right) on Mean Blood Pressure (Top) and Heart Rate (Bottom) in Conscious SHRs

parison.[15)] Levcromakalim evoked a rapid decrease in blood pressure and subsequent significant reflex tachycardia soon after oral administration, while compound **7d** reduced blood pressure with slow onset of action and without causing reflex tachycardia. In addition, the stable hypotensive effects induced by **7d** (1 mg/kg) lasted over 7 h.

In summary, the search for novel $K^+$ channel openers with a non-benzopyran skeleton different from **1** has led to the discovery of a new series of (*Z*)-2-(α-alkoxyimino)benzylpyridines (**6** and **7**) synthesized by using a (*Z*)-dominant condensation reaction of benzoylpyridines **8** with *O*-alkylhydroxylamines in the presence of pyrrolidine, followed by *m*-CPBA oxidation.

The results of the structure–activity relationship study (SAR) of the (*Z*)-2-(α-alkoxyimino)benzylpyridines (**6** and **7**) may be summarized as follows. A bulky group as the oxime substituent, especially the *tert*-butyl group, showed the most potent activity based on $K^+$ channel opener action. A halogeno group at C5 on the benzene ring was required for the most potent vasorelaxant and vasodilating activities, though strongly electron-withdrawing groups such as nitro and cyano groups, showed the most potent activity in the previous $K^+$ channel openers with [6,6]-fused ring systems, represented by **1**. Moreover, introduction of a halogeno or cyano group at the 4-position enhanced the activities. In addition, the 4,5-disubstituted benzylpyridine *N*-oxides showed a significantly long-lasting increase in the coronary blood flow (CBF). (*Z*)-2-[5-Bromo-α-(*tert*-butoxyimino)-4-fluoro-2-hydroxybenzyl]-3-hydroxypyridine 1-oxide **7d**, one of the most active compounds, showed stable and long-lasting hypotensive effects without causing tachycardia in conscious SHRs.

## Experimental

All melting points were determined on a Yanagimoto micro melting 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 an internal standard, and coupling constants (*J*) are given in hertz (Hz). Elemental analyses were performed by Takeda Analytical Research Laboratories, Ltd. and results obtained were within ±0.4% of the theoretical values. Column chromatography was performed using silica gel (Merck Kieselgel 60, 70—230 mesh). When necessary, THF was distilled from sodium metal/benzophenone ketyl.

**1,5-Dibromo-2-methoxymethoxybenzene (9a)** Chloromethyl methyl ether (5 ml, 65.8 mmol) was added dropwise to a cooled (0 °C) solution of 2,4-dibromophenol (9.15 g, 53.2 mmol) and diisopropylethylamine (12.5 ml, 71.5 mmol) in $CH_2Cl_2$ (100 ml). After stirring at room temperature for 5 h, the reaction mixture was poured into water. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **9a** (15.43 g, 98%) as a colorless oil. $^1$H-NMR ($CDCl_3$) δ: 3.51 (3H, s), 5.23 (2H, s), 7.04 (1H, d, *J*=8.8 Hz), 7.35 (1H, dd, *J*=8.8, 2.6 Hz), 7.68 (1H, d, *J*=2.6 Hz).

Compounds **9b—e** were obtained similarly. **9b**; yield 97%. A colorless oil. $^1$H-NMR ($CDCl_3$) δ: 3.51 (3H, s), 5.22 (2H, s), 7.08 (1H, d, *J*=8.8 Hz), 7.22 (1H, dd, *J*=8.8, 2.4 Hz), 7.54 (1H, d, *J*=2.4 Hz). **9c**; yield 97%. A colorless oil. $^1$H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.52 (3H, s), 5.21 (2H, s), 7.01—7.06 (2H, m), 7.37 (1H, s). **9d**; yield 95%. A colorless oil. $^1$H-NMR ($CDCl_3$) δ: 3.52 (3H, s), 5.24 (2H, s), 6.58—6.70 (1H, m), 6.93 (1H, dd, *J*=10.4, 2.8 Hz), 7.47 (1H, dd, *J*=8.8, 6.2 Hz). **9e**; yield quant. A colorless oil. $^1$H-NMR ($CDCl_3$) δ: 3.51 (3H, s), 5.22 (2H, s), 7.27 (1H, s), 7.62 (1H, s).

**3-Hydroxy-2-(2-hydroxybenzoyl)pyridine (8a, b, e, f, and j) General Procedure for Method A** A solution of *n*-butyllithium in hexane (30 ml, 48 mmol) was added dropwise to a cooled (−78 °C) solution of 1,5-dibromo-2-methoxymethoxybenzene (**9a**, 12.17 g, 41.1 mmol) in diethyl ether (170 ml) under an argon atmosphere, and the mixture was stirred at this temperature for 1 h. 2-Cyano-3-trimethylsilyloxypyridine

(**10**, 8.13 g, 42.3 mmol) was added to the mixture at −78 °C. The whole was stirred with warming to room temperature for 3 h, then quenched with water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in 1 N HCl (60 ml) and ethanol (100 ml), and the mixture was stirred under reflux for 2 h, then evaporated to dryness. The residue was dissolved in ethyl acetate and this solution was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The obtained yellow crystals were washed with isopropyl ether to give **8a** (8.22 g, 68%).

The yields, melting points, elemental analyses, and $^1$H-NMR data of **8a**, **b**, **e**, **f**, and **j** are listed in Table 1.

**2-Methoxymethoxy-5-nitrobenzaldehyde (11a)** Chloromethyl methyl ether (17 ml, 224 mmol) was added dropwise to a cooled (0 °C) mixture of 5-nitrosalicylaldehyde (**19a**, 25.01 g, 150 mmol) and $K_2CO_3$ (20.70 g, 150 mmol) in *N*,*N*-dimethyl formamide (DMF) (150 ml). The reaction mixture was stirred at room temperature for 5 h, poured into water, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **11a** (28.51 g, 90%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.57 (3H, s), 5.43 (2H, s), 7.40 (1H, d, $J$=9.2 Hz), 8.42 (1H, dd, $J$=9.2, 2.8 Hz), 8.73 (1H, d, $J$=2.8 Hz), 10.50 (1H, s).

**5-Cyano-2-methoxymethoxybenzaldehyde (11b)** A mixture of 5-bromosalicylaldehyde (**19c**, 25.01 g, 124 mmol), cuprous cyanide (14.38 g, 145 mmol), and DMF (100 ml) was stirred under reflux under an argon atmosphere for 3 h. It was poured into a solution of ferric chloride hexahydrate (55.15 g) and concentrated HCl (13 ml) in water (160 ml). This mixture was stirred at room temperature for 30 min followed by extraction with ethyl acetate. The extract was washed successively with diluted HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Chloromethyl methyl ether (15 ml, 197 mmol) was added dropwise to a cooled (0 °C) mixture of the residue (**19b**), $K_2CO_3$ (27.53 g, 199 mmol), and DMF (200 ml). The whole was stirred at room temperature for 5 h, poured into water, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **11b** (10.39 g, 44%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.55 (3H, s), 5.38 (2H, s), 7.35 (1H, d, $J$=8.8 Hz), 7.79 (1H, dd, $J$=8.8, 2.0 Hz), 8.14 (1H, d, $J$=2.0 Hz), 10.45 (1H, s).

**5-Bromo-4-fluoro-2-methoxymethoxybenzylalcohol (26c)** Chloromethyl methyl ether (22 ml, 290 mmol) was added dropwise to a cooled (0 °C) mixture of 5-bromo-4-fluorosalicylic acid (**24c**, 40.16 g, 99.9 mmol) and $K_2CO_3$ (27.61 g, 200 mmol) in acetone (500 ml). After stirring at room temperature for 5 h, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. A solution of the residue in diethyl ether (300 ml) was cooled (0 °C) , and $LiAlH_4$ (3.81 g, 100 mmol) was added portionwise . Stirring was continued at room temperature for 30 min, then the reaction mixture was poured into water. The whole was stirred at room temperature for 30 min, then filtered through Celite, and the filtrate was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **26c** (24.01 g, 91%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 2.03 (1H, t, $J$=6.4 Hz), 3.48 (3H, s), 4.65 (2H, d, $J$=6.4 Hz), 5.20 (2H, s), 6.96 (1H, d, $J$= 10.4 Hz), 7.51 (1H, d, $J$=8.0 Hz).

Compounds **26a**, **b**, and **d** were obtained similarly. **26a**; yield 89%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 2.11 (1H, br s), 3.49 (3H, s), 4.67 (2H, s), 5.22 (2H, s), 6.99 (1H, dd, $J$=8.0, 1.8 Hz), 7.13 (1H, d, $J$= 1.8 Hz), 7.25 (1H, d, $J$=8.0 Hz). **26b**; yield 99%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 2.11 (1H, t, $J$=5.8 Hz), 3.49 (3H, s), 4.64 (2H, d, $J$=5.8 Hz), 5.19 (2H, s), 6.97 (1H, d, $J$=10.6 Hz), 7.36 (1H, d, $J$=8.2 Hz). **26d**; yield 83%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.48 (3H, s), 4.65 (2H, s), 5.20 (2H, s), 7.24 (1H, s), 7.58 (1H, s).

**4-Chloro-2-methoxymethoxybenzaldehyde (11c)** A mixture of 4-chloro-2-methoxymethoxybenzyl alcohol (**26c**, 14.69 g, 72.5 mmol), activated $MnO_2$ (41.03 g), and $CHCl_3$ (300 ml) was stirred at room temperature for 10 h. After removal of the $MnO_2$ by filtration, the filtrate was evaporated. The residue was purified by column chromatography to give **11c** (11.00 g, 76%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.54 (3H, s), 5.30 (2H, s), 7.07 (1H, dd, $J$=8.4, 1.6 Hz), 7.26 (1H, d, $J$= 1.6 Hz), 7.78 (1H, d, $J$=8.4 Hz), 10.42 (1H, s).

**3-Hydroxy-2-(2-hydroxybenzoyl)pyridine (8c, d, and g) General Procedure for Method B** (1) Coupling Reaction of **11** with **12**: A solution of *tert*-butyllithium in pentane (5.2 ml, 8.84 mmol) was added dropwise to a cooled (−78 °C) solution of 2-bromo-3-(2-trimethylsilylethoxymethoxy)pyridine (**12**, 1.21 g, 3.98 mmol) in THF (20 ml) under an argon atmosphere. After stirring at this temperature for 1 h, a solution of 2-methoxymethoxy-5-nitrobenzaldehyde (**11a**, 0.89 g, 4.22 mmol) in THF (20 ml) was added dropwise to the mixture. The whole was stirred with warming to room temperature for 3 h, then poured into water, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **20a** (0.91 g, 52%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: −0.09 (9H, s), 0.78 (2H, t, $J$=8.2 Hz), 3.25—3.52 (2H, m), 3.41 (3H, s), 5.06 (1H, d, $J$=7.2 Hz), 5.14 (1H, d, $J$=7.2 Hz), 5.28 (2H, s), 5.59 (1H, d, $J$=6.4 Hz), 6.25 (1H, d, $J$=6.4 Hz), 7.18 (1H, d, $J$=9.2 Hz), 7.26 (1H, dd, $J$=8.2, 4.8 Hz), 7.42 (1H, dd, $J$=8.2, 1.2 Hz), 7.98 (1H, d, $J$=2.8 Hz), 8.11 (1H, dd, $J$=9.2, 2.8 Hz), 8.30 (1H, dd, $J$=4.8, 1.2 Hz).

Compounds **20b** and **c** were obtained similarly. **20b**; yield 47%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: −0.07 (9H, s), 0.79 (2H, t, $J$=8.0 Hz), 3.24—3.55 (2H, m), 3.41 (3H, s), 5.04 (1H, d, $J$=7.2 Hz), 5.13 (1H, d, $J$=7.2 Hz), 5.26 (2H, s), 6.22 (1H, br.s), 7.16 (1H, d, $J$=8.8 Hz), 7.26 (1H, dd, $J$=8.4, 4.8 Hz), 7.31 (1H, d, $J$=2.2 Hz), 7.41 (1H, dd, $J$=8.4, 1.6 Hz), 7.49 (1H, dd, $J$=8.8, 2.2 Hz), 8.28 (1H, dd, $J$=4.8, 1.6 Hz). **20c**; yield 58%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: −0.09 (9H, s), 0.79 (2H, t, $J$=8.2 Hz), 3.25—3.55 (2H, m), 3.41 (3H, s), 5.06 (1H, d, $J$=7.2 Hz), 5.13 (1H, d, $J$=7.2 Hz), 5.28 (2H, s), 6.23 (1H, br s), 6.81—6.93 (2H, m), 7.37—8.08 (3H, m), 8.27 (1H, dd, $J$=4.8, 1.2 Hz).

(2) $MnO_2$ Oxidation and Subsequent Acidic Hydrolysis Reaction: A mixture of 2-(α-hydroxy-2-methoxymethoxy-5-nitrobenzyl)-3-(2-trimethylsilylethoxymethoxy)pyridine (**20a**, 9.23 g, 21.2 mmol), activated $MnO_2$ (20.31 g), and $CHCl_3$ (200 ml) was stirred at room temperature for 10 h. After removal of the $MnO_2$ by filtration, the filtrate was evaporated. The residue was dissolved in 1 N $H_2SO_4$ (40 ml) and acetone (150 ml), and the mixture was stirred under reflux for 3 h, then concentrated. The residue was dissolved in ethyl acetate. This solution was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The obtained yellow crystals were washed with isopropyl ether to give **8c** (4.37 g, 79%).

The yields, melting points, elemental analyses, and $^1$H-NMR data of **8c**, **d**, and **g** are listed in Table 1.

**5-Bromo-4-fluoro-2-methoxymethoxybenzylcyanide (13b)** Methanesulfonyl chloride (8.5 ml, 110 mmol) was added dropwise to a cooled (0 °C) solution of 5-bromo-4-fluoro-2-methoxymethoxybenzyl alcohol (**26c**, 24.10 g, 90.9 mmol) and triethylamine (18 ml, 129 mmol) in $CH_2Cl_2$ (300 ml). After stirring at room temperature for 5 h, the reaction mixture was poured into water. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Sodium cyanide (9.44 g, 187 mmol) was added portionwise to a cooled (0 °C) mixture of the residue, sodium iodide (14.67 g, 97.9 mmol), and DMSO (80 ml), and the whole was stirred at room temperature for 10 h, poured into water, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **13b** (18.68 g, 75%) as colorless crystals. mp 79—81 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 3.49 (3H, s), 3.64 (2H, s), 5.23 (2H, s), 7.01 (1H, d, $J$=9.8 Hz), 7.50 (1H, d, $J$=7.4 Hz).

Compounds **13a** and **c** were obtained similarly. **13a**; yield 86%. A colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.49 (3H, s), 3.64 (2H, s), 5.22 (2H, s), 7.02 (1H, d, $J$= 10.4 Hz), 7.38 (1H, d, $J$=8.0 Hz). **13c**; yield 91%. mp 76—77 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 3.50 (3H, s), 3.65 (2H, s), 5.23 (2H, s), 7.29 (1H, s), 7.59 (1H, s).

**3-Hydroxy-2-(2-hydroxybenzoyl)pyridine (8h, i, k, l, and m) General Procedure for Method C** (1) Coupling Reaction of **13** and **14**: A cooled (0 °C) mixture of 5-bromo-4-fluorobenzylcyanide (**13b**, 42.05 g, 153 mmol), 2-bromo-3-methoxymethoxypyridine (**14**, 33.51 g, 154 mmol), sodium *p*-toluenesulfinate ( 55.62 g, 312 mmol), and THF (600 ml) was treated portionwise with NaH (in oil, 13.02 g, 326 mmol), and the mixture was stirred under reflux under an argon atmosphere for 2 h. It was then poured into ice-water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The obtained colorless crystals were washed with isopropyl ether to give **22b** (54.71 g, 87%). mp 101—102 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 3.36 (3H, s), 3.39 (3H, s), 5.14 (1H, d, $J$=7.0 Hz), 5.18 (1H, d, $J$=7.0 Hz), 5.21 (1H, d, $J$=7.0 Hz), 5.25 (1H, d, $J$=7.0 Hz), 5.89 (1H, s), 6.98 (1H, d, $J$=10.0 Hz), 7.26 (1H, dd, $J$=8.4, 4.6 Hz), 7.47 (1H, dd, $J$=8.4, 1.4 Hz), 7.56 (1H, d, $J$=7.6 Hz), 8.28 (1H, dd, $J$=4.6, 1.4 Hz).

Compounds **22a** and **c** were obtained similarly. **22a**; yield 70%. mp 94—95 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.36 (3H, s), 3.39 (3H, s), 5.13 (1H, d, $J$=7.0 Hz), 5.17 (1H, d, $J$=7.0 Hz), 5.20 (1H, d, $J$=7.0 Hz), 5.24 (1H, d, $J$=7.0 Hz), 5.88 (1H, s), 6.99 (1H, d, $J$=10.6 Hz), 7.25 (1H, dd, $J$=8.4, 4.6 Hz), 7.41 (1H, d, $J$=8.2 Hz), 7.46 (1H, dd, $J$=8.4, 1.4 Hz), 8.28 (1H, dd, $J$=4.6, 1.4 Hz). **22c**; yield 73%. mp 144.5—146 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.35 (3H, s), 3.40 (3H, s), 5.10—5.27 (4H, m), 5.87 (1H, s), 7.20—7.32 (2H, m), 7.47 (1H, dd, $J$=8.4, 1.2 Hz), 7.62 (1H, s), 8.27 (1H, dd, $J$=4.6, 1.2 Hz).

(2) Oxidative Decyanation Reaction: A mixture of 2-(5-bromo-α-cyano-4-fluoro-2-methoxymethoxybenzyl)-3-methoxymethoxypyridine (**22b**, 1.0 g, 2.43 mmol), $K_2CO_3$ (0.34 g, 2.46 mmol), water (5 ml), and DMSO (25 ml) was stirred at room temperature under an oxygen atmosphere for 2.5 d. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **23b** (0.95 g, 98%) as colorless crystals. mp 59—60.5 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.20 (3H, s), 3.45 (3H, s), 4.82 (2H, s), 5.20 (2H, s), 6.96 (1H, d, $J$=10.2 Hz), 7.33 (1H, dd, $J$=8.6, 4.6 Hz), 7.57 (1H, dd, $J$=8.6, 1.4 Hz), 7.99 (1H, d, $J$=7.8 Hz), 8.24 (1H, dd, $J$=4.6, 1.4 Hz).

Compounds **23a** and **c** were obtained similarly. **23a**; yield 96%. mp 81—82 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.21 (3H, s), 3.45 (3H, s), 4.82 (2H, s), 5.21 (2H, s), 6.99 (1H, d, $J$=10.6 Hz), 7.34 (1H, dd, $J$=8.6, 4.6 Hz), 7.59 (1H, dd, $J$=8.6, 1.2 Hz), 7.86 (1H, d, $J$=8.4 Hz), 8.25 (1H, dd, $J$=4.6, 1.2 Hz). **23c**; yield 93%. mp 70—72 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.20 (3H, s), 3.45 (3H, s), 4.83 (2H, s), 5.21 (2H, s), 7.27 (1H, s), 7.34 (1H, dd, $J$=8.6, 4.6 Hz), 7.58 (1H, dd, $J$=8.6, 1.2 Hz), 7.98 (1H, d, $J$=7.8 Hz), 8.24 (1H, dd, $J$=4.6, 1.2 Hz).

(3) Acidic Hydrolysis Reaction: A mixture of 2-(5-bromo-4-fluoro-2-methoxymethoxybenzoyl)-3-methoxymethoxypyridine (**23b**, 25.24 g, 63.1 mmol), 1 N $H_2SO_4$ (30 ml), and acetone (200 ml) was stirred under reflux for 5 h. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The solution was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The obtained yellow crystals were washed with isopropyl ether to give **8i** (18.33 g, 93%).

The yields, melting points, elemental analyses, and $^{1}$H-NMR data of **8h**, **i**, **k**, **l**, and **m** are listed in Table 1.

**2-(5-Bromo-4-cyano-2-methoxymethoxybenzoyl)-3-methoxymethoxypyridine (23e)** A mixture of 2-(5-bromo-4-fluoro-2-methoxymethoxybenzoyl)-3-methoxymethoxypyridine (**23b**, 45.14 g, 113 mmol), KCN (24.00 g, 359 mmol), and DMSO (300 ml) was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **23e** (41.51 g, 85%) as colorless crystals. mp 77—78 °C. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.22 (3H, s), 3.48 (3H, s), 4.89 (2H, s), 5.25 (2H, s), 7.38 (1H, dd, $J$=8.6, 4.4 Hz), 7.45 (1H, s), 7.56—7.68 (1H, m), 7.87 (1H, s), 8.23 (1H, dd, $J$=4.4, 1.0 Hz).

Compound **23d** was obtained similarly. **23d**; yield 25%. $^{1}$H-NMR ($CDCl_3$) $\delta$: 3.23 (3H, s), 3.49 (3H, s), 4.89 (2H, s), 5.26 (2H, s), 7.40 (1H, dd, $J$=8.6, 4.2 Hz), 7.47 (1H, s), 7.58—7.67 (1H, m), 7.73 (1H, s), 8.22—8.28 (1H, m).

**(*Z*)-2-[5-Bromo-α-(*tert*-butoxyimino)-2-hydroxybenzyl]-3-hydroxypyridine (6a) and (*E*)-2-[5-Bromo-α-(*tert*-butoxyimino)-2-hydroxybenzyl]-3-hydroxypyridine (6b) General Procedure for 2-(α-Alkoxyimino-2-hydroxybenzyl)-3-hydroxypyridines (6) *via* the Stereoselective Condensation Reaction** A solution of pyrrolidine (0.43 ml, 5.15 mmol) in ethanol (1 ml) was added dropwise to a cooled (−78 °C) mixture of 2-(5-bromo-2-hydroxybenzoyl)-3-hydroxypyridine (**8a**, 0.50 g, 1.70 mmol) and *O-tert*-butylhydroxylamine hydrochloride (0.32 g, 2.55 mmol) in ethanol (5 ml). The reaction mixture was stirred at −25 °C for 8 h, poured into water, and extracted with ethyl acetate. The organic layer was washed successively with 1 N HCl and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **6a** (0.48 g, 78%) and **6b** (0.043 g, 7%).

The yields, melting points, elemental analyses, and $^{1}$H-NMR data of (*Z*)-2-(α-alkoxyimino-2-hydroxybenzyl)-3-hydroxypyridines (**6d**, **e**, **g**, **l**, **n**—**p**, and **s**) synthesized by a method similar to that used for **6a** and **6b** are listed in Table 2.

**(*Z*)-2-[5-Bromo-α-(*tert*-butoxyimino)-2-hydroxybenzyl]-3-hydroxypyridine (6a) and (*E*)-2-[5-Bromo-α-(*tert*-butoxyimino)-2-hydroxybenzyl]-3-hydroxypyridine (6b)** A mixture of 2-(5-bromo-2-hydroxybenzoyl)-3-hydroxypyridine (**8a**, 0.68 g, 2.31 mmol), *O-tert*-butylhydroxylamine hydrochloride (0.44 g, 3.51 mmol), triethylamine (2.0 ml, 14.3 mmol), and ethanol (10 ml) was stirred under reflux for 5 h and then poured into water. The organic layer was washed successively with 1 N HCl and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography to give **6a** (0.58 g, 69%) and **6b** (0.19 g, 22%).

The yields, melting points, elemental analyses, and $^{1}$H-NMR data of (*Z*)-2-(α-alkoxyimino-2-hydroxybenzyl)-3-hydroxypyridines (**6a**—**c**, **f**, **i**—**k**, and **m**—**s**) synthesized by a method similar to that used for **6a** and **6b** are listed in Table 2.

**(*Z*)-2-[5-Bromo-α-(*tert*-butoxyimino)-4-fluoro-2-hydroxybenzyl]-3-hydroxypyridine 1-Oxide (7d) General Procedure for (*Z*)-2-(α-Alkoxyimino-2-hydroxybenzyl)-3-hydroxypyridine 1-Oxides (7)** A mixture of (*Z*)-2-[5-bromo-α-(*tert*-butoxyimino)-4-fluoro-2-hydroxybenzyl]-3-hydroxypyridine (**6n**, 17.13 g, 44.7 mmol), 70% *m*-CPBA (22.31 g, 90.5 mmol), and $CHCl_3$ (600 ml) was stirred at room temperature for 11 h followed by addition of aqueous $NaHSO_3$. The whole was stirred for 1 h, then the obtained organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The obtained colorless crystals were washed with ethyl acetate to give **7d** (16.95 g, 95%).

The yields, melting points, elemental analyses, and $^{1}$H-NMR data of (*Z*)-2-(α-alkoxyimino-2-hydroxybenzyl)-3-hydroxypyridine *N*-oxides **7** are listed in Table 3.

**Single-Crystal X-Ray Analysis of 6a** Crystals of **6a** were grown from ethanol and subjected to crystallographic analyses. The crystal belonged to the monoclinic space group $P2_{1/n}$ with the following unit cell parameters; $a$=9.006(1) Å, $b$=16.453(1) Å, $c$=12.081(1) Å, $\beta$=103.78(1)°, $V$=1738.5(1) Å$^3$, $Z$=4. The final R-factor and weighted R-factor were 0.065 and 0.067, respectively.

**Single-Crystal X-Ray Analysis of 7d** Crystals of **7d** were grown from ethanol and subjected to crystallographic analyses. The crystal belonged to the monoclinic space group $P2_{1/n}$ with the following unit cell parameters; $a$=11.178(1) Å, $b$=17.630(1) Å, $c$=9.396(1) Å, $\beta$=112.69(1)°, $V$=1708.2(2) Å$^3$, $Z$=4. The final R-factor and weighted R-factor were 0.063 and 0.067, respectively.

***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 113.1 mM NaCl, 4.6 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 3.5 mM $NaH_2PO_4$, 21.9 mM $NaHCO_3$ and 10 mM 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** Tetraethylammonium chloride (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), a screening compound was added cumulatively (3, 10 and 30 $\mu$M). Similar experiments were performed using 80 mM KCl instead of TEA and $BaCl_2$.

**Coronary Blood Flow Measurement in Anesthetized Dogs** Male beagle dogs (10—12 kg) were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and the chest was opened to expose the heart under artificial ventilation. An exteriorized circulation pathway between the left carotid artery and the left circumflex of the heart was made to measure coronary flow by means of an electromagnetic probe attached to it. All data were input to a computer *via* an A/D converter for data analysis. The test compounds were dissolved in saline containing polyethylene glycol 400 (50%) except for diltiazem (in saline), and were injected into the pathway at 0.1 ml/kg volume.

**Blood Pressure Measurement in SHR** Male spontaneously hypertensive rats (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% gum arabic solution and administered orally in a volume of 2 ml/kg.

**Acknowledgements** We wish to thank Drs. K. Meguro, A. Nagaoka, T. Naka, and K. Nishikawa for their encouragement and helpful discussions throughout this work. We thank S. Fujiwara for the biological assays, and A. Fujishima for X-ray crystallographic analyses.

## References

1) Cook N. S.(ed.), "Potassium Channels, Structure, Classification, Function and Therapeutic Potential," Ellis Horwood Ltd., Chichester, 1990.
2) Kolb H. A., *Rev. Physiol. Biochem. Pharmacol.*, **15**, 51—79 (1990).
3) Cook N. S., *Trends Pharmacol. Sci.*, **9**, 21—28 (1988).
4) Anderson K-E., *Pharmacol. Toxicol.*, **70**, 244—254 (1992).
5) Edwards G., Weston A. H., *Trends Pharmacol. Sci.*, **11**, 417—422 (1990).
6) Buckingham R. E., Clapham J. C., Hamilton T. C., Longman S. D., Norton J., Poyser R. H., *J. Cardiovasc. Pharmacol.*, **8**, 798—804 (1986).
7) *a*) Smith D. G., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 3187—3191; *b*) Burrel G., Cassidy F., Evans J. M., Lightowler D., Stemp G., *J. Med. Chem.*, **33**, 3023—3027 (1990); *c*) Ashwood V. A., Cassidy F., Evans J. M., Gagliardi S., Stemp G., *ibid.*, **34**, 3261—3267 (1991); *d*) Buckle D. R., Eggleston D. S., Houge-Frydrych C. S. V., Pinto I., Readshaw S. A., Smith D. G., Webster R. A. B., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2763—2771; *e*) Buckle D. R., Arch J. R. S., Edge C., Foster K. A., Houge-Frydrych C. S. V., Pinto I., Smith D. G., Taylor J. F., Taylor S. G., Tedder J. M., Webster R. A. B., *J. Med. Chem.*, **33**, 919—926 (1991); *f*) Sanfilippo P. J., McNally J. J., Press J. B., Fitzpatrick L. J., Urbanski M. J., Katz L. B., Giardino E., Falotico R., Salata J., Moore J. B., Miller W., *ibid.*, **35**, 4425—4433 (1992); *g*) Almansa C., Gómez L. A., Cavalcanti F. L., Rodríguez R., Carceller E., Bartrolí J., García-Rafanel J., Forn J., *ibid.*, **36**, 2121—2133 (1993).
8) Yamamoto S., Hashiguchi S., Miki S., Igata Y., Watanabe T., Shiraishi M., *Chem. Pharm. Bull.*, **44**, 734—745 (1996).
9) Vorbrüggen H., Krolikiewicz K., *Synthesis*, **1983**, 316—319.
10) *a*) Marsais F., Le Nard G., Quéguiner G., *Synthesis*, **1982**, 235—237; *b*) Comins D. L., La Munyon D. H., *Tetrahedron Lett.*, **29**, 773—776 (1988); *c*) Sengupta S., Snieckus V., *ibid.*, **31**, 4267—4270 (1990).
11) Miyashita A., Suzuki Y., Ohta K., Higashino T., *Heterocycles*, **39**, 345—356 (1994).
12) Selikson S. J., Watt D. S., *J. Org. Chem.*, **40**, 267—268 (1975) and references cited therein.
13) *a*) Bradshaw J. S., South J. A., Hales R. H., *J. Org. Chem.*, **37**, 2381—2383 (1972); *b*) Idoux J. P., Gupton J. T., McCurry C. K., Crews A. D., Jurss C. D., Colon C., Rampi R. C., *ibid.*, **48**, 3771—3773 (1983) and references cited therein.
14) *a*) Cassidy F., Evans J. M., Smith D. M., Stemp G., Edge C., Williams D. J., *J. Chem. Soc., Chem. Commun.*, **1989**, 377—378; *b*) Thomas W. A., Whitcombe I. W. A., *ibid.*, **1990**, 528—529; *c*) Gericke R., Harting J., Leus I., Schittenhelm C., *J. Med. Chem.*, **34**, 3074—3085 (1991).
15) Kusumoto K., Awane Y., Kitayoshi T., Fujiwara S., Hashiguchi S., Terashita Z., Shiraishi M., Watanabe T., *J. Cardiovasc. Pharmacol.*, **24**, 929—936 (1994).