1,4:3,6-Dianhydrohexitol Nitrate Derivatives. II.[1] Synthesis and Antianginal Activity of Aryl- or Arylcarbonylpiperazine Derivatives[2]

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A series of 5-(4-aryl- or 4-arylcarbonylpiperazin-1-yl)-5-deoxy-1,4:3,6-dianhydro-L-iditol 2-nitrates was prepared in order to obtain orally active, nitrate-type vasodilators with reduced side effects. Our drug design was based on a small reduction in the lipophilicity compared to that of 5-deoxy-5-[4-(3-phenylthiopropyl)piperazin-1-yl]-1,4:3,6-dianhydro-L-iditol 2-nitrate (1, KF14124). Compounds 4h (aryl = benzimidazol-2-yl), 4i (arylcarbonyl = nicotinoyl), and 4w (arylcarbonyl = 3-furoyl) showed potent anti-ischemic activity in a lysine-vasopressin-induced angina pectoris model (rats), and their structure–activity relationships are discussed. Compound 4i exhibited potent vasodilation of the coronary artery in anesthetized dogs and also exhibited potent preload reducion in a heart failure model (dogs) as compared with isosorbide dinitrate (2), nicorandil (3), and KF14124 (1). Furthermore, 4i showed much weaker acute lethal toxicity and less central nervous system depression than 1 in mice. Thus, 4i (KW-3196) is under development as a vasodilator and a drug for treating angina pectoris.

Keywords nitrate; dianhydrohexitol; vasodilator; heart failure; angina pectoris; cyclic guanosine monophosphate

Over 100 years after their discovery, organic nitrates are still in widespread use for the treatment of acute and chronic ischemic heart diseases as well as congestive heart failure. As might be expected from the similarity of their chemical structures, all organic nitrates share common pharmacological properties, including the basic mechanism of action.[3] However, it seems that mechanistic differences do exist among various members of this group of compounds.[3,4] Differences in chemical structures also have obvious consequences for the pharmacokinetic behavior of the organic nitrates, a fact that is of great clinical importance.[4] In the previous paper,[1] we reported that a new nitrate derivative, 5-deoxy-5-[4-(3-phenylthiopropyl)piperazin-1-yl]-1,4:3,6-dianhydro-L-iditol 2-nitrate (**1**, KF14124), exhibited better oral antianginal activity than isosorbide dinitrate (**2**, ISDN) or nicorandil (**3**). However, **1** (KF14124) also showed several critical side effects such as relatively potent acute lethal toxicity (minimum lethal dose = 200 mg/kg, *p.o.*) and central nervous system (CNS) depression (50—100 mg/kg, *p.o.*). Thus, the aim of the present work was to screen compounds comparable to **1** in overall pharmacological profile, but with reduced side effects. Structure–activity relationships of **1** indicated that the phenylthiopropyl group flanking the piperazinyl sugar was not an absolute requirement for good antianginal activity and this moiety could be replaced by a number of less lipophilic substituents such as five- or six-membered heterocycles. Decreasing the lipophilicity of compounds is expected to change their pharmacokinetics and to suppress their CNS penetration. Thus, our drug design was based on a small reduction in the lipophilicity compared to that of **1**. This paper describes the synthesis of a series of 4-aryl- and 4-arylcarbonylpiperazine derivatives (**4**) and the

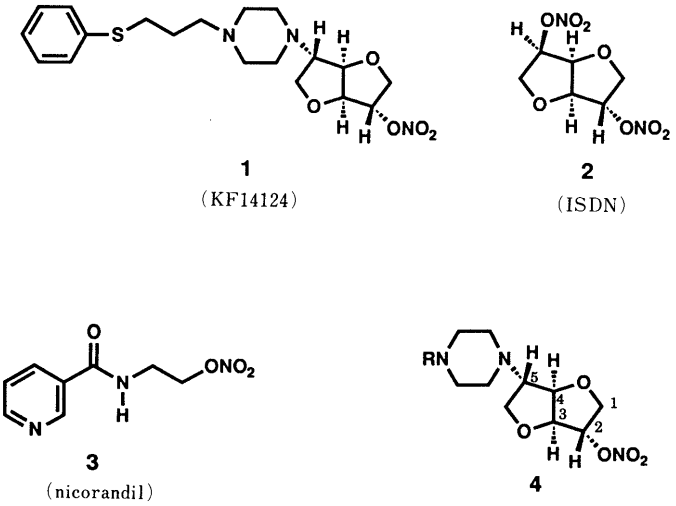


Chart 1

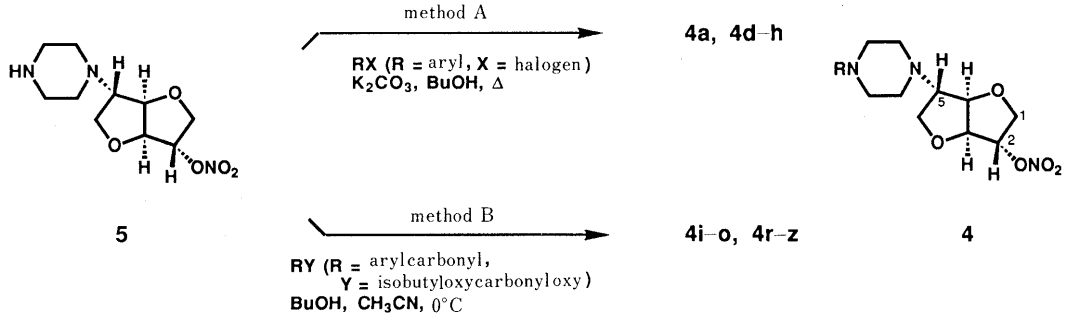


Chart 2

evaluation of their oral antianginal activity along with their acute lethal toxicity.[5]

Chemistry The general method for preparation of compounds is shown in Chart 2. An easily available nitrate **5**[6,7] was treated with aryl halide under a basic condition to afford the target compounds **4a** and **4d**—**h** (method A). On the other hand, treatment of **5** with mixed anhydrides of aryl carboxylic acid and isobutyl chloroformate gave **4i**—**o** and **4r**—**z** (method B).

Compound **4b**, having a 2-methoxylphenyl substituent, was prepared by reaction of 5-amino-5-deoxy-1,4:3,6-dianhydro-L-iditol 2-nitrate (**6**)[7] with *N*,*N*-bis(chloroethyl)-2-methoxyaniline (Chart 3).

The target compounds can be obtained alternatively by nitration of polyol derivatives into which R has already

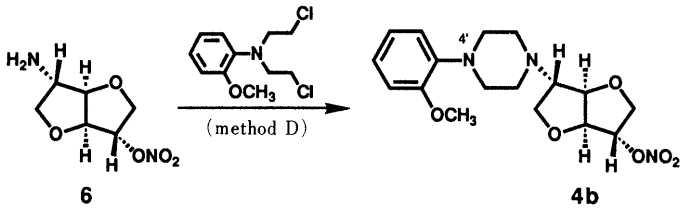


Chart 3

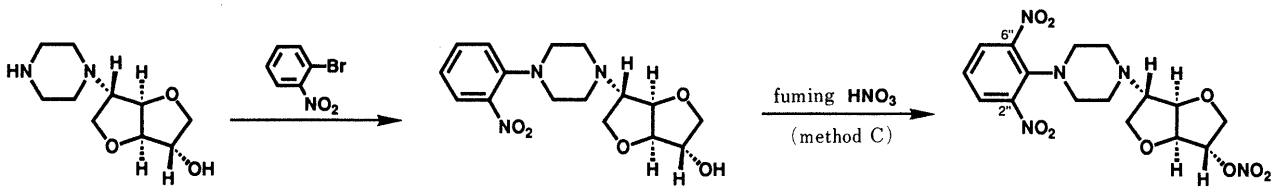


Chart 4

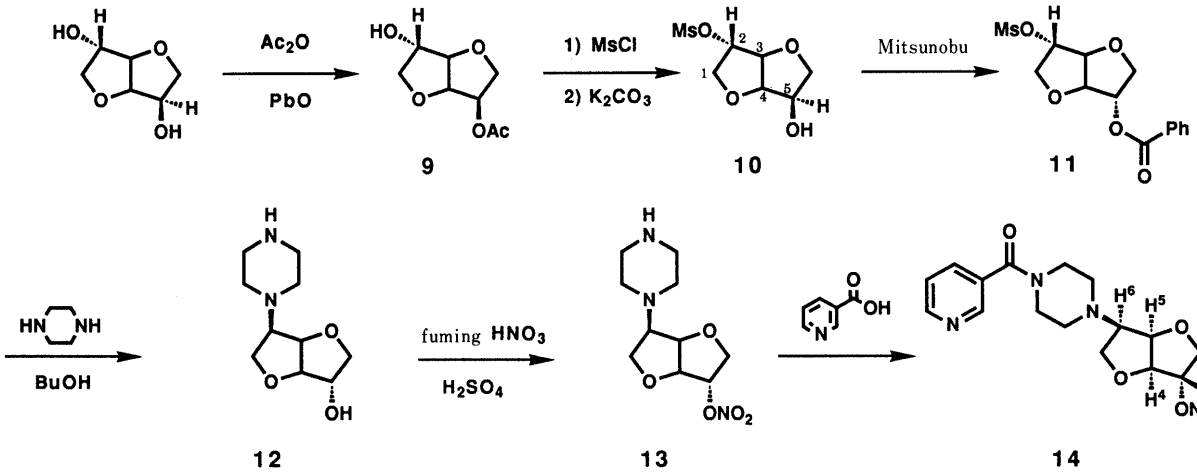


Chart 5

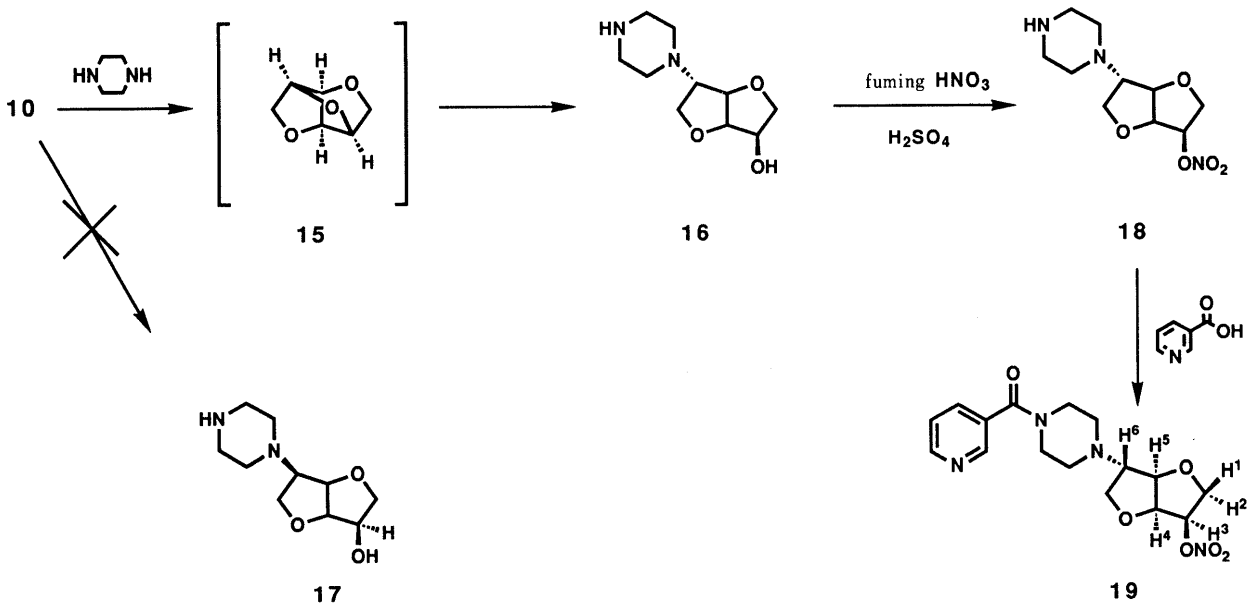
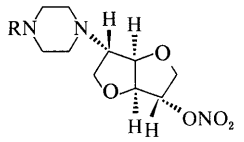


Chart 6

TABLE I. Physical Properties of Aryl-Type Compounds



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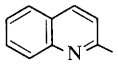
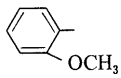
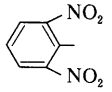
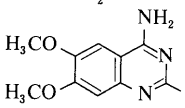
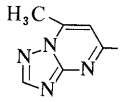
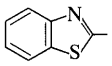
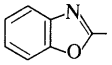
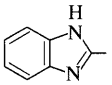
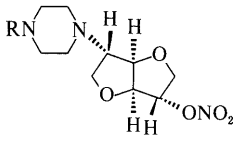
Compd.	R	Yield (%)	Method[a]	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
4a		17	A	219	$C_{19}H_{22}N_4O_5 \cdot 2HCl \cdot H_2O$[b]	47.80	5.48	11.73	47.40	5.21	11.74
4b		40	C	202.1—207.3	$C_{17}H_{23}N_3O_6 \cdot 2HCl \cdot 0.5H_2O$[c]	45.64	5.85		45.41	5.71	
4c		6	D	204.5—205.0	$C_{16}H_{19}N_5O_9 \cdot HCl \cdot 0.3H_2O$[d]	41.13	4.44	14.99	41.30	4.44	14.59
4d		59	A	253—261	$C_{20}H_{26}N_6O_7 \cdot 3HCl \cdot 0.5H_2O$[e]	41.35	5.20	14.46	41.11	5.49	14.38
4e		49	A	228.0—230.0	$C_{16}H_{21}N_7O_5 \cdot 2HCl \cdot 0.5H_2O$[f]	40.60	5.11	20.71	40.39	5.32	20.55
4f		18	A	225.0—229.5	$C_{17}H_{20}N_4O_5S \cdot 2HCl \cdot 0.5H_2O$[g]	43.04	4.89	11.81	43.17	4.79	11.42
4g		28	A	232.3—232.9	$C_{17}H_{20}N_4O_6 \cdot 2HCl \cdot 0.5H_2O$[h]	44.55	5.05	12.22	44.50	5.27	12.06
4h		34	A	223—227	$C_{17}H_{21}N_5O_5 \cdot 2HCl \cdot H_2O$[i]	43.79		15.02	43.76		14.68

a) After purification by silica gel chromatography, the evaporation residue was dissolved in $CHCl_3$ followed by addition of 10 ml of ethyl acetate saturated with HCl gas. The resulting precipitate was collected by filtration, washed with ethyl acetate, and dried to afford an analytical sample. *b*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{19}H_{23}N_4O_5$: 387.1668. Found: 387.1675. *c*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{24}N_3O_6$: 366.1665. Found: 366.1639. *d*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{20}N_5O_9$: 426.1261. Found: 426.1261. *e*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{20}H_{27}N_6O_7$: 463.1941. Found: 463.1951. *f*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{22}N_7O_5$: 392.1682. Found: 392.1692. *g*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{21}N_4O_5S$: 393.1233. Found: 393.1252. *h*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{21}N_4O_6$: 377.1461. Found: 377.1464. *i*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{22}N_5O_5$: 376.1621. Found: 376.1633.

TABLE II. Physical Properties of Arylcarbonyl-Type Compounds



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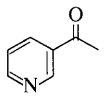
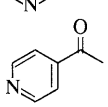
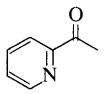
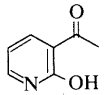
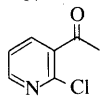
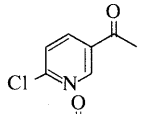
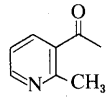
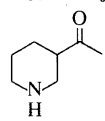
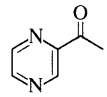
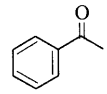
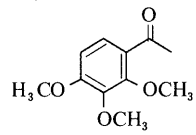
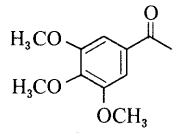
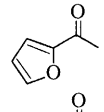
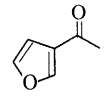
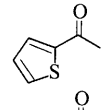
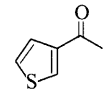
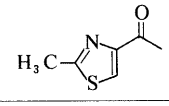
Compd.	R	Yield (%)	Method	mp (°C)[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
4i		41	B	176.0—180.0	$C_{16}H_{20}N_4O_6 \cdot 2HCl$	40.45	5.56	11.79	40.57	5.53	11.45
4j		24	B	164—168	$C_{16}H_{20}N_4O_6 \cdot 2HCl \cdot 2H_2O$[b]	40.60	5.53	11.83	40.45	5.68	11.52
4k		35	B	168—169	$C_{16}H_{20}N_4O_6 \cdot 2HCl \cdot 2.5H_2O$[c]	39.84	5.64	11.61	39.72	5.36	11.49

TABLE II. (continued)

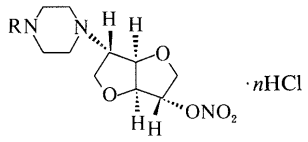
Compd.	R	Yield (%)	Method	mp (°C)[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
4l		32	B	Hygroscopic	$C_{16}H_{20}N_4O_7 \cdot HCl \cdot 3H_2O$[d]	40.81	5.77	11.89	40.96	5.80	11.79
4m		73	B	Hygroscopic	$C_{16}H_{19}ClN_4O_6 \cdot 2HCl$	40.73	4.48	11.87	40.60	4.54	11.51
4n		64	B	145—146	$C_{16}H_{19}ClN_4O_6 \cdot HCl \cdot H_2O$[e]	42.39	4.89	12.36	42.03	4.67	12.02
4o		84	B	188—189	$C_{17}H_{22}N_4O_6 \cdot 2HCl \cdot 3H_2O$[f]	40.40	5.98	11.08	40.16	5.31	10.30
4q		78	E	160—(dec.)	$C_{16}H_{26}N_4O_6 \cdot 2HCl \cdot 1.5H_2O$[g]	40.85	6.64	11.91	40.62	6.68	11.54
4r		91	B	164	$C_{15}H_{19}N_5O_6 \cdot HCl \cdot 1.5H_2O$[h]	42.01	5.41	16.33	42.02	5.11	15.97
4s		85	B	200—(dec.)	$C_{17}H_{21}N_3O_6 \cdot HCl \cdot 0.5H_2O$[i]	49.94	5.67	10.27	50.27	5.72	10.29
4t		42	B	152.0—152.5	$C_{20}H_{27}N_3O_9 \cdot HCl$	49.03	5.76	8.57	48.67	5.97	8.27
4u		41	B	65	$C_{20}H_{27}N_3O_9 \cdot HCl \cdot H_2O$[j]	47.29	5.95	8.27	47.14	6.06	8.21
4v		31	B	183—185	$C_{15}H_{19}N_3O_7 \cdot HCl \cdot H_2O$[k]	44.17	5.43	10.30	43.99	5.34	10.07
4w		50	B	213—217	$C_{15}H_{19}N_3O_7 \cdot HCl \cdot 0.3H_2O$[l]	45.59	5.25	10.63	45.61	5.47	10.53
4x		70	B	180—196	$C_{15}H_{19}N_3O_6S \cdot HCl$	44.39	4.97	10.35	44.53	4.98	10.13
4y		56	B	198—200	$C_{15}H_{19}N_3O_6S \cdot HCl$	44.39	4.96	10.35	44.21	5.04	10.18
4z		29	B	87.0—88.0	$C_{15}H_{20}N_4O_6S \cdot HCl \cdot 1.8H_2O$[m]	39.75	5.47		39.97	5.27	

a) See footnote *a* in Table I. *b*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{21}N_4O_6$: 365.1461. Found: 365.1472. *c*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{21}N_4O_6$: 365.1461. Found: 365.1477. *d*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{21}N_4O_7$: 381.1411. Found: 381.1422. *e*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{20}ClN_4O_6$: 399.1072 (^{35}Cl). Found: 399.1077 (^{35}Cl). *f*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{23}N_4O_6$: 379.1618. Found: 379.1647. *g*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{16}H_{27}N_4O_6$: 371.1931. Found: 371.1916. *h*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{15}H_{20}N_5O_6$: 366.1413. Found: 366.1422. *i*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{17}H_{22}N_3O_6$: 364.1509. Found: 364.1511. *j*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{20}H_{28}N_3O_9$: 454.1825. Found: 454.1828. *k*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{15}H_{20}N_3O_7$: 354.1301. Found: 354.1317. *l*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{15}H_{20}N_3O_7$: 354.1301. Found: 354.1292. *m*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{15}H_{21}N_4O_6S$: 385.1182. Found: 385.1176.

been introduced (Chart 4). Compound **8**, prepared by reaction of **7** with *o*-bromonitrobenzene, was nitrated with fuming HNO_3 to afford **4c**, in which a phenyl group is also nitrated at the 6″-position.

Compound **4p**, in which the N atom of the piperizine ring was protected with a *tert*-butyloxycarbonyl (*t*-Boc) group, was obtained according to the procedure described in Chart 2, and then deprotected with HCl to afford **4q**.

TABLE III. Spectral Data for Compounds **4**



4

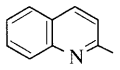
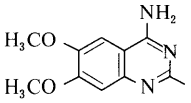
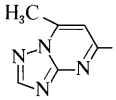
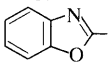
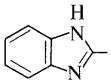
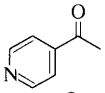
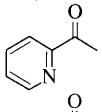
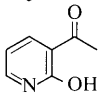
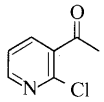
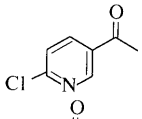
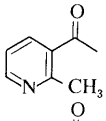
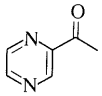
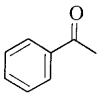
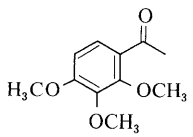
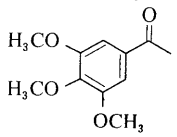
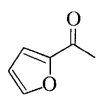
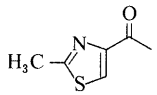
Compd. No.	R	IR (KBr) ν (cm^{-1})	MS m/z (M^+)	^{1}H-NMR (DMSO-d_6) δ (J=Hz)
4a		2960, 2360, 1644, 1276	386	8.47 (1H, d, J=9.6), 8.29 (1H, d, J=7.3), 7.94 (1H, d, J=7.3), 7.79 (1H, t, J=7.3), 7.59 (1H, d, J=9.6), 7.51 (1H, t, J=7.3), 5.45 (1H, m), 5.33 (1H, m), 4.89 (1H, m), 2.8—5.0 (13H, m)
4d		3170, 2570, 1640, 1595, 1276	462	9.04 (1H, br s), 8.74 (1H, br s), 7.80 (1H, s), 7.68 (1H, s), 5.45 (1H, m), 5.30 (1H, m), 4.87 (1H, m), 3.88 (3H, s), 3.86 (3H, s), 3.0—4.3 (13H, m)
4e		2522, 1673, 1638, 1538, 1277	391	8.80 (1H, s), 7.27 (1H, s), 5.45 (1H, m), 5.34 (1H, m), 4.88 (1H, m), 3.1—5.6 (13H, m), 2.66 (3H, s)
4g		3024, 2360, 1733, 1640, 1280	376	7.47 (1H, d, J=7.8), 7.37 (1H, d, J=7.8), 7.21 (1H, dd, J=9.0, 7.8), 7.10 (1H, dd, J=9.0, 7.8), 5.44 (1H, m), 5.34 (1H, m), 4.87 (1H, m), 3.2—4.9 (13H, m)
4h		2950, 1647, 1281	375	13.81 (1H, br s), 7.44 (2H, m), 7.30 (2H, m), 5.44 (1H, m), 5.20 (1H, m), 4.85 (2H, m), 2.6—4.5 (13H, m)
4j		1646, 1438, 1280	364	8.92 (2H, d, J=6.3), 7.90 (2H, d, J=6.3), 5.45 (1H, m), 5.34 (1H, m), 4.95 (1H, m), 4.27 (1H, m), 4.16 (1H, m), 4.07 (2H, m), 3.93 (1H, m), 3.05—5.25 (8H, m)
4k		1652, 1455, 1279	364	8.63 (1H, d, J=5.6), 8.00 (1H, dd, J=7.9, 7.8), 7.71 (1H, d, J=7.8), 7.56 (1H, dd, J=7.9, 5.6), 5.44 (1H, m), 5.32 (1H, m), 4.85 (1H, m), 3.0—4.8 (13H, m)
4l		3430, 1726, 1670, 1640, 1280	380	9.52 (1H, br s), 7.60 (1H, d, J=6.8), 7.53 (1H, d, J=6.5), 6.30 (1H, m), 5.43 (1H, m), 5.28 (1H, m), 4.83 (1H, m), 2.7—4.7 (13H, m)
4m		2300, 1642, 1615, 1434, 1406, 1300, 1283	398 (^{35}Cl)	8.51 (1H, d, J=4.9), 7.98 (1H, d, J=7.6), 7.56 (1H, dd, J=7.6, 4.9), 5.44 (1H, m), 5.27 (1H, m), 4.83 (1H, m), 4.17 (2H, m), 4.07 (2H, m), 2.90—4.05 (9H, m)
4n		1654, 1639, 1433, 1279	398 (^{35}Cl)	8.54 (1H, s), 7.98 (1H, d, J=8.3), 7.64 (1H, d, J=8.3), 5.45 (1H, m), 5.30 (1H, m), 4.86 (1H, m), 4.24 (1H, m), 4.16 (1H, m), 4.07 (2H, m), 2.95—4.65 (9H, m)
4o		1651, 1641, 1441, 1281	378	8.75 (1H, d, J=5.6), 8.35 (1H, d, J=7.8), 7.79 (1H, dd, J=7.8, 5.6), 5.45 (1H, m), 5.33 (1H, m), 4.85 (1H, m), 4.24 (1H, m), 4.17 (1H, m), 4.07 (2H, m), 3.93 (1H, m), 3.00—5.15 (8H, m), 2.64 (3H, s)
4r		2440, 1667, 1643, 1428, 1279	365	8.91 (1H, s), 8.79 (1H, d, J=2.6), 8.69 (1H, d, J=2.6), 5.44 (1H, m), 5.27 (1H, m), 4.84 (1H, m), 4.17 (2H, m), 4.06 (2H, m), 2.85—4.05 (9H, m)
4s		1645, 1630, 1424, 1285	363	7.47 (5H, s), 5.44 (1H, m), 5.27 (1H, m), 4.85 (1H, m), 4.10—4.30 (2H, m), 4.07 (2H, m), 2.95—4.05 (9H, m)
4t		2350, 1644, 1598, 1466, 1429, 1292, 1275, 1095	453	7.00 (1H, d, J=8.6), 6.87 (1H, d, J=8.6), 5.43 (1H, m), 5.24 (1H, m), 4.82 (1H, m), 4.10—4.25 (2H, m), 4.06 (2H, m), 3.83 (3H, s), 3.79 (3H, s), 3.77 (3H, s), 2.85—4.00 (9H, m)
4u		1642, 1584, 1463, 1417, 1278, 1125	453	6.75 (2H, s), 5.44 (1H, m), 5.28 (1H, m), 4.84 (1H, m), 4.10—4.30 (2H, m), 4.07 (2H, m), 3.81 (6H, s), 3.70 (3H, s), 2.95—4.00 (9H, m)
4v		1644, 1629, 1480, 1426, 1297, 1276	353	7.87 (1H, m), 7.10 (1H, m), 6.65 (1H, m), 5.44 (1H, m), 5.25 (1H, m), 4.84 (1H, m), 2.90—4.70 (13H, m)

TABLE III. (continued)

Compd. No.	R	IR (KBr) ν (cm^{-1})	MS m/z (M^+)	^{1}H-NMR (DMSO-d_6) δ (J=Hz)
4w		1645, 1633, 1424, 1285	353	8.10 (1H, s), 7.76 (1H, m), 6.70 (1H, m), 5.44 (1H, m), 5.28 (1H, m), 4.85 (1H, m), 2.8—4.7 (13H, m)
4x		1642, 1628, 1426, 1291	369	7.80 (1H, d, J=5.1), 7.50 (1H, d, J=3.7), 7.15 (1H, dd, J=5.1, 3.7), 5.44 (1H, m), 5.26 (1H, m), 4.85 (1H, m), 2.9—4.7 (13H, m)
4y		1645, 1631, 1428, 1284	369	7.88 (1H, s), 7.64 (1H, d, J=5.0), 7.25 (1H, d, J=5.0), 5.44 (1H, m), 5.26 (1H, m), 4.85 (1H, m), 2.8—4.6 (13H, m)
4z		1658, 1642, 1436, 1277, 846	384	8.06 (1H, s), 5.44 (1H, m), 5.31 (1H, m), 4.85 (1H, m), 2.9—5.0 (13H, m), 2.70 (3H, s)

The physical, analytical, and spectral data of these compounds are listed in Tables I, II, and III.

Since compound **4i** exhibited the most potent activity, as shown in Table IV, preparation of its stereoisomers was examined. The (*exo*, *endo*) isomer of **4i** was synthesized as shown in Chart 5. 1,4:3,6-Dianhydro-D-glucitol 2-methanesulfonate (**10**) was originally prepared by direct mesylation of 1,4:3,6-dianhydro-D-glucitol followed by a tedious purification process (yield, 6%).[1,7] Recently, Stoss *et al.* reported regioselective acylation of 1,4:3,6-dianhydro-D-glucitol using acetic anhydride and leadoxide to afford 1,4:3,6-dianhydro-D-glucitol 5-acetate **9** in a good yield. Compound **9** was transformed to **10** by mesylation followed by hydrolysis. Compound **10** was subjected to the Mitsunobu reaction (PPh_3, diethyl azodicarboxylate, benzoic acid) in order to invert the configuration of the hydroxyl group at the 5-position to give the benzoate **11** (68%). Then, **11** was reacted in a sealed tube with 10 eq of piperazine in BuOH at 160 °C to give the piperazine derivative **12**, which was then nitrated and acylated by treatment with the mixed anhydride of nicotinic acid under a basic condition to give compound **14** (15% from **11**). NMR analyses (nuclear Overhauser effect (NOE), *etc.*) of **14** confirmed its configuration. The (*endo*, *exo*) isomer of **4i** was synthesized as shown in Chart 6. Reaction of **10** with piperazine under reflux was originally expected to give the (*endo*, *endo*) isomer **17**. However, the (*endo*, *exo*) isomer **16** was obtained in a 50 to 60% yield. We assume that an intermediate **15**[9,10] was formed by an intramolecular S_N2 reaction, and then reacted with piperazine to afford a double-inverted conpound **16**. Then, **19** was prepared in a manner similar to that described for **14**, using **16** instead of **12**. NMR analyses (NOE, *etc.*) of **19** also confirmed its configuration.

Results and Discussion

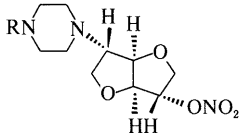
The antianginal activity of compounds was evaluated, at first, by using a lysine-vasopressin-induced angina pectoris model in rats[11] and the acute lethal toxity was examined in mice (Table IV).

An arylpiperazine moiety is often present in compounds having α_1-blocking activity.[12] For example, urapidil or prazosin has the 2-methoxyphenylpiperazine or the quinazolinylpiperazine moiety, respectively. It would be interesting, therefore to see whether arylpiperazinyl derivatives of **4** might exhibit vasodilatory activity *via* α_1-blocking activity in addition to the stimulation of guanylate cyclase. Thus, a series of compounds was examined (**4a**—**h** in Table IV). Compound **4h** (R=benzimidazol-2-yl, *p.o.*) showed potent activity and compounds **4d** (*p.o.*), **4f** (i.p.), and **4g** (i.p.) showed some activity in the lysine-vasopressin-induced angina pectoris model. Since oral administration of compounds **4f** or **4g** did not inhibit the T-wave elevation (data not shown), the oral bioavailability of such compounds seemed to be very low. The standard error of the mean (S.E.M.) for **4c** was very large. In general, these compounds showed lower water solubility (below 1 mg/ml) than that of **1** (KF14124, 5 mg/ml), which might explain the above results.

Then, arylcarbonyl groups were introduced into the piperazine ring in order to decrease the lipophilicity of the compounds and increase the water solubility. These compounds (**4i**—**z**) showed good water solubility (more than 5 mg/ml). Among them, **4i** (R=nicotinoyl), and **4w** (R=3-furoyl) showed potent antianginal activity, and **4n** (R=6-chloronicotinoyl), **4q** (R=nipecotinoyl), **4t** (R=2,3,4-trimethoxybenzoyl), **4v** (R=2-furoyl), and **4z** (R=(2-methylthiazol-4-yl)carbonyl) tended to inhibit T-wave elevation. In the picolinoyl derivative **4k** or the isonicotinoyl derivative **4j**, the activity associated with **4i** was diminished or eliminated, repectively. Since **4i**, **4j**, and **4k** are regioisomers, the 3-position of pyridine in **4i** was the preferred location for the carbonyl group. Substitution at the 2-position of this preferred nicotinoyl group led to loss of the activity (**4l**, **4m**, and **4o**). Thienoyl derivatives **4x** and **4y** showed decreased activity. Stereoisomers of **4i** (**14** and **19**) showed diminished or no activity. The values of the minimum lethal dose (MLD) for these compounds were larger than 300 mg/kg (*p.o.*). Thus, these compounds seem to be less acutely toxic than **1** (KF14124, MLD=200 mg/kg (*p.o.*)).[1] After the examination of several compounds at lower doses (10 and 3 mg/kg, *p.o.*), only **4i** and **4w** showed activity at a dose of 10 mg/kg.

For selected compounds (**4h, i, w**), the arterio- and veno-dilatory activities were examined. The arterio-dilatory activity was evaluated in the coronary artery of

TABLE IV. Activity in a Lysine-Vasopressin-Induced Angina Model and Acute Lethal Toxicity



4

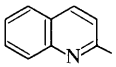
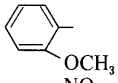
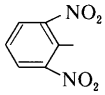
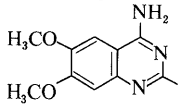
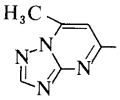
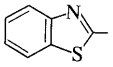
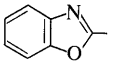
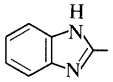
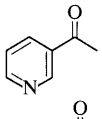
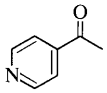
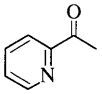
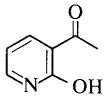
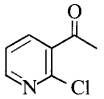
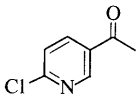
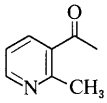
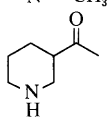
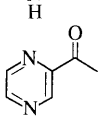
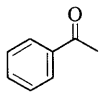
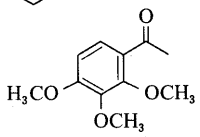
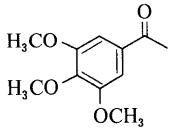
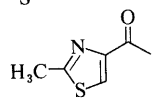
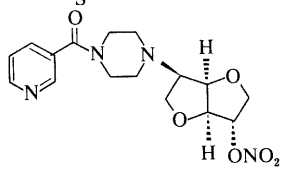
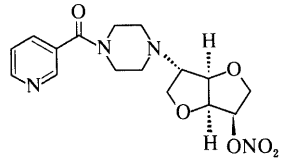
Compd.	R	Elevation in T-wave[a]				MLD[b] mg/kg, *p.o.*
		Dose, mg/kg	Control (%)	Treated (%)	Δ (inhibition, %)	
4a		25 (i.p.)	89.3±18.3	92.7± 4.1	−3.8	>300
4b		25 (i.p.)	99.8±32.0	77.4±19.6	+22.4	>300
4c		25 (i.p.)	138.0±28.6	99.7±60.6	+27.8	NT[c]
4d		30 (*p.o.*)	88.9±11.4	55.9± 8.6	+37.1	>300
4e		25 (i.p.)	105.0±21.8	97.8±15.9	+6.9	>300
4f		12.5 (i.p.)	110.9±17.3[d]	73.2± 6.3	+34.0	>300
4g		25 (i.p.)	171.5±46.5	114.1±34.7	+33.5	>300
4h		30 (*p.o.*) 10 (*p.o.*)	149.7±28.0 105.6±30.5	52.9±20.2[e] 95.2±10.5	+64.7 +9.8	>300
4i		30 (*p.o.*) 10 (*p.o.*) 3 (*p.o.*)	141.1±28.9 63.3± 9.2 63.3± 9.2	69.7±20.0[e] 33.1± 5.7[f] 50.6±10.5	+50.6 +52.3 +20.1	>300
4j		30 (*p.o.*)	116.7±18.5	153.1±39.3	−31.2	NT[c]
4k		30 (*p.o.*)	116.7±18.5	76.6± 8.7	+34.4	>300
4l		30 (*p.o.*)	155.1±46.8	162.9±88.9	−5.0	NT[c]
4m		30 (*p.o.*)	116.7±18.5	116.5±14.6	+0.2	>300
4n		30 (*p.o.*)	153.2±20.3	90.2±12.9	+41.1	>300
4o		30 (*p.o.*)	153.2±20.3	130.3±27.5	+14.9	>300
4q		30 (*p.o.*)	238.0±47.9	151.6±45.4	+36.3	>300
4r		30 (*p.o.*)	116.7±18.5	128.0±19.6	−9.7	>300

TABLE IV. (continued)

Compd.	R	Elevation in T-wave[a]			MLD[b] mg/kg, *p.o.*
		Dose, mg/kg	Control (%)	Treated (%)	Δ (inhibition, %)
4s		30 (*p.o.*)	116.7±18.5	93.1±15.1	+20.2	>300
4t		30 (*p.o.*)	116.7±18.5	66.5±12.7	+43.0	>300
4u		30 (*p.o.*)	116.7±18.5	107.4±13.9	+8.0	>300
4v		30 (*p.o.*)	116.7±18.5	71.2± 9.6	+39.0	>300
4w		10 (*p.o.*) 3 (*p.o.*)	138.4±19.8 138.4±19.8	59.0±21.6[e] 95.6±30.6	+57.4 +30.9	>300
4x		30 (*p.o.*)	153.2±20.3	102.0±17.2	+33.4	>300
4y		30 (*p.o.*)	153.2±20.3	123.1±24.9	+19.6	>300
4z		30 (*p.o.*)	158.4±50.4	89.6± 9.3	+43.4	>300
14		30 (*p.o.*)	123.1± 9.3	87.5±23.5	+28.9	>300
19		25 (i.p.)	155.1±46.8	183.2±64.1	−15.3	>300
1 (KF14124)		30 (*p.o.*) 10 (*p.o.*)	111.2±21.2 128.5±18.5[g]	37.3±11.2[e] 76.9± 8.6[e,g]	+66.5 +40.2	200
3 (nicorandil)		30 (*p.o.*) 10 (*p.o.*)	141.1±28.9[h] 141.1±28.9[h]	33.5±14.3[f,h] 70.0±13.9[e,h]	+76.3 +50.4	>300

a) Results are expressed as mean values±S.E.M. (unless otherwise mentioned, the number of experiments is 4 for i.p., and 6 for *p.o.*). *b*) Minimum lethal dose (see Experimental section). *c*) Not tested. *d*) Number of experiments is 6. *e,f*) Significant difference from control group (*e*) $p<0.05$, (*f*) $p<0.01$; unpaired Student's *t* test). *g*) Number of experiments is 8. *h*) Number of experiments is 10.

anesthetized dogs following local intraarterial administration of the compounds[13] and the results were expressed as the ratio of the increase in coronary blood flow by the compounds to that by nicorandil (**3**) (Table V). Compounds **4i** and **4w** showed potent arterio-dilatory activity, which was comparable to that of nicorandil (**3**) and superior to that of ISDN (**2**). The aryl derivative **4h** was less active. Veno-dilatory activity was evaluated in the propranolol-induced heart failure model in dogs (Table VI).[14] In this test, the inhibitory effect on increased left ventricular end-diastolic pressure (LVEDP) was used as an index of preload reduction (veno-dilation). As described in the previous paper,[1] nicorandil (**3**) did not decrease LVEDP, presumably because it is an arterio-dilator rather than a veno-dilator, and ISDN (**2**) showed weak activity because of its first-pass effect. Compound **4i** potently inhibited the increased LVEDP even at 60 min after intraduodenal administration. This long duration of action is remarkable in nitrate-type compounds. Compound **4i** exhibited potent activity even at 0.1 mg/kg (i.d.). The pharmacological data indicate that **4i** relaxes both arterial and venous smooth muscles, resulting in the reduction of elevated pre- and afterload. Since elevation of pre- and afterload is the characteristic hemodynamic derangement in patients with

TABLE V. Coronary Vasodilating Activity of Nitrates (CBF)

Compd.	CBF[a]
4h	0.20[b]
4i	1.06[b]
4w	1.14[b]
2 (ISDN)	0.62[b]
3 (nicorandil)	1.00[b]

a) Results of coronary blood flow (CBF) are expressed as relative potency with respect to that of nicorandil. See Experimental section. *b*) The value is the mean of 2 experiments.

TABLE VI. Activity in a Propranolol-Induced Heart Failure Model

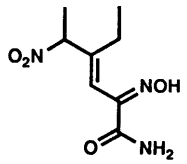
Compd.	Dose (i.d.) Dose, mg/kg	% decrease in LVEDP[a]		
		15 min[b] (%)	30 min[b] (%)	60 min[b] (%)
4h	0.3[c]	NT[d]	NT[d]	58.6± 9.7
4i	0.3[c]	43.9± 8.6[e]	82.8±12.0[f]	70.9±26.5[e]
	0.1[c]	58.6±20.3	65.1±15.5	41.6±12.4
4w	0.3[g]	30.3±10.0	29.6±14.1	14.4±10.5
2 (ISDN)	0.3[h,i]	14.9± 6.5	13.1± 5.6	1.6± 5.0
	0.1[h]	4.2± 3.1	1.0± 4.9	−1.9± 5.6
3 (nicorandil)	0.3[h,i]	9.7± 7.1	9.4± 6.9	2.1±10.3

a) The values are the mean values ± S.E.M.; left venticular end-diastolic pressure (LVEDP). *b*) Time after intraduodenal administration of the compound. *c*) Number of experiments is 5. *d*) Not tested. *e,f*) Significant difference from control group (*e*) $p<0.05$, (*f*) $p<0.01$; unpaired Student's *t* test). *g*) Number of experiments is 4. *h*) Number of experiments is 6. *i*) Reference 1.

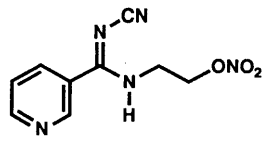
congestive heart failure or angina pectoris, **4i** (KW-3196) was chosen for further evaluation as an antianginal drug.

Studies on the oral acute toxicity of **4i** showed that the value of 50% lethal dose (LD_{50}) was more than 1000 mg/kg (*p.o.*) and CNS depressant actions such as reflex depression and behavioral depression were not observed at 300 mg/kg (*p.o.*). Thus, compound **4i** seemed to lack the problems associated with **1** (KF14124, $LD_{50}=550$ mg/kg, *p.o.*).[1]

In the radioligand binding assay, compound **4i** showed no substantial affinity for any of the following receptors; adrenaline α_1 and α_2, serotonin 5-HT_{1A}, 5-HT_2, and 5-HT_3, histamine H_1 and H_2, muscarine M_1 and M_2, dopamine D_1 and D_2, and adenosine A_1 and A_2. The values of 50% inhibition concentration (IC_{50}) for binding were more than 100 μM. These binding data indicate that the vasodilatory activity of **4i** cannot be attributed to adrenaline α_1 antagonism. Cumulative applications of **4i**, ISDN, and nicorandil relaxed the rabbit aorta precontracted by 10^{-6} M L-phenylephrine.[15] The values of 50% effective concentration (EC_{50}) for relaxation were 6.4±2.5 ($n=6$), 5.13±1.29 ($n=4$), and 8.15±1.24 μM ($n=5$), respectively. The effect of **4i** on the contraction was significantly reduced by 60 min preincubation of the rabbit aorta with 10^{-5} M methylene blue ($EC_{50}>100$ μM) and was significantly potentiated by 30 min pretreatment of the tissue with 10^{-5} M zaprinast ($EC_{50}=0.29\pm0.11$ μM ($n=6$)). These results are similar to those obtained with glyceryl trinitrate or ISDN.[16] Since methylene blue and zaprinast are known to be inhibitors of guanylate cyclase and cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (type V PDE), respectively, the fundamental action of **4i** is specculated to involve an increase in the c



20
(FK409)



21
(KRN2391)

Chart 7

GMP level in the cell.[16,17] Further, compound **4i** inhibited the contraction of the rabbit vena cava (L-phenylephrine, 10^{-5} M; $EC_{50}=0.055\pm0.010$ μM) more potently than that of aorta (L-phenylephrine, 10^{-6} M; $EC_{50}=6.4\pm2.5$ μM). This veno-selectivity (EC_{50} for aorta/EC_{50} for vena cava = 120) is superior to that of ISDN (EC_{50} for aorta/EC_{50} for vena cava = 20) and is partly in agreement with the *in vivo* result that **4i** reduced LVEDP more potently than ISDN in a propranolol-induced heart failure model. In addition, although compound **4i** has a nicotinoyl group like nicorandil, K^+ channel opening activity was not observed in this compound, as will be reported elsewhere.

Currently, FK409 (**20**) is being developed as an antianginal agent, which is not a nitrate but seems to act *via* the same mechanism as that of nitrates (stimulation of guanylate cyclase).[18] On the other hand, a new nicorandil-type K^+ channel opener, KRN2391 (**21**), has been reported (Chart 7).[19] Now, we present a new type of nitrate **4i**, which is characterized by potent orally active vasodilation with veno-selectivity.

In summary, we have described a series of vasodilators, aryl or arylcarbonyl substituted piperazinyl-1,4 : 3,6-dianhydro-L-iditol 2-nitrate derivatives. Among these compounds, **4i** was proved to be a superior vasodilator to ISDN, nicorandil, and KF14124. Furthermore, **4i** did not show strong acute toxicity. Compound **4i** (KW-3196) is under development as a vasodilator and a drug for treating angina pectoris.

Experimental

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-GX270 FT NMR or a Hitachi R-90H FT NMR spectrometer with Me_4Si as an internal standard, and mass spectra on a JMS-SX102 instrument. Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-810 spectrometer. Elemental analyses were performed by the analytical department of our laboratories. Since most of the compounds are very hygroscopic, they contained some water when elemental analyses were performed.

Chemistry The following procedures are representative of the general methods that are described in the text.

Method A. 5-[4-(Benzothiazol-2-yl)piperazin-1-yl]-5-deoxy-1,4 : 3,6-dianhydro-L-iditol 2-Nitrate Dihydrochloride (4f) A mixture of compound **5**[1] (0.90 g, 3.47 mmol), 2-chlorobenzothiazole (0.57 g, 3.36 mmol), K_2CO_3 (0.52 g, 3.76 mmol), and BuOH (25 ml) was refluxed for 7 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (50 : 1) as an eluent. The product was dissolved in $CHCl_3$, and to this solution was added EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring and the precipitated crystals were collected by filtration and dried to give compound **4f** as the hydrochloride (0.29 g, 18%). IR (KBr): 2975 (br), 2422 (br), 1636, 1277 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.85 (1H, d, $J=7.5$ Hz), 7.55 (1H, d, $J=7.5$ Hz), 7.34 (1H, dd, $J=9.0$, 7.5 Hz), 7.16 (1H, dd, $J=9.0$, 7.5 Hz), 5.45 (1H, m), 5.34 (1H, m), 4.87 (1H, m), 3.1—4.9 (13H, m). Compounds **4a**, **d**, **e**, **g**, and **h** were prepared in a manner similar to that described for **4f**, using the respective aryl halide instead of

2-chlorobenzothiazole and their spectral data are listed in Table III.

Method B. 5-Deoxy-5-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]-1,4 : 3,6-dianhydro-L-iditol 2-Nitrate Dihydrochloride (4i) A mixture of nicotinic acid (0.74 g, 5.61 mmol), Et_3N (1.56 ml, 11.2 mmol), and a solvent mixture of 2-BuOH and CH_3CN (5 : 1) (12 ml) was stirred at 0 °C, and to this solution was added dropwise a solution of isobutyl chloroformate (0.74 ml, 5.64 mmol) in a solvent mixture of 2-BuOH and CH_3CN (5 : 1) (1.6 ml). The mixture was stirred at 0 °C for a further 5 min. Then, a solution of compound **5**[1] (1.45 g, 5.59 mmol) in a solvent mixture of 2-BuOH and CH_3CN (5 : 1) (6 ml) was added and the whole was stirred at 0 °C for 2 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (50 : 1) as an eluent. The product was dissolved in $CHCl_3$. To this solution was added EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring and the precipitated crystals were collected by filtration and dried to give compound **4i** as the hydrochloride (1.00 g, 41%). IR (KBr): 1643, 1440, 1280 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.89 (1H, s), 8.84 (1H, d, J=5.3 Hz), 8.27 (1H, d, J=7.9 Hz), 7.82 (1H, dd, J=7.9, 5.3 Hz), 5.45 (1H, m), 5.34 (1H, m), 4.86 (1H, m), 4.27 (1H, m), 4.17 (1H, m), 4.07 (2H, m), 3.94 (1H, m), 3.10—5.25 (8H, m), $[\alpha]_D^{15}$=22.9 (c=0.998, acetone). Compounds **4j**—**o** and **4r**—**z** were prepared in a similar manner using the respective aryl carboxylic acid instead of nicotinic acid, and their spectral data are listed in Table III.

Method C. 5-Deoxy-5-[4-(2-methoxyphenyl)piperazin-1-yl]-1,4 : 3,6-dianhydro-L-iditol 2-Nitrate Dihydrochloride (4b) A mixture of 5-amino-5-deoxy-1,4 : 3,6-dianhydro-L-iditol 2-nitrate[7] (**5**, 1.90 g, 10.0 mmol), *o*-[*N*,*N*-bis(chloroethyl)amino]anisole (4.47 g, 18.0 mmol), Et_3N (2.8 ml, 20.1 mmol), NaI (8.00 g, 53.4 mmol), and methylethylketone (50 ml) was refluxed for 38 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$ as an eluent. The product was dissolved in $CHCl_3$, and to this solution was added EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring and the precipitated crystals were collected by filtration and dried to give compound **4b** as the hydrochloride (1.75 g, 40%). IR (KBr): 2980 (br), 2350 (br), 1643, 1456, 1277 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.87—7.10 (4H, m), 5.45 (1H, m), 5.35 (1H, m), 4.86 (1H, m), 3.80 (3H, s), 2.90—4.65 (13H, m). MS m/z: 365 (M^+).

Method D. 5-Deoxy-5-[4-(2,6-dinitrophenyl)piperazin-1-yl]-1,4 : 3,6-dianhydro-L-iditol 2-Nitrate Hydrochloride (4c) Fuming HNO_3 (2.44 ml) was cooled to 0 °C, and CH_3CN (4.8 ml) and Ac_2O (4.8 ml) were added. To this mixture was added a solution of compound **8** (3.97 g, 11.8 mmol) in CH_3CN (15.5 ml) over 15 min. The mixture was stirred at 0 °C for a further 20 min, and neutralized with an aqueous saturated $NaHCO_3$ solution followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$ as the eluent. The product obtained from the first fraction was dissolved in $CHCl_3$, and to this solution was added EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring and the precipitated crystals were collected by filtration and dried to give compound **4c** as the hydrochloride (0.36 g, 6%). IR (KBr): 2864 (br), 2180 (br), 1641, 1533, 1344, 1273 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.21 (2H, d, J=8.1 Hz), 7.62 (1H, t, J=8.1 Hz), 5.43 (1H, m), 5.25 (1H, m), 4.81 (1H, m), 4.16—4.30 (1H, m), 3.87—4.16 (3H, m), 2.80—3.85 (9H, m). MS m/z: 425 (M^+).

Method E. 5-Deoxy-5-(4-nipecotinoylpiperazin-1-yl)-1,4 : 3,6-dianhydro-L-iditol 2-Nitrate Dihydrochloride (4q) A mixture of compound **4p** obtained by method C (1.80 g, 3.83 mmol), EtOH (20 ml), and 1 N HCl (20 ml) was stirred at room temperature for 6 d. The mixture was concentrated under reduced pressure, and the residue was triturated with EtOAc. The crystals were collected by filtration and drid to give compound **4q** as the hydrochloride (1.33 g, 78%). IR (KBr): 1642, 1441, 1278, 1088, 857 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.45 (1H, m), 5.31 (1H, m), 4.85 (1H, m), 2.7—4.6 (18H, m), 1.45—1.95 (4H, m). MS m/z: 370 (M^+).

5-Deoxy-5-[4-(pyridin-3-ylcarbonyl)piperadin-1-yl]-1,4 : 3,6-dianhydro-D-glucitol 2-Nitrate (14) A solution of diethyl azodicarboxylate (27.5 ml, 178.4 mmol) in anhydrous THF (100 ml) was added to a mixture of compound **10** (20.0 g, 89.3 mmol), PPh_3 (46.8 g, 178.4 mmol), benzoic acid (21.8 g, 178.5 mmol), and anhydrous tetrahydrofuran (THF) (1.3 l) followed by stirring at room temperature overnight. The mixture was concentrated, and the residue was purified by silica gel column chromatography with $CHCl_3$ as an eluent to give compound **11** (20.0 g, 68%); ^{1}H-NMR ($CDCl_3$) δ: 8.03 (2H, d, J=8.0 Hz), 7.6 (1H, dd, J=7.5, 7.5 Hz), 7.46 (2H, dd, J=8.0, 7.5 Hz), 5.47 (1H, m), 5.18 (1H, m), 4.90 (1H, m), 4.84 (1H, m), 4.16 (1H, m), 4.08 (2H, m), 4.03 (1H, m), 3.10 (3H, s). A mixture of compound **11** (12.7 g, 38.7 mmol), piperazine (36.4 g, 422.8 mmol), and BuOH (100 ml) was heated at 160 °C in a sealed tube for 22 h. The mixture was concentrated, and piperazine in the residue was azeotropically evaporated with toluene several times. The residue was purified by column chromatography on Diaion SP 207 (Mitsubishi Kasei Co.) with H_2O to MeOH–H_2O (3 : 7) as an eluent, and recrystallized from EtOAc to give compound **12** as a crude product; ^{1}H-NMR (DMSO-d_6) δ: 5.35 (1H, m), 4.50 (1H, m), 4.19 (1H, m), 2.2—4.1 (14H, m). Concentrated H_2SO_4 (3.9 ml) was added to the above crude compound **12** in H_2O (7.4 ml) (solution A). A solution of urea (1.73 g, 28.8 mmol) in concentrated H_2SO_4 (39.0 ml) was added to fuming HNO_3 (86%) (26 ml) at −15 °C. Then, solution A was solwly added thereto at −15 °C over 30 min to 1 h followed by stirring at the same temperature for a further 2 h. The reaction mixture was gradually poured into H_2O (210 ml) with stirring, neutralized with 1 N NaOH at 0 °C, and extracted with $CHCl_3$ 5 to 10 times. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (10 : 1 to 0 : 1) as an eluent to give 5-deoxy-5-(piperazin-1-yl)-1,4 : 3,6-dianhydro-D-glucitol 2-nitrate (**13**) (6.3 g, 27% from **11**). ^{1}H-NMR ($CDCl_3$) δ: 5.33 (1H, m), 4.5—4.75 (2H, m), 2.2—4.5 (14H, m). Compound **14** was prepared in a manner similar to that described for **4i**, using **13** instead of **5**. The yield was 57%. Recrystallization of the solid from iso-PrOH produced an analytical sample of **14** as colorless needles, mp 162—164 °C. IR (KBr): 1626, 1589, 1443, 1274, 1009, 861 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.50—8.65 (2H, m), 7.76 (1H, d, J=7.9 Hz), 7.37 (1H, m), 5.35 (1H, H^3, m), 4.70 (1H, H^4, m), 4.63 (1H, H^5, m), 4.30 (1H, H^1, m), 4.11 (1H, m), 4.01 (1H, m), 3.72 (1H, m), 2.84 (1H, H^6, m), 2.2—4.0 (8H, m). NOE between H^5 and H^6 was observed, but that between H^3 and H^4 was not. MS m/z: 364 (M^+). *Anal.* Calcd for $C_{16}H_{24}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.62; H, 5.49; N, 15.29.

5-Deoxy-2-[4-(pyridine-3-ylcarbonyl)piperazin-1-yl]-1,4 : 3,6-dianhydro-D-glucitol 5-Nitrate (19) Compound **18** was prepared in a manner similar to that described for **13**.

Compound **19** was prepared in a manner similar to that described for **4i**, using **18** instead of **5**. The yield was 48%. Recrystallization of the solid from iso-PrOH produced an analytical sample of **19** as colorless crystals, mp 136—136 °C. IR (KBr); 1633, 1586, 1440, 1278, 1095, 1009, 876, 853 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.60—8.75 (2H, m), 7.75 (1H, d, J=7.7 Hz), 7.36 (1H, m), 5.34 (1H, H^3, m), 4.93 (1H, H^4, m), 4.44 (1H, H^5, m), 4.20 (1H, H^1, m), 4.07 (1H, H^8, m), 2.81 (1H, H^6, m), 2.3—4.0 (10H, m). NOE between H^3 and H^4 was larger than that between H^5 and H^6. MS m/z: 364 (M^+) *Anal.* Calcd for $C_{16}H_{24}N_4O_6$: C, 57.74; H, 15.38. Found: C, 52.71; H, 5.47; N, 15.60.

Biology Lysine-Vasopressin-Induced Angina Pectoris Model in the Rat[11] Male Wistar rats weighing 210—250 g were used as experimental animals. The electrocardiogram (ECG lead II) was measured with an electrocardiograph and recorded on a polygraph (RPM-6200, Nihon Kohden, Tokyo, Japan). Oral (*p.o.*) and intraperitoneal (i.p.) administrations of a test compound to rats were performed at 20 and 10 min before anesthetization, respectively. Ten minutes after anesthetization with urethane (1.2 g/kg, i.p.), lysine-vasopressin (Sigma Co., Ltd.; V-2875, 0.3 I.U./kg) was intravenously injected into the rats. Then, the T-wave elevation was observed in the ECG. The T-wave heights were measured before and at 15 to 30 s after the lysine-vasopressin injection in rats with and without test compound treatment, and then, the T-wave elevation % of was calculated in each rat. The control value was obtained in each experiment.

Propranolol-Induced Heart Failure Model in the Dog[14] Adult mongrel dogs of either sex, weighing 8—22 kg, were used for the experiment. The animals were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and artificially ventilated with a respirator (made by Takashima Co., for big animals) following tracheal intubation. The right common carotid artery was cannulated and the manometer for measurement of left ventricular pressure (Millar Tip) was advanced to the left ventricular cavity. Left ventricular pressure (LVP), the maximum rate of change of left ventricular pressure (LV dP/dt_{max}), and left ventricular end-diastolic pressure (LVEDP) were measured by the Millar Tip transducer. The systemic blood pressure (BP) was measured with a pressure transducer (MPU-0.5, Nihon Kohden) attached to a catheter placed in the femoral artery, and heart rate (HR) was measured with a cardiotachometer (AT610-G, Nihon Kohden) from BP. All measurements were recorded on a polygraph (RPM-6200, Nihon Kohden) or an a pen-recorder (RAT-1200, Nihon Kohden). After values of all parameters had stabilized, a bolus intravenous injection of propranolol at a dose of 2 mg/kg was performed. Thereafter, propranolol (0.05 mg/kg/min, i.v.) was continuously infused to

evoke heart failure. An increase of 5 to 15 mmHg in LVEDP was considered as a sign of heart failure. After occurrence of heart failure, the test compound was intraduodenally administered. After administration of the test compound, LVEDP, LVP, LV dP/dt_{max}, BP, and HR were recorded every 15 min. Precent decrease in LVEDP was calculated as follows: [mean value before injection of drug-mean value after injection of drug] × 100/mean value before injection of drug.

Arteriodilation The compounds were evaluated for arteriodilation by a method modified from that of Morikawa *et al.* [13]

Adult mongrel dogs of either sex, weighing 12—30 kg, were anesthetized with sodium pentobarbital (35 mg/kg, i.v.). The trachea was intubated and the animal was ventilated. The ventilation rates (20 cycles/min) and tidal volumes were adjusted so as to maintain the arterial blood pH, pCO_2, and pO_2 within physiological limits. Catheters were placed in the right femoral artery and vein, and the heart rate and mean blood pressure were monitored. An electromagnetic flow probe of the extracorporeal type (Model MF-27, Nihon Kihon Kohden) was placed in the middle of the shunt perfusing the left circumflex artery in order to evaluate the increase in coronary blood flow (CBF).

The test compound (100 μg) in a volume of 10 μl was injected with a microinjector into a rubber tube connected to the arterial shunt over a period of 5 s. Despite the injection of drugs, neither coronary blood pressure nor heart rate changed. The resulting changes in blood flow were assessed. Before and after the administration of each compound, 100 μg of nicorandil was administered as a relative control.

Acute Lethal Toxicity Groups of 3 male ddY mice weighing 20—25 g were given a single *p.o.* injection of compounds in saline at doses of 100, 200, and 300 mg/kg (0.2 ml per 20 g body weight) and were monitored for 7 d. Minimum lethal doses (MLD) were determined after 7 d based on observation of the death of at least one mouse.

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