Synthesis and Structure–Activity Relationships of 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols as New Calcium Blockers

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A series of 2-(4-benzhydryl-1-piperazinyl)-1-phenylethanols (4) was synthesized and evaluated for calcium entry-blocking activity, assessed as inhibitory activity on calcium current in rat hippocampal pyramidal neurons by using a patch-clamp technique (10^{-5} M), and cerebral vasodilating activity, assessed in terms of increase of vertebral blood flow after intravenous administration (1 mg/kg) in anesthetized dogs. Alkoxy substituents on the phenyl ring of the phenylethanol moiety conferred potent calcium entry-blocking activity and potent cerebral vasodilating activity. Among these compounds, 4i (NC-1100) was selected as the best analog. Some pharmacological properties of 4i are presented.

Key words calcium blocker; cerebral vasodilator; 2-(4-benzhydryl-1-piperazinyl)-1-phenylethanol; structure–activity relationship; NC-1100

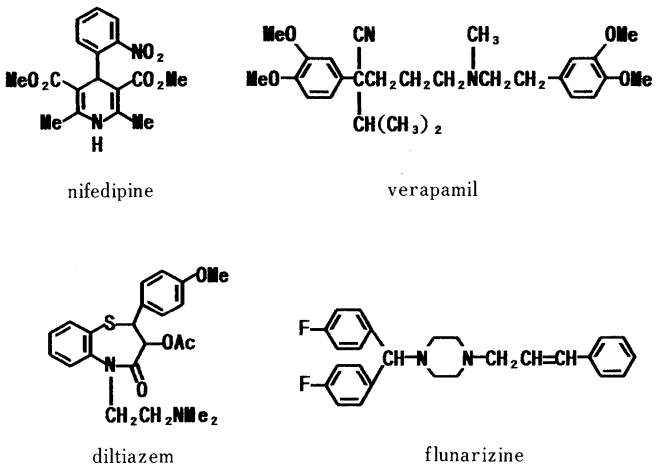
Calcium blockers have been widely used for the treatment of cardiovascular disorders. The chemical structures of the major selective blockers are classified into four groups: dihydropyridines, phenylalkylamines, 1,5-benzothiazepines and diphenylpiperazines, represented by nifedipine, verapamil, diltiazem and flunarizine, respectively. From the viewpoint of activity, dihydropyridines, phenylalkylamines and 1,5-benzothiazepines have been classified as subgroup 1A (agents selective for slow calcium channels in myocardium) and diphenylpiperazines have been classified as subgroup 1B (agents with no perceived actions on the slow calcium inward current in myocardium).[1] The compounds in subgroup 1A have been used mainly as agents for treatment for hypertension and angina and the compounds in subgroup 1B have been used as cerebral vasodilators. Recently, the beneficial effect of flunarizine on ischemic brain damage, triggered by calcium overload, has been reported.[2] Alps *et al.* reported that many calcium blockers have neuroprotective properties against ischemic injury in the hippocampus of the Mongolian gerbil.[3] A number of pharmacological studies and modifications of compounds in subgroup 1A have been reported,[4] while there have been only a few reports concerning the compounds in subgroup 1B.

We describe in this paper the synthesis and pharmacological activities of 2-(4-benzhydryl-1-piperazinyl)-1-phenylethanols, which may be classified into subgroup 1B, as new calcium blockers.

Synthesis

Most ketones (**3**) were synthesized by general methods according to Chart 1. Thus, acetophenones (**1**) were brominated with bromine[5] or $CuBr_2$[6] to afford α-bromoketones (**2**) and then condensed with 1-benzhydrylpiperazine in 2-propanol in the presence of triethylamine. The 4-acetoxy derivative (**3n**) was synthesized by acetylation of the 4-hydroxy derivative (**3c**) with acetic anhydride as shown in Chart 1. The yields, melting points, ^{1}H-NMR and analytical data of ketones (**3**) are summarized in Table I.

Reduction of ketones (**3**) with sodium borohydride (method A) or lithium aluminum hydride (method B) yielded alcohols (**4**). The relative configurations of diastereomeric products (**4r**, **4s**) were determined from their ^{1}H-NMR spectra. The coupling constants of the benzylic proton of **4r** (δ, 4.80) and **4s** (δ, 4.14) are 3 and 10 Hz, respectively. These data suggest that the relative configurations of **4r** and **4s** are *erythro* and *threo*, respectively.[7] 4-Ethoxy (**4e**) and 4-allyloxy derivatives (**4f**) were obtained from the 4-hydroxy derivative (**4c**) by alkylation using ethyl bromide and allyl bromide, respectively, in EtOH in the presence of potassium hydroxide (method C). Unsubstituted (**4a**) and nitro derivatives (**4q**) were derived from a reaction of styrene oxide (**5**) with 1-benzhydrylpiperazine in EtOH (method D) as shown in Chart 2. The free base of **4** was transformed to its hydrochloride in a usual manner. The yields, melting points and ^{1}H-NMR data of the free bases of the alcohol (**4**) are summarized in Table II, and the melting points and analytical data of the hydrochlorides are summarized



nifedipine verapamil

diltiazem flunarizine

Fig. 1

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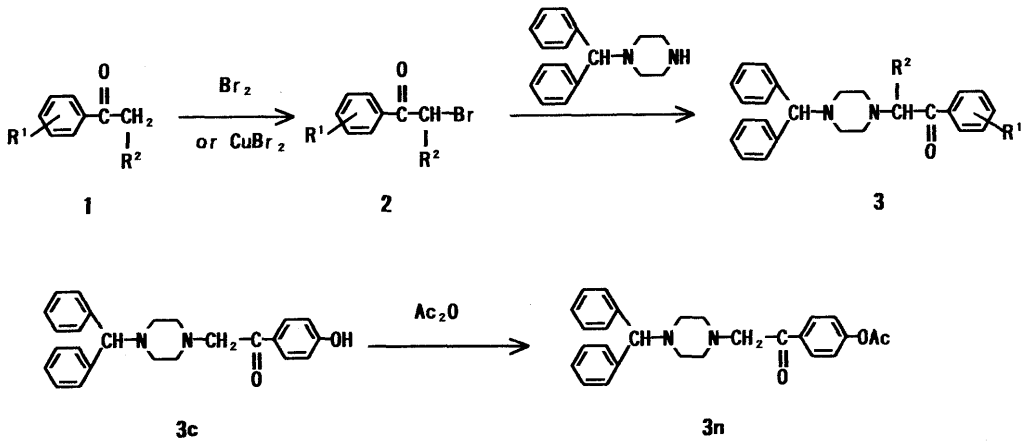
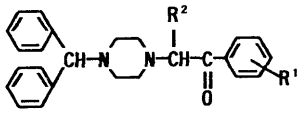


Chart 1

TABLE I. Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanones (**3**)



No.	R^1	R^2	Yield[b] (%)	mp (°C)	Formula	HR-MS Found (Calcd)	^{1}H-NMR (J, Hz)	Solvent[c]
3a	H	H	65	91—92	$C_{25}H_{26}N_2O$	370.2046 (370.2045)	2.4—2.7 (8H, m), 3.81 (2H, s), 4.24 (1H, s), 7.1—7.6 (13H, m), 7.99 (2H, dd, 1, 8)	A
3b	2-OH	H	83	Oil	$C_{25}H_{26}N_2O_2$	386.1997 (386.1994)	2.3—3.2 (6H, m), 3.3—3.4 (2H, m), 3.5—3.8 (2H, m), 4.2—4.3 (1H, m), 6.7—8.0 (14H, m)	A
3c	4-OH	H	85	82—87	$C_{25}H_{26}N_2O_2$	386.1995 (386.1994)	2.4—2.7 (8H, m), 3.76 (2H, s), 4.22 (1H, s), 6.83 (2H, d, 8), 7.1—7.5 (10H, m), 7.89 (2H, d, 8)	A
3d	4-OMe	H	67	84—85	$C_{26}H_{28}N_2O_2$	400.2150 (400.2151)	2.4—2.7 (8H, m), 3.74 (2H, s), 3.85 (3H, s), 4.24 (1H, s), 6.91 (2H, m), 7.1—7.5 (10H, m), 7.99 (2H, m)	A
3g	4-OCH_2Ph	H	87	151	$C_{32}H_{32}N_2O_2$	476.2464 (476.2464)	2.4—2.7 (8H, m), 3.73 (2H, s), 4.24 (1H, s), 5.12 (2H, s), 6.98 (2H, m), 7.1—7.5 (15H, m), 7.99 (2H, m)	A
3h	2-OH, 4-OMe	H	75	Oil	$C_{26}H_{28}N_2O_3$	416.2096 (416.2100)	2.4—2.8 (8H, m), 3.65 (2H, s), 3.81 (3H, s), 4.25 (1H, s), 6.3—6.5 (2H, m), 7.1—7.5 (10H, m), 7.8—7.9 (1H, m)	A
3i	3,4-$(OMe)_2$	H	95	204—207	$C_{27}H_{30}N_2O_3 \cdot 2HCl$	430.2255 (430.2256)	3.4—4.0 (8H, m), 3.90 (3H, s), 3.93 (3H, s), 5.10 (2H, s), 5.45 (1H, br s), 7.11 (1H, d, 9), 7.3—7.5 (6H, m), 7.56 (1H, d, 2), 7.71 (1H, dd, 9, 2), 7.7—7.9 (4H, m)	B
3j	2,4-$(OMe)_2$	H	70	141—142	$C_{27}H_{30}N_2O_3$	430.2257 (430.2256)	2.4—2.7 (8H, m), 3.78 (2H, s), 3.84 (3H, s), 3.87 (3H, s), 4.24 (1H, s), 6.44 (1H, d, 2), 6.52 (1H, dd, 2, 9), 7.1—7.5 (10H, m), 7.82 (1H, d, 9)	A
3k	2,3,4-$(OMe)_3$	H	86	119	$C_{28}H_{32}N_2O_4$	460.2365 (460.2362)	2.4—2.7 (8H, m), 3.77 (2H, s), 3.85 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 4.24 (1H, s), 6.68 (1H, d, 9), 7.1—7.5 (10H, m), 7.45 (1H, d, 9)	A
3l	3,4,5-$(OMe)_3$	H	94	141—143	$C_{28}H_{32}N_2O_4$	460.2365 (460.2362)	2.4—2.7 (8H, m), 3.74 (2H, s), 3.89 (6H, s), 3.91 (3H, s), 4.25 (1H, s), 7.35 (2H, s), 7.1—7.5 (10H, m)	A
3m	4-Me	H	64	Oil	$C_{26}H_{28}N_2O$	384.2200 (384.2202)	2.39 (3H, s), 2.4—2.7 (8H, m), 3.79 (2H, s), 4.25 (1H, s), 7.1—7.5 (12H, m), 7.88 (2H, d, 8)	A
3n[a]	4-OAc	H	68	Oil	$C_{27}H_{28}N_2O_3$	428.2104 (428.2100)	2.32 (3H, s), 2.4—2.7 (8H, m), 3.76 (2H, s), 4.24 (1H, s), 7.1—7.3 (8H, m), 7.4—7.5 (4H, m), 8.0—8.1 (2H, m)	A
3o	4-Cl	H	62	100—101	$C_{25}H_{25}ClN_2O$	404.1652 (404.1655)	2.4—2.7 (8H, m), 3.74 (2H, s), 4.24 (1H, s), 7.1—7.5 (12H, m), 7.95 (2H, m)	A
3p	4-Br	H	62	Oil	$C_{25}H_{25}BrN_2O$	448.1148 (448.1150)	2.3—2.7 (8H, m), 3.72 (2H, s), 4.24 (1H, s), 7.1—7.5 (10H, m), 7.57 (2H, d, 9), 7.87 (2H, d, 9)	A
3r	4-OH	Me	60	221—223	$C_{26}H_{28}N_2O_2 \cdot 2HCl$	400.2152 (400.2151)	1.63 (3H, d, 7), 3.3—4.0 (8H, m), 5.3—5.6 (2H, m), 6.93 (2H, m), 7.3—7.5 (6H, m), 7.7—7.9 (4H, m), 7.99 (2H, d, 9)	B

a) **3n** was obtained by acetylation of **3c** with Ac_2O. *b*) Yields have not been optimized. *c*) Solvent for ^{1}H-NMR: A; $CDCl_3$, B; CD_3OD.

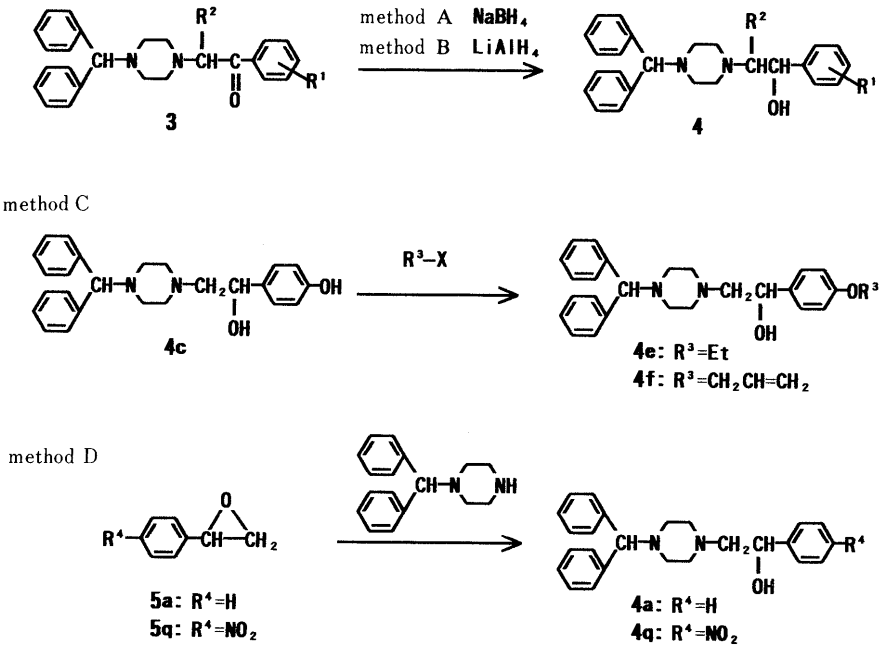
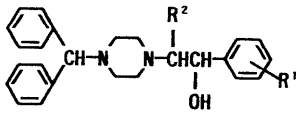


Chart 2

TABLE II. Free Bases of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols (**4**)



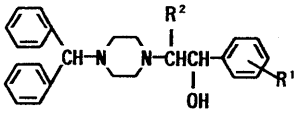
No.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	^{1}H-NMR (J, Hz) ($CDCl_3$)
4a	H	H	D	41	115—116	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.69 (1H, dd, 4, 10), 7.1—7.5 (15H, m)
4b	2-OH	H	B	65	171—173	2.3—2.9 (10H, m), 4.25 (1H, s), 4.84 (1H, dd, 5, 7), 6.81 (1H, dt, 1, 7), 6.87 (1H, dd, 1, 8), 7.02 (1H, dd, 2, 7), 7.1—7.5 (11H, m)
4c	4-OH	H	A	79	155	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.64 (1H, t, 7), 6.75 (2H, dt, 3, 9), 7.1—7.5 (12H, m)
4d	4-OMe	H	A	71	126—127	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 3.79 (3H, s), 4.24 (1H, s), 4.65 (1H, dd, 5, 8), 6.87 (2H, dt, 3, 9), 7.1—7.5 (12H, m)
4e	4-OEt	H	C	60	124—125	1.39 (3H, d, 7), 2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.01 (2H, q, 7), 4.24 (1H, s), 4.64 (1H, dd, 6, 8), 6.85 (2H, dt, 3, 9), 7.1—7.5 (12H, m)
4f	4-$OCH_2CH=CH_2$	H	C	64	100	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 3.96 (1H, br s), 4.24 (1H, s), 4.51 (2H, m), 4.64 (1H, dd, 5, 9), 5.26 (1H, dd, 2, 10), 5.39 (1H, dd, 2, 17), 6.04 (1H, m), 6.88 (2H, d, 9), 7.1—7.5 (12H, m)
4g	4-OCH_2Ph	H	B	79	129	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 3.95 (1H, br s), 4.24 (1H, s), 4.64 (1H, dd, 5, 9), 5.05 (2H, s), 6.94 (1H, dd, 2, 5), 7.1—7.5 (17H, m)
4h	2-OH, 4-OMe	H	B	62	161—162	2.4—2.9 (10H, m), 3.75 (3H, s), 4.24 (1H, s), 4.77 (1H, t, 6), 6.36 (1H, dd, 3, 8), 6.44 (1H, d, 3), 6.91 (1H, d, 8), 7.1–7.5 (10H, m)
4i	3,4-$(OMe)_2$	H	A	75	85	2.4—2.6 (8H, m), 2.7—2.8 (2H, m), 3.86 (3H, s), 3.89 (3H, s), 4.25 (1H, s), 4.65 (1H, dd, 5, 9), 6.82 (1H, d, 8), 6.86 (1H, dd, 2, 8), 6.94 (1H, d, 2), 7.1—7.5 (10H, m)
4j	2,4-$(OMe)_2$	H	A	62	102—103	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 3.77 (3H, s), 3.79 (3H, s), 4.24 (1H, s), 5.01 (1H, dd, 3, 10), 6.42 (1H, d, 2), 6.49 (1H, dd, 2, 8), 7.1—7.5 (11H, m)
4k	2,3,4-$(OMe)_3$	H	A	70	128	2.3—2.6 (8H, m), 2.7—2.9 (2H, m), 3.83 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 4.24 (1H, s), 4.97 (1H, dd, 3, 10), 6.67 (1H, d, 9), 7.1—7.5 (12H, m)
4l	3,4,5-$(OMe)_3$	H	B	77	173	2.4—2.6 (8H, m), 2.7—2.8 (2H, m), 3.82 (3H, s), 3.86 (6H, s), 4.25 (1H, s), 4.62 (1H, dd, 4, 11), 6.59 (2H, s), 7.1—7.5 (10H, m)
4m	4-Me	H	A	68	140—141	2.32 (3H, s), 2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.66 (1H, dd, 4, 10), 7.1—7.5 (14H, m)
4n	4-OAc	H	A	16	158.5—160	2.28 (3H, s), 2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.69 (1H, dd, 3, 10), 7.0—7.5 (14H, m)

TABLE II. (continued)

No.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	^{1}H-NMR (J, Hz) ($CDCl_3$)
4o	4-Cl	H	A	69	142—143	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.67 (1H, dd, 3, 11), 7.1—7.5 (14H, m)
4p	4-Br	H	A	67	153—155	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.24 (1H, s), 4.64 (1H, dd, 4, 11), 7.1—7.5 (14H, m)
4q	4-NO_2	H	D	45	147—148	2.3—2.6 (8H, m), 2.7—2.8 (2H, m), 4.26 (1H, s), 4.78 (1H, dd, 3, 10), 7.1—7.5 (10H, m), 7.53 (2H, d, 9), 8.19 (2H, d, 9)
4r (ery)	4-OH	Me	A	29	118	0.82 (3H, d, 7), 2.3—2.8 (9H, m), 4.21 (1H, s), 4.80 (1H, d, 3), 6.74 (2H, d, 8), 7.1—7.5 (12H, m)
4s (thr)	4-OH	Me	A	30	180	0.76 (3H, d, 7), 2.3—2.8 (9H, m), 4.14 (1H, d, 10), 4.25 (1H, s), 6.69 (2H, d, 8), 7.1—7.5 (12H, m)

a) Method A, $NaBH_4$. Method B, $LiAlH_4$. Method C, **4c** was alkylated with alkyl halide. Method D, 1-benzhydrylpiperazine was treated with styrene oxide. *b*) Yields have not been optimized.

TABLE III. Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanol Hydrochlorides (**4**)



No.	mp (°C, dec.)	Formula	Analysis (%) Found (Calcd)		
			C	H	N
4a	238—240	$C_{25}H_{28}N_2O \cdot 2HCl$	67.30 (67.41)	6.82 6.79	6.34 6.29)
4b	224—225	$C_{25}H_{28}N_2O_2 \cdot HCl$	70.52 (70.66	6.78 6.88	6.64 6.59)
4c	214	$C_{25}H_{28}N_2O_2 \cdot HCl$	70.63 (70.66	6.84 6.88	6.67 6.59)
4d	223—225	$C_{26}H_{30}N_2O_2 \cdot 2HCl$	65.48 (65.68	6.86 6.78	5.96 5.89)
4e	208	$C_{27}H_{32}N_2O_2 \cdot 2HCl$	65.88 (66.25	6.89 7.00	5.72 5.72)
4f	192	$C_{28}H_{32}N_2O_2 \cdot HCl \cdot 0.5H_2O$	71.19 (70.94	6.98 7.23	6.02 5.91)
4g	187	$C_{32}H_{34}N_2O_2 \cdot HCl$	74.35 (74.62	6.74 6.85	5.49 5.44)
4h	176	$C_{26}H_{30}N_2O_3 \cdot HCl \cdot 0.5H_2O$	67.32 (67.30	6.77 6.95	6.02 6.04)
4i	175	$C_{27}H_{32}N_2O_3 \cdot 2HCl \cdot H_2O$	62.09 (61.95	6.92 6.93	5.36 5.35)
4j	178	$C_{27}H_{32}N_2O_3 \cdot 2HCl \cdot 1.5H_2O$	60.95 (60.90	6.94 7.00	5.29 5.26)
4k	189	$C_{28}H_{34}N_2O_4 \cdot 2HCl \cdot 0.75H_2O$	61.29 (61.26	6.70 6.88	4.89 5.10)
4l	222	$C_{28}H_{34}N_2O_4 \cdot HCl$	67.38 (67.39	6.97 7.07	5.48 5.61)
4m	128—129	$C_{26}H_{30}N_2O \cdot HCl$	73.73 (73.83	7.30 7.39	6.56 6.62)
4n	222—225	$C_{27}H_{30}N_2O_3 \cdot HCl \cdot 0.25H_2O$	68.62 (68.78	6.61 6.73	5.79 5.94)
4o	236—238	$C_{25}H_{27}ClN_2O \cdot HCl$	67.61 (67.72	6.39 6.36	6.27 6.32)
4p	249—251	$C_{25}H_{27}BrN_2O \cdot HCl \cdot 0.5H_2O$	60.56 (60.43	5.80 5.88	5.63 5.64)
4q	236—238	$C_{25}H_{27}N_3O_3 \cdot HCl \cdot 0.5EtOH$	65.42 (65.47	6.44 6.55	8.66 8.81)
4r (ery)	201	$C_{26}H_{30}N_2O_2 \cdot HCl \cdot 0.5H_2O$	69.63 (69.71	7.11 7.20	6.43 6.25)
4s (thr)	211—212	$C_{26}H_{30}N_2O_2 \cdot HCl \cdot 0.5H_2O$	69.94 (69.71	7.18 7.20	6.12 6.25)

in Table III.

Pharmacological Results and Discussion

The alcohol derivatives (**4**) listed in Table III were initially tested *in vitro* for calcium entry-blocking activity, assessed as inhibitory activity on calcium current in pyramidal neurons from the rat hippocampus by using the nystatin perforated-patch technique (10^{-5} M).[8] They were then evaluated for cerebral vasodilating activity *in vivo*, assessed in terms of increase of vertebral blood flow after intravenous administration (1 mg/kg) in anesthetized dogs. The test results are summarized in Table IV.

One propanol (**4r**) in which a hydroxy group was substituted on the benzene ring (R^1) at the 4-position, and three ethanols, unsubstituted (**4a**) or substituted with either a 2-hydroxy (**4b**) or a 4-hydroxy group (**4c**), were evaluated for calcium entry-blocking activity and cerebral vasodilating activity. Significant differences were found in the activities among these four compounds. Both **4c** and **4r** showed *in vitro* calcium entry-blocking activity and *in vivo* cerebral vasodilating activity, while **4b** showed very weak activity in both tests and **4a** was potent *in vitro* but very weak in *vivo*. Thus, the substituents on the benzene ring appeared to affect the activities, while the methyl substituent on the alcohol moiety (R^2) did not. On the basis of these results, a variety of 1-(4-substituted)phenylethanol derivatives were synthesized and initially evaluated for calcium entry-blocking activity. Single substitution by an electron-withdrawing substituent such as chlorine (**4o**) or bromine (**4p**) caused a loss of activity, but an acetoxy (**4n**) or a nitro group (**4q**) resulted in moderate activity. The introduction of an electron-donating alkoxy group such as a methoxy (**4d**), an ethoxy (**4e**) or an allyloxy group (**4f**) enhanced the *in vitro* activity with the exception of a benzyloxy group (**4g**), while the introduction of a methyl group (**4m**) decreased the activity. These results suggest that the electron density on the benzene ring did not affect the calcium entry-blocking activity. Therefore, our synthetic efforts were directed mainly toward producing compounds substituted with hydroxy and alkoxy groups. Thus, compounds **4h—l**, di- and trisubstituted with methoxy and hydroxy groups on the benzene ring, were synthesized and evaluated. The dimethoxy compounds (**4i, 4j**) showed potent activity,

TABLE IV. Calcium Blocking Activities and Cerebral Vasodilating Activities of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols (4)

No.	Ca entry-blocking activity[a] inhibn. (%) 1.0×10^{-5} M	Cerebral vasodilating activity[b] (%) 1 mg/kg, i.v.
4a	17.8±3.6	25
4b	2.7±2.5	26
4c	11.2±5.4	76
4d	22.8±4.4	64
4e	24.2±4.3	
4f	24.2±5.1	93[c]
4g	0.0±1.2	
4h	12.5±4.7	
4i	20.2±1.9	135[c]
4j	37.2±4.0	123
4k	17.0±3.1	149[c]
4l	13.2±1.1	95
4m	5.2±1.5	
4n	12.8±3.7	
4o	0.0±1.1	
4p	0.0±5.4	39[d]
4q	16.4±7.6	
4r	15.0±3.0	66[e]
4s		60[f]
Nicardipine	30.0±4.9	
Flunarizine	30.0±4.2	91

a) Inhibitory activity of calcium current in hippocampal pyramidal neurons. *b*) Activity for increasing vertebral blood flow in dogs. *c*) Tested in solution in distilled water. *d*) Tested in solution in 20% DMSO. *e*) Evaluated as 1/2 tartaric acid salt. *f*) Evaluated as tartaric acid salt.

TABLE V. Effects of **4i**, Flunarizine and Papaverine Administered Intravenously on VBF[a] and FBF[b] in Anesthetized Dogs

	Dose mg/kg	Maximum change (%±S.E.) VBF	Maximum change (%±S.E.) FBF	ED_{50}[c] (μg/kg)
4i (NC-1100)	0.1	52.8±10.7	6.4± 3.4	
	0.3	108.9±13.3	15.3± 5.2	94
	1.0	135.3±28.1	21.2±14.9	
Flunarizine	0.1	21.1± 5.2	—	
	0.3	48.5± 5.5	—	313
	1.0	91.2±15.9	4.8± 3.7	
Papaverine	0.1	29.7± 5.2	15.2± 1.9	
	0.3	87.2±13.9	34.4±12.4	148
	1.0	133.8±23.5	97.6±40.8	

a) Vertebral blood flow. *b*) Femoral blood flow. *c*) Doses causing 50% increase of preadministration values of vertebral blood flow.

while the trimethoxy compounds (**4k**, **4l**) were somewhat less active than the monomethoxy compound (**4d**). Indeed, the 2,4-dimethoxy compound (**4j**) showed stronger calcium entry-blocking activity than nicardipine or flunarizine.

Similar results were obtained in the *in vivo* model of cerebral vasodilating activity. Most compounds with methoxy substituents on the benzene ring showed good effects. The dimethoxy compounds (**4i**, **4j**) showed the most potent activity in this series. On the other hand, despite its weak *in vitro* calcium entry-blocking activity, the trimethoxy compound (**4k**) displayed very strong cerebral vasodilating activity *in vivo*. This difference in the potency might have been due to differences in the sensitivity of pyramidal neurons and smooth muscle cells to the compounds. These pharmacological results suggest that this series of 2-(4-benzhydryl-1-piperazinyl)-1-phenylethanols (**4**) may be classified into subgroup 1B on the basis of their chemical structures and pharmacological properties.

Finally, based on detailed pharmacological and toxicological evaluation, **4i** (NC-1100) was selected as a candidate for further development. As can be seen in Table V, NC-1100 is a selective and more potent cerebral vasodilator than flunarizine, a representive cerebral vasodilator.[9] The results of a detailed pharmacological characterization of NC-1100 will be reported elsewhere.

Experimental

Melting points determined with a Yamato MP-21 apparatus were uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-50 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-EX400 NMR spectrometer with tetramethylsilane as the internal standard. High-resolution mass spectra (MS) were obtained on a JEOL JMS-SX102 mass spectrometer. Elemental analyses (C, H, N) were performed on a Heraus C, H, N-Rapid instrument.

1-Benzhydrylpiperazine, α-bromoacetophenone, 4′,α-dibromoacetophenone and styrene oxide were commercial products. The other substituted α-bromoacetophenones or α-bromopropiophenone (**2**) were prepared by bromination with bromine or $CuBr_2$ of the corresponding acetophenones or propiophenone (**1**), which were obtained commercially. 4-Nitrostyrene oxide (**5**) was prepared by chlorination of commercially available 4-nitroacetophenone, followed by reduction with sodium borohydride and treatment with aqueous NaOH.

General Procedure for the Preparation of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanones (3) A solution of 11.9 g (47 mmol) of 1-benzhydrylpiperazine and 5.2 g (52 mmol) of triethylamine in 60 ml of 2-propanol was added dropwise to a solution of 13.6 g (47 mmol) of α-bromo-2′,3′,4′-trimethoxyacetophenone in 50 ml of 2-propanol over 30 min under room temperature. The reaction mixture was stirred for 3 h at room temperature, then poured into 200 ml of ice-water and the resultant oily residue was extracted with 150 ml of AcOEt. The organic solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from ethanol to give 14.8 g (68%) of 2-(4-benzhydryl-1-piperazinyl)-1-(2,3,4-trimethoxyphenyl)ethanone (**3k**) as a white powder.

Compounds **3a—j**, **3l**, **3m**, **3o**, **3p**, and **3r** were obtained by a procedure similar to that described for **3k**. Physical properties and spectral data of these compounds are listed in Table I.

Preparation of 1-(4-Acetoxyphenyl)-2-(4-benzhydryl-1-piperazinyl)ethanone (3n) Anhydrous sodium acetate (0.2 g) and Ac_2O (6.3 g, 62 mmol) were added to a solution of 10.0 g (26 mmol) of **3c** in 50 ml of CH_2Cl_2 and the mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* and AcOEt and saturated aqueous $NaHCO_3$ were added. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by chromatography (silica gel, $CHCl_3$–MeOH) gave 7.5 g (68%) of 1-(4-acetoxyphenyl)-2-(4-benzhydryl-1-piperazinyl)ethanone (**3n**) as a pale yellow oil. Physical properties and spectral data of **3n** are listed in Table I.

General Procedure for the Preparation of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols (4) by Method A A mixture of 3.8 g (30 mmol) of **3k** in 100 ml of EtOH and 30 ml of $CHCl_3$ was treated with 2.27 g (60 mmol) of sodium borohydride in portions over 20 min at 0—5 °C. After the reaction was complete, 10% aqueous NH_4Cl was added to the mixture and the organic layer was extracted with 200 ml of AcOEt. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from $CHCl_3$ to give 9.70 g (70%) of the free base of 2-(4-benzhydryl-1-piperazinyl)-1-(2,3,4-trimethoxyphenyl)ethanol (**4k**) as a white powder. The free base of **4k** was transformed to its dihydrochloride in a usual manner.

Compounds **4c**, **4d**, **4i**, **4j**, **4m—p**, **4r** and **4s** were obtained by a procedure similar to that described for **4k**. The relative configuration of **4r** and **4s** was discussed above. Physical properties and spectral and analytical data of these compounds are listed in Tables II and III.

General Procedure for the Preparation of Substituted 2-(4-Benzhydryl-

1-piperazinyl)-1-phenylethanols (4) by Method B A solution of 3.0 g (6.3 mmol) of **3g** in 20 ml of tetrahydrofuran (THF) was added dropwise to a suspension of 0.6 g of $LiAlH_4$ in 24 ml of THF at 0 °C over a period of 30 min. After the reaction was complete, a mixed solution of AcOEt–THF (1 : 1 w/w) was added dropwise at 0 °C and the mixture was poured into saturated aqueous NH_4Cl. The separated oily residue was extracted twice with AcOEt, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from $CHCl_3$–EtOH to give 2.37 g (79%) of the free base of 2-(4-benzhydryl-1-piperazinyl)-1-(4-benzyloxyphenyl)ethanol (**4g**) as a white powder. The free base of **4g** was transformed to its hydrochloride in a usual manner.

Compounds **4b**, **4h** and **4l** were obtained by a procedure similar to that described for **4g**. Physical properties and spectral data of these compounds are listed in Tables II and III.

General Procedure for the Preparation of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols (4) by Method C A solution of 4.0 g (10 mmol) of **4c** and 1.3 g of potassium hydroxide in 40 ml of EtOH was treated with 2.24 g (19 mmol) of allyl bromide at room temperature, and the mixture was stirred overnight. The solvent was removed *in vacuo*, and AcOEt and saturated aqueous NH_4Cl were added to the residue. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by chromatography (silica gel, $CHCl_3$–MeOH) and crystallization from Et_2O–hexane gave 2.09 g (47%) of the free base of 1-(4-allyloxyphenyl)-2-(4-benzhydryl-1-piperazinyl)ethanol (**4f**) as a white powder. The free base of **4f** was transformed to its hydrochloride in a usual manner.

Compound **4e** was obtained by a procedure similar to that described for **4f**. Physical properties and spectral and analytical data of these compounds are listed in Tables II and III.

General Procedure for the Preparation of Substituted 2-(4-Benzhydryl-1-piperazinyl)-1-phenylethanols (4) by Method D A solution of 2.52 g (10 mmol) of 1-benzhydrylpiperazine and 1.44 g (14 mmol) of styrene oxide in 20 ml of EtOH was stirred for 44 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica gel, $CHCl_3$). Crystallization from EtOH gave 1.52 g (41%) of the free base of 2-(4-benzhydryl-1-piperazinyl)-1-phenylethanol (**4a**) as a white powder. The free base of **4a** was transformed to its dihydrochloride in a usual manner.

Compound **4q** was obtained by a procedure similar to that described for **4a**. Physical properties and spectral and analytical data of these compounds are listed in Tables II and III.

Assay Procedure for Cerebral Vasodilating Activity Mongrel dogs of both sexes each weighing about 10 kg were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and artificially ventilated. The right vertebral artery was isolated from the surrounding tissues, and the blood flow was measured with a flow probe attached the artery, connected to an electric flow meter (MF-27, Nihon Koden Co., Ltd.). Each of the test compounds was dissolved in an appropriate solvent (*e.g.* aqueous solution of 5% tartaric acid), and injected into the right cephalic vein *via* a cannula at a dose of 1 mg/kg. The potency was expressed as the maximum percentage increase in vertebral blood flow.

Assay Procedure for Calcium Entry-Blocking Activity The neurons were acutely dissociated from the rat hippocampus as described by Takahashi *et al.*[10] The ionic composition of the external solution for recording Ca^{2+} current was (in mM): NaCl 145, $BaCl_2 \cdot 6H_2O$ 5, CsCl 5, glucose 10, *N*-2-hydroxyethylpiperidine-*N'*-2-ethanesulfonic acid (HEPES) 10, and tetrodotoxin 3×10^{-7} M (pH 7.4). The pipette solution for the nystatin perforated patch recording was KCl 150 mM and nystatin 100 μg/ml (pH 7.2). Control and test external solutions were applied to a dissociated neuron using the Y-tube method described by Murase *et al.*[11] The Ca^{2+} current was recorded by use of the nystatin perforated-patch clamp technique under the voltage-clamp conditions. The current was recorded with a patch-clamp amplifier (Nihon Koden, type CEZ-2300), monitored on a storage oscilloscope (Iwatsu, type MS-5100A) and simultaneously recorded on video tape. High-voltage-activated I_{Ca} ($HVA\text{-}I_{Ca}$) was elicited by 40 ms step pulses from a holding potential of -50 to -10 mV with an interval of 20 s. The drug was tested at 1×10^{-5} M. The percent inhibition of activity was determined from the $HVA\text{-}I_{Ca}$ with administration of each compound in comparison with the control value. The value was expressed as the mean ± standard error of the mean (S.E.M.).

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