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Benzylpiperazine Derivatives. II.[1] Syntheses and Cerebral Vasodilating Activities of 1-[(3-Alkyl-3-hydroxy-3-phenyl)propyl]-4-benzylpiperazine Derivatives

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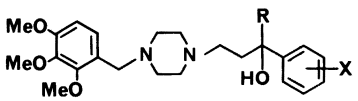
Analogs of 1-[(3-alkyl-3-hydroxy-3-phenyl)propyl]-4-(2,3,4-trimethoxybenzyl)piperazine (**1**) were prepared and tested for cerebral vasodilating activity. It was found that the potency depends positively on the number of methoxyl groups on the benzyl moiety, and the homopiperazine analogs seem to be equipotent to the corresponding piperazines.

From the standpoints of potency and ease of synthesis, **8k** was selected for further study. Further analogs, which have various substituents in place of the benzyl moiety of **8k**, were prepared and tested for cerebral vasodilating activity. These analogs were less potent than **8k**. It was suggested that the benzyl moiety of **8k** plays an important role in the high cerebral vasodilating activity.

Keywords——piperazine; homopiperazine; benzylpiperazine; acylation; alkylation; Grignard reaction; cerebral vasodilator

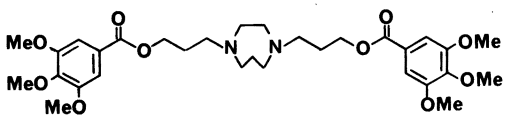
A previous report from our laboratory described the syntheses and biological properties of 1-[(3-alkyl-3-hydroxy-3-phenyl)propyl]-4-(2,3,4-trimethoxybenzyl)piperazine derivatives (**1**) as a novel class of compounds with interesting cerebral vasodilating activity.[1] Encouraged by these results, we undertook further studies to prepare other analogs of **1**.



2 HCl

1: R = Me or Et
X = 2,4- or 3,4-Cl_2

Chart 1



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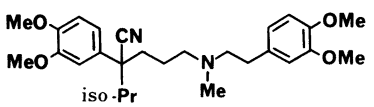

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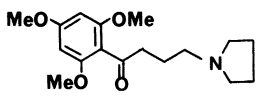

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Chart 2

Results and Discussion

Analogs of 1

Several compounds, which have various substitution patterns of methoxyl groups on the phenyl moiety, are used clinically as vasodilators; these include dilazep (**2**), verapamil (**3**) and buflomedil (**4**). Therefore, the number and the locations of methoxyl groups of **1** were varied in order to clarify the role of the substituents. In addition, the piperazine moiety of **1** was changed to homopiperazine.

The compounds were prepared by methods A and B as shown in Chart 3. Thus, in method A, 3-alkyl-3-(3,4-dichlorophenyl)-3-hydroxypropyl chloride (**7**),[1] was allowed to react with 1-(substituted benzyl)piperazine (**5**) to give 1-[3-alkyl-3-(3,4-dichlorophenyl)-3-hydroxypropyl]-4-(substituted benzyl)piperazines (**8**) (Table I).

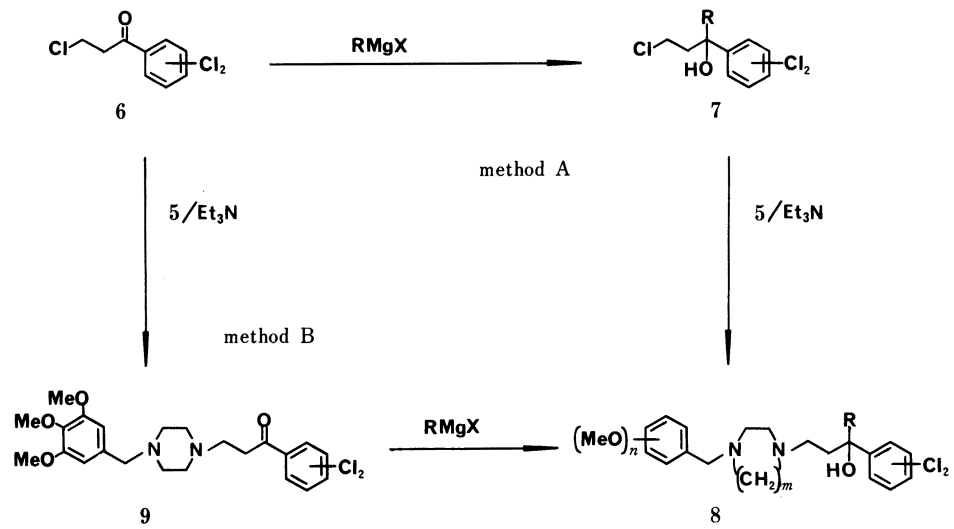


Chart 3

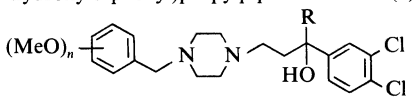
From the data in Table I, it is likely that the greater the number of methoxyl group in the benzyl moiety, the stronger the cerebral vasodilating activity. A similar situation was reported for the negative inotropic action of verapamil derivatives.[2]

Since the 3,4,5-trimethoxyphenyl moiety is often present in pharmaceuticals,[3] the effect of an alkyl group (R) at the benzylic position on the potency was examined in the 1-(3,4,5-trimethoxybenzyl)piperazine series in order to compare the results with those in the 1-(2,3,4-trimethoxybenzyl)piperazine series reported previously.

The compounds were prepared by method B as shown in Chart 3. 1-(3,4,5-Trimethoxybenzyl)piperazine (**5h**) was condensed with ω,3,4-trichloropropiophenone (**6a**)[4] to give benzoylethylpiperazine (**9a**), and **9b** was obtained in a similar manner. In these cases the yields were nearly quantitative. In our previous study, benzoylethylpiperazines similar to **9** were prepared by the Mannich reaction of 1-(substituted benzyl)piperazine, acetophenone and paraformaldehyde, but the yields were poor compared to that of the present method. As **9** is the key intermediate in this method, the present method was preferred. Next, **9** was subjected to the Grignard reaction. In this step about a 10-fold excess of Grignard reagent was used, as before (Table II).

The ethyl residue showed the most potent activity (Table II), and the effects of the alkyl group on the potency in the 1-(3,4,5-trimethoxybenzyl)piperazine series seem to be the same

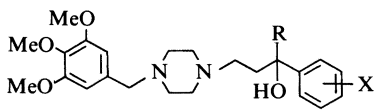
TABLE I. 1-Benzyl-4-(3-hydroxy-3-phenyl)propylpiperazine Salts (**8**) Prepared by Method A



Compd. No.	$(OMe)_n$	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Potency[a]
8a	2-OMe	Me	16	232—235 (dec.)	MeOH	$C_{22}H_{28}Cl_2N_2O_2 \cdot 2HCl$	53.24 (53.37	6.09 6.05	5.64 5.63)	0.48
8b	3-OMe	Me	24	220—222 (dec.)	MeOH	$C_{22}H_{28}Cl_2N_2O_2 \cdot 2HCl$	53.24 (53.24	6.09 6.12	5.64 5.75)	N.T.
8c	4-OMe	Me	26	246—247 (dec.)	EtOH	$C_{22}H_{28}Cl_2N_2O_2 \cdot 2HCl$	53.24 (53.05	6.09 6.18	5.64 5.62)	0.56
8d	2,3-$(OMe)_2$	Me	15	224—226 (dec.)	MeOH	$C_{23}H_{30}Cl_2N_2O_3 \cdot 2HCl \cdot H_2O$	50.75 (50.77	6.30 6.24	5.15 5.08)	0.68
8e	2,4-$(OMe)_2$	Me	32	222—224 (dec.)	EtOH	$C_{23}H_{30}Cl_2N_2O_3 \cdot 2HCl$	52.49 (52.22	6.13 6.13	5.32 5.31)	1.33
8f	3,4-$(OMe)_2$	Me	26	190—191 (dec.)	MeOH–H_2O	$C_{23}H_{30}Cl_2N_2O_3 \cdot 2MA$[b]	54.31 (54.18	5.59 5.57	4.09 4.04)	0.94
8g	3,5-$(OMe)_2$	Me	17	222—223 (dec.)	EtOH	$C_{23}H_{30}Cl_2N_2O_3 \cdot 2HCl$	52.49 (52.47	6.13 6.16	5.32 5.33)	0.40
8h	3,4,5-$(OMe)_3$	Me	21	189—191 (dec.)	MeOH–H_2O	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2MA$	53.71 (53.61	5.63 5.55	3.91 3.86)	1.43
8i	2,4,6-$(OMe)_3$	Me	7	210—211 (dec.)	EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2HCl \cdot H_2O$	50.19 (50.16	6.32 6.30	4.88 4.84)	1.24
8j[c]	3,4,5-$(OMe)_3$	Me	21	223—225 (dec.)	EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	50.99 (50.99	6.24 6.43	4.96 5.00)	1.40
8k	3,4,5-$(OMe)_3$	Et	24	184—186	EtOH	$C_{25}H_{34}Cl_2N_2O_4 \cdot 2MA$	54.33 (54.09	5.80 5.71	3.84 4.01)	1.46
8l	3,5-$(OMe)_2$	Et	18	233—234 (dec.)	EtOH	$C_{24}H_{32}Cl_2N_2O_3 \cdot 2HCl$	53.35 (53.36	6.34 6.39	5.18 5.08)	1.36
8m	4-OMe	Et	18	255—256 (dec.)	EtOH	$C_{23}H_{30}Cl_2N_2O_2 \cdot 2HCl$	54.13 (54.25	6.32 6.47	5.49 5.44)	0.83

a) The potency is expressed as the ratio of cerebral vasodilating activity to that of papaverine taken as 1. N.T. = not tested. *b*) Maleate. *c*) 2,4-Dichloro derivative of **8h**.

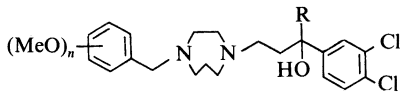
TABLE II. 1-Benzyl-4-(3-hydroxy-3-phenyl)propylpiperazine Salts (**8**) Prepared by Method B



Compd. No.	R	X	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Potency[a]
8n	C_2H_5	2,4-Cl_2	21	236—240 (dec.)	EtOH	$C_{25}H_{34}Cl_2N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	51.83 (52.10	6.44 6.63	4.84 4.88)	1.34
8o	n-C_3H_7	3,4-Cl_2	17	178—181 (dec.)	EtOH	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2MA$[b]	54.92 (54.71	5.96 5.91	3.77 3.76)	1.29
8p	n-C_3H_7	2,4-Cl_2	22	225—227 (dec.)	EtOH	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2HCl$	53.44 (53.19	6.55 6.62	4.79 4.77)	1.20
8q	n-C_4H_9	3,4-Cl_2	24	182—185 (dec.)	EtOH	$C_{27}H_{38}Cl_2N_2O_4 \cdot 2MA$	55.48 (55.35	6.12 6.14	3.70 3.72)	0.36
8r	n-C_4H_9	2,4-Cl_2	29	221—222 (dec.)	iso-PrOH	$C_{27}H_{38}Cl_2N_2O_4 \cdot 2HCl \cdot 0.25H_2O$	53.79 (53.79	6.77 6.81	4.65 4.64)	0.70
8s	n-C_5H_{11}	3,4-Cl_2	30	183—185 (dec.)	MeOH	$C_{28}H_{40}Cl_2N_2O_4 \cdot 2MA$	56.03 (55.70	6.27 6.21	3.63 3.57)	Inact.
8t	n-C_5H_{11}	2,4-Cl_2	19	212—215 (dec.)	iso-PrOH	$C_{28}H_{40}Cl_2N_2O_4 \cdot 2HCl \cdot H_2O$	53.34 (53.34	7.03 7.03	4.44 4.48)	Inact.
8u	n-C_6H_{13}	3,4-Cl_2	24	181—183 (dec.)	MeOH	$C_{29}H_{42}Cl_2N_2O_4 \cdot 2MA$	56.56 (56.47	6.41 6.59	3.57 3.54)	Inact.
8v	n-C_6H_{13}	2,4-Cl_2	35	206—209 (dec.)	iso-PrOH	$C_{29}H_{42}Cl_2N_2O_4 \cdot 2HCl \cdot H_2O$	54.04 (53.90	7.19 7.17	4.35 4.34)	Inact.

a, *b*) See footnotes *a*) and *b*), respectively, of Table I.

TABLE III. 1-Benzyl-4-(3-hydroxy-3-phenyl)propylhomopiperazine Salts (**8**) Prepared by Method A



Compd. No.	$(OMe)_n$	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)			Potency[a]
							C	H	N	
8w	3,4,5-$(OMe)_3$	H	42	157—160	EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2MA$[b]	53.71 (53.56)	5.63 5.59	3.91 3.89)	0.80
8x	2,3,4-$(OMe)_3$	Me	10	201—203 (dec.)	MeOH	$C_{25}H_{34}Cl_2N_2O_4 \cdot 2OX$[c] $\cdot 0.5H_2O$	50.74 (50.63	5.73 5.84	4.08 4.15)	1.36
8y	2,3,4-$(OMe)_3$	Et	7	179—182 (dec.)	iso-PrOH	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2OX$	52.10 (52.03	5.83 5.95	4.05 4.18)	1.78
8z	3,4,5-$(OMe)_3$	Et	27	168—170	MeOH	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2MA \cdot H_2O$	53.62 (53.88	6.09 5.91	3.68 3.67)	1.69

a, b) See footnotes *a*) and *b*), respectively, of Table I. *c*) Oxalate.

as in the 1-(2,3,4-trimethoxybenzyl)piperazine series reported previously.

Homopiperazine analogs were prepared by method A (Table III). The homopiperazines seem to be equipotent to the corresponding piperazines, but they are expensive and difficult to purify. From the standpoints of potency and ease of synthesis, **8k** was selected for further study.

Modification of the Benzyl Moiety

As mentioned above, the highest activity is observed when R is an ethyl group and the activity seems to depend positively on the number of methoxyl groups on the benzyl moiety. However, the role of the trimethoxybenzyl moiety itself in the activity remained unclear. Therefore, we synthesized compounds with various substituents in place of the benzyl moiety of **8k**, and tested their cerebral vasodilating activities.

The compounds were prepared by the methods shown in Charts 4—6. In method C, 1-[3-(3,4-dichlorophenyl)-3-hydroxypentyl]piperazine (**10**) was used as the key intermediate and various derivatives were prepared by acylation or alkylation of this compound. Preparation of **10** was as follows; 3-(3,4-dichlorophenyl)-3-hydroxypentyl chloride (**7b**)[1] was allowed to react with piperazine hexahydrate (2 eq) to give **10** along with the 1,4-disubstituted piperazine **11**. Acylation or alkylation of **10** was done by usual procedures (Table IV).

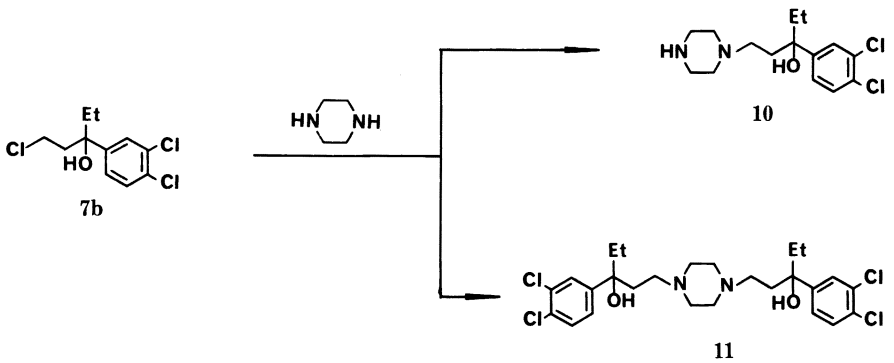


Chart 4

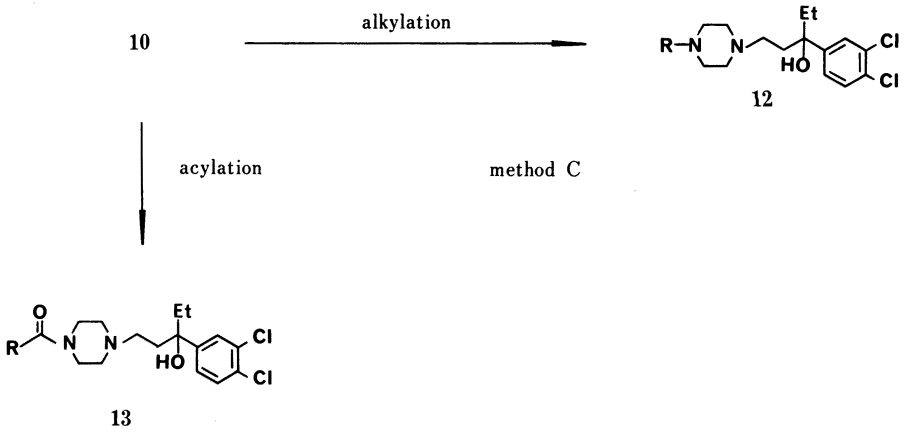


Chart 5

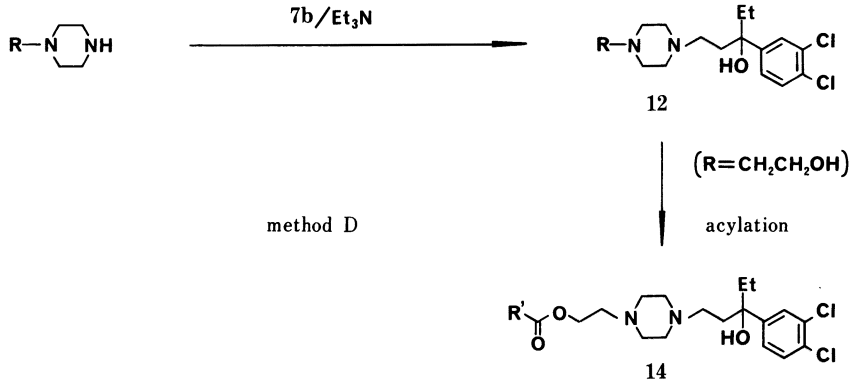


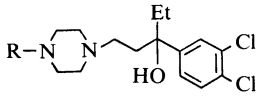
Chart 6

In method D, monosubstituted piperazines were allowed to react with **7b** to give 1,4-disubstituted piperazines **12c—i**. Monosubstituted piperazines were commercially available except for 1-(3,4,5-trimethoxyphenyl)piperazine and 1-[α-(2-pyridyl)benzyl]piperazine. The former was prepared according to the literature[5] and the latter was prepared by the reaction of α-(2-pyridyl)benzyl chloride[6] with piperazine. The hydroxyethyl derivative **12i** was further acylated to give **14a**, **b** (Table V).

From the results listed in Tables IV and V, the following structure–activity relationships can be deduced. In general, as a substituent in place of the benzyl moiety of **8k**, sterically small substituents (**10**,**12d**) appear to favor high activity and compounds containing bulky derivatives (**11**, **12c**, **12g** and **14b**) are inactive. However, bulky 3,4,5-trimethoxyphenylalkyl derivatives, especially **8k**, show exceptionally high activity. Acyl derivatives are almost inactive. It seems clear that the trimethoxybenzyl moiety of **8k** plays an important role in the cerebral vasodilating activity.

From the beginning of this series of studies, we have worked on the assumption that the 3-alkyl-3-hydroxy-3-phenylpropyl moiety of **1** plays a similar role in cerebral vasodilating activity to the cinnamyl group of cinnarizine, and the former results in higher activity. However, the results for **12c** and **12g** indicate that a 3-alkyl-3-hydroxy-3-phenylpropyl moiety can not directly replace the cinnamyl group without considerable or complete loss of activity; the two groups are not bioisosteric in our case. The mechanisms of cerebral vasodilating

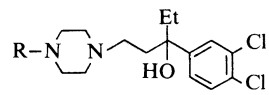
TABLE IV. 1-Substituted 4-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]piperazines Prepared by Method C



Compd. No.	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)			Potency[a]
						C	H	N	
10	H	44	227—229 (dec.)	MeOH	$C_{15}H_{22}Cl_2N_2O \cdot 2HCl$	46.17 (45.80)	6.20 6.35	7.18 7.32)	1.03
11	A[b]	2	206—208	AcOEt	$C_{26}H_{34}Cl_4N_2O_2$	56.95 (57.17)	6.25 6.33	5.11 5.24)	Inact.
12a	iso-Pr	46	249—251 (dec.)	MeOH–EtOH	$C_{18}H_{28}Cl_2N_2O \cdot 2HCl \cdot 0.5H_2O$	48.99 (49.05	7.08 6.92	6.35 6.36)	Inact.
12b	TMP–CH_2CH_2[c]	8	240—242 (dec.)	EtOH	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2HCl$	53.44 (53.49	6.55 6.57	4.79 4.68)	1.00
13a	MeCO	30	182—186	MeCOMe	$C_{17}H_{24}Cl_2N_2O_2 \cdot HCl \cdot 0.25H_2O$	51.01 (50.96	6.42 6.37	7.00 6.85)	Inact.
13b	TMP–CO	45	159—162	EtOH	$C_{25}H_{32}Cl_2N_2O_5 \cdot HCl$	54.80 (54.51	6.07 5.95	5.11 5.08)	0.53
13c	TMP–CH_2CO	17	158—160	AcOEt	$C_{26}H_{34}Cl_2N_2O_5$	59.43 (59.64	6.52 6.57	5.33 5.27)	Inact.
13d	TMP–CH=CHCO	39	205—210 (dec.)	MeOH–AcOEt	$C_{27}H_{34}Cl_2N_2O_5 \cdot HCl \cdot 0.5H_2O$	55.63 (55.88	6.22 6.14	4.81 5.03)	Inact.

a) See footnote *a*) of Table I. *b*) A: 3-(3,4-dichlorophenyl)-3-hydroxypentyl. *c*) TMP: 3,4,5-trimethoxyphenyl.

TABLE V. 1-Substituted 4-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]piperazines Prepared by Method D



Compd. No.	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)			Potency[a]
						C	H	N	
12c	$(Ph)_2CH$	34	209—212 (dec.)	MeOH–Et_2O	$C_{28}H_{32}Cl_2N_2O \cdot 2HCl$	60.44 (60.21	6.16 6.03	5.03 5.01)	Inact.
12d	Me	23	230—234 (dec.)	EtOH	$C_{16}H_{24}Cl_2N_2O$	47.54 (47.32	6.48 6.57	6.93 6.98)	0.82
12e	Ph	19	216—220 (dec.)	MeOH	$C_{21}H_{26}Cl_2N_2O \cdot 2HCl$	54.09 (54.24	6.05 6.09	6.01 6.02)	N.T.
12f	TMP[b]	8	178—179 (dec.)	EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot HCl \cdot 1.5H_2O$	52.71 (52.83	6.63 6.57	5.12 5.08)	0.20
12g	$(Ph\text{-}4F)_2CH$[c]	18	150—151	EtOH	$C_{28}H_{30}Cl_2F_2N_2O$	64.74 (65.23	5.82 5.99	5.39 5.41)	Inact.
12h	Ph(2-Py)CH[d]	45	161—163 (dec.)	CH_3CN	$C_{27}H_{31}Cl_2N_3O \cdot 4OX$	49.77 (49.66	4.65 4.62	4.98 4.88)	0.62
12i	$HOCH_2CH_2$	14	230—233 (dec.)	MeOH	$C_{17}H_{26}Cl_2N_2O_2 \cdot 2HCl$	47.02 (47.12	6.50 6.44	6.45 6.69)	0.72
14a	$AcOCH_2CH_2$	16	169—171 (dec.)	EtOH	$C_{19}H_{28}Cl_2N_2O_3 \cdot 2MA$[f]	51.03 (51.07	5.71 5.77	4.41 4.35)	0.22
14b	TMP–$COOCH_2CH_2$	16	162—167	EtOH	$C_{27}H_{36}Cl_2N_2O_6 \cdot 2MA$	53.37 (53.30	5.63 5.49	3.56 3.47)	Inact.

a, b) See footnotes *a*) and *c*), respectively, of Table IV. *c*) Ph-4F: 4-fluorophenyl. *d*) 2-Py: 2-pyridyl. *e*) Oxalate. *f*) Maleate.

action of **1** and cinnarizine are likely to be different.

Experimental

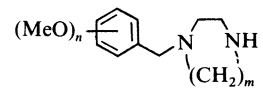
Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Hitachi R-24A NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Silica gel 60 F_{254} (Merck) thin layer chromatography plates were used for thin layer chromatography. For column chromatography, Silica gel 60 (Merck) and alumina N, Akt. I (Woelm) were used. An Aldrich Kugelrohr apparatus was used for bulb-to-bulb distillation.

General Method for Benzyl(homo)piperazines——a) By Leuckart–Wallach Reaction[7a]: 3,4,5-Trimethoxybenzaldehyde (49.1 g) and anhydrous piperazine (43 g) were heated in an oil bath at 90—100 °C. Formic acid (45 ml) was added dropwise to the molten mixture, and the whole was stirred for 5 h, then 20% NaOH aq. was added and the reaction mixture was refluxed for 2 h. After the mixture had cooled to room temperature, the product was extracted with benzene (200 ml × 2). The benzene layer was washed with sat. NaCl aq. and concentrated under reduced pressure. The residue was distilled by Kugelrohr apparatus to give a clear oil, which solidified on standing. HCl–MeOH was added to a methanol solution of the oil, and the precipitated solid was filtered off and recrystallized from EtOH. **5h**: mp 210—211 °C (dec.).

Compounds **5a**—**i** were obtained in the same manner as described for **5h**. The yields, melting points and elementary analytical data are given in Table VI. The homopiperazine analogs **5j, k** failed to crystallize, so they were used in the next step without further purification.

b) By the Method of Craig and Young[7f]: 3,4,5-Trimethoxybenzyl chloride[8] (43.4 g) in EtOH (400 ml) was added

TABLE VI. Substituted Benzyl(homo)piperazine Dihydrochlorides **5**



Compd. No.	$(OMe)_n$	m	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
5a	2-OMe[a]	2	35	207—209	EtOH	$C_{12}H_{18}N_2O\cdot 2HCl$	51.62 (51.62	7.22 7.26	10.03 10.02)
5b	3-OMe[b]	2	35	216—218	EtOH	$C_{12}H_{18}N_2O\cdot 2HCl$	51.62 (51.63	7.22 7.21	10.03 10.05)
5c	4-OMe[c]	2	27	253—255 (dec.)	EtOH	$C_{12}H_{18}N_2O\cdot 2HCl\cdot H_2O$	48.49 (48.33	7.46 7.48	9.42 9.64)
5d	2,3-$(OMe)_2$	2	32	215—218 (dec.)	EtOH	$C_{13}H_{20}N_2O_2\cdot 2HCl$	50.49 (50.45	7.17 7.23	9.59 9.39)
5e	2,4-$(OMe)_2$	2	34	187—188 (dec.)	EtOH	$C_{13}H_{20}N_2O_2\cdot 2HCl\cdot 0.25H_2O$	49.76 (49.72	7.23 7.18	8.93 9.05)
5f	3,4-$(OMe)_2$[d]	2	34	228—229 (dec.)	MeOH–Et_2O	$C_{13}H_{20}N_2O_2\cdot 2HCl\cdot 0.5H_2O$	49.06 (48.79	7.29 7.31	8.80 8.95)
5g	3,5-$(OMe)_2$	2	35	220—221 (dec.)	EtOH–Et_2O	$C_{13}H_{20}N_2O_2\cdot 2HCl\cdot 0.25H_2O$	49.76 (49.70	7.23 7.19	8.93 8.90)
5h	3,4,5-$(OMe)_3$[e]	2	47[f]	210—211 (dec.)	EtOH	$C_{14}H_{22}N_2O_3\cdot 2HCl$	49.56 (49.34	7.13 7.26	8.26 8.12)
5i	2,4,6-$(OMe)_3$	2	36	218—224 (dec.)	MeOH–Et_2O	$C_{14}H_{22}N_2O_3\cdot 2HCl$	49.56 (49.61	7.13 7.14	8.26 8.24)
5j	2,3,4-$(OMe)_3$	3	50			[g]			
5k	3,4,5-$(OMe)_3$	3	43			[g]			

a) For free base and maleate, see ref. 7*b*). *b*) For free base and maleate, see ref. 7*c*). *c*) Lit.[7d] mp 261—263 °C. *d*) Lit.[7e] mp 222—226 °C. For free base, see J. R. Boissier, R. Ratouis and C. Dumont, *J. Med. Chem.*, **6**, 541 (1963). *e*) For free base, see H. G. Morren, Belg. Patent 560330 (1958) [*Chem. Abstr.*, **53**, 16169*c* (1959)]. *f*) See experimental section. *g*) Used in the next step without purification.

dropwise to a mixture of piperazine·$6H_2O$ (38.8 g) and piperazine·2HCl·H_2O (35.4 g) in EtOH (200 ml) at 60 °C. After being stirred for 2 h at 60 °C, the mixture was allowed to cool. The precipitated solid was filtered off and the solution was concentrated under reduced pressure. Then 1.5 N HCl (200 ml) and benzene (200 ml) were added to the residue, and the water layer was separated, made basic with 20% NaOH and extracted with benzene (200 ml × 2) by the salting-out technique. Concentration of the benzene layer gave free **5h** (38.5 g).

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]-4-(3,4,5-trimethoxybenzyl)piperazine Dimaleate (8k)——Method A: A mixture of **5h** (1.7 g), 3-(3,4-dichlorophenyl)-3-hydroxypentyl chloride (1.27 g), triethylamine (2.2 g) and xylene (30 ml) was refluxed for 9 h. The cooled mixture was washed with water and dried over $MgSO_4$. After removal of the solvent by evaporation, maleic acid (0.8 g) and MeOH (30 ml) were added to the residue. The precipitated solid was filtered off and recrystallized from MeOH–water. **8k**: 0.75 g (yield, 21%), mp 184—186 °C (dec.).

Compounds **8a**—**m** and **8w**—**z** were obtained in the same manner as described for **8k**. The yields, melting points and elementary analytical data are given in Tables I and III.

1-(3,4-Dichlorobenzoylethyl)-4-(3,4,5-trimethoxybenzyl)piperazine Dihydrochloride (9a)——A mixture of **5h** (3.0 g), ω,3,4-trichloropropiophenone (2.1 g), triethylamine (3.1 g) and xylene (50 ml) was refluxed for 9 h. The cooled mixture was washed with water and dried over $MgSO_4$. Removal of the solvent by evaporation gave free **9a** (3.5 g, yield, 85%) as a pale brown oil. The oil, which solidified on standing, was used in the next step without further purification. An analytical sample was prepared as follows; HCl–MeOH was added to an ethanol solution of the oil to give a precipitated solid, which was filtered off and recrystallized from MeOH. **9a**: mp 211—215 °C (dec.). *Anal.* Calcd for $C_{23}H_{28}Cl_2N_2O_4 \cdot 2HCl$: C, 51.13; H, 5.60; N, 5.18. Found: C, 51.00; H, 5.55; N, 5.07.

9b was obtained in the same manner as described for **9a**. Crude free base of **9b** (15.4 g) was obtained from **5h** (10.6 g) as a pale brown oil and used in the next step without further purification. **9b**: mp 206—207 °C (dec.). *Anal.* Calcd for $C_{23}H_{28}Cl_2N_2O_4 \cdot 2HCl$: C, 51.13; H, 5.60; N, 5.18. Found: C, 51.13; H, 5.58; N, 5.17.

1-[3-(2,4-Dichlorophenyl)-3-hydroxypentyl]-4-(3,4,5-trimethoxybenzyl)piperazine Dihydrochloride (8n)——Method B: A small portion of a solution of ethyl iodide (68.9 g) in dry Et_2O (100 ml) was added dropwise to magnesium turnings (10.7 g) under a nitrogen atmosphere. After the spontaneous reaction had begun, residual ethyl iodide solution was added at a rate sufficient to maintain gentle reflux. When the addition was complete, the mixture was stirred for 1 h at room temperature then cooled in an ice-bath. The free base of **9b** (15.8 g) in dry benzene (200 ml) was added dropwise, and the reaction mixture was stirred for 2 h. After the usual work-up, the product was chromatographed on silica gel with AcOEt. Concentration of the eluate gave 10.1 g of the free base of **8n** as a brown oil. HCl–MeOH was added to a methanol solution of the oil and the resulting precipitate was filtered off and recrystallized from EtOH. **8n**: 7.8 g (yield, 40%), mp 236—240 °C (dec.).

Compounds **8o**—**v** were obtained in the same manner as described for **8n**. The yields, melting points and elementary analytical data are given in Table II.

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]piperazine (10) and 1,4-Bis[3-(3,4-dichlorophenyl)-3-hydroxypentyl]-piperazine (11)——Piperazine hexahydrate (77.7 g), **7b** (53.5 g) and xylene (500 ml) were refluxed for 5 h. The cooled mixture was washed with 10% NaOH then water and dried over $MgSO_4$. After removal of the solvent by evaporation, the oily residue was chromatographed on alumina. Concentration of the AcOEt eluate gave 1.7 g of **11**. An analytical sample was recrystallized from AcOEt. Elution with AcOEt–MeOH (2 : 1) gave 28 g of **10** as an oil. To obtain an analytical sample, the free base was converted to the dihydrochloride and recrystallized from MeOH. The yields, melting points and elementary analysis data are given in Table IV.

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]-4-(3,4,5-trimethoxyphenethyl)piperazine Dihydrochloride (12b)——Method C: A mixture of 3,4,5-trimethoxyphenethyl chloride[9] (1.7 g), **10** (2.3 g), triethylamine (0.8 g) and xylene (50 ml) was refluxed for 30 h. The cooled mixture was washed with water and extracted with 3 N HCl. The aqueous layer was made basic with 1 N NaOH then extracted with benzene. The benzene layer was dried and concentrated. The residual brown oil was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (20 : 1) gave the free base of **12b** (0.7 g), which was converted to the dihydrochloride and recrystallized from EtOH.

Compound **12a** was obtained in a similar manner. The yields, melting points and elementary analytical data are given in Table IV.

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]-4-(3,4,5-trimethoxycinnamoyl)piperazine Hydrochloride (13d)——Method C: 3,4,5-Trimethoxycinnamic acid (1.5 g) and **10** (2.0 g) were dissolved in AcOEt (50 ml) and the mixture was cooled in an ice-bath. Then dicyclohexylcarbodiimide (DCC) (1.3 g) was added and the reaction mixture was kept in an ice box overnight. The precipitated solid was filtered off and 3 N HCl was added to the filtrate. Deposited crude **13d** was collected and recrystallized from AcOEt–MeOH.

Compounds **13a**—**c** were obtained in a similar manner. The yields, melting points and elementary analytical data are given in Table IV.

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]-4-[α-(2-pyridyl)benzyl]piperazine Tetraoxalate (12h)——A solution of piperazine (26.6 g) and α-(2-pyridyl)benzyl chloride[6] (6.3 g) in xylene (250 ml) was refluxed overnight. The mixture was washed with water and sat. NaCl, then dried over $MgSO_4$. Evaporation of the solvent gave crude 1-[α-(2-pyridyl)benzyl]piperazine (3.5 g). To obtain an analytical sample, the crude product was converted to the hydrochloride and recrystallized from EtOH. mp 245—247 °C (dec.). *Anal.* Calcd for $C_{16}H_{19}N_3 \cdot HCl \cdot 0.25H_2O$: C,

65.29; H, 6.94; N, 14.28. Found: C, 65.36; H, 7.00; N, 14.29.

A solution of the crude product obtained above (2.0 g), **7b** (1.9 g) and triethylamine (1.45 g) in xylene (100 ml) was refluxed overnight, then washed with water followed by sat. NaCl, and dried over $MgSO_4$. After removal of the solvent, the product was chromatographed on silica gel. Elution with AcOEt gave the free base of **12h** (1.2 g), which was converted to the tetraoxalate and recrystallized from CH_3CN.

1-[3-(3,4-Dichlorophenyl)-3-hydroxypentyl]-4-(2-hydroxyethyl)piperazine Dihydrochloride (12i)——Method D: A solution of triethylamine (1.6 g), 1-piperazineethanol (2 g) and **7b** (4.3 g) in xylene (40 ml) was refluxed for 4.5 h. The mixture was washed with water and dried. The solvent was evaporated off and the residue was diluted with EtOH (20 ml). Then HCl–MeOH was added and the precipitated solid was filtered off. Recrystallization from MeOH gave **12i** (0.94 g).

Compounds **12c**—**g** were obtained in a similar manner. The yields, melting points and elementary analytical data are given in Table V.

1-(2-Acetoxyethyl)-4-[3-(3,4-dichlorophenyl)-3-hydroxypentyl]piperazine Dimaleate (14a)——Triethylamine (1.7 g) and **12i** (2.1 g) were dissolved in CH_2Cl_2 and the mixture was cooled in an ice-bath. Acetyl bromide (0.9 g) in CH_2Cl_2 (10 ml) was added dropwise and the mixture was stirred for 1.5 h, washed with water, and dried over $MgSO_4$. The solvent was evaporated off and the residue was diluted with EtOH (10 ml). Maleic acid (1.21 g) in EtOH (25 ml) was added and the precipitated solid was collected. Recrystallization from EtOH gave **14a** (2.4 g).

Compound **14b** was obtained in a similar manner. The yields, melting points and elementary analytical data are given in Table V.

Biological Testing Method——The cerebral blood flow-increasing activity was measured by using the amount of vertebral blood flow as an index.[10] The potency of the test compounds was evaluated as described previously.[1]

References and Notes

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