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Benzylpiperazine Derivatives. VI.[1] Design and Syntheses of Vinylogs of 1-Benzyl-4-diphenylmethylpiperazine Derivatives and Their Cerebral Vasodilating Activities

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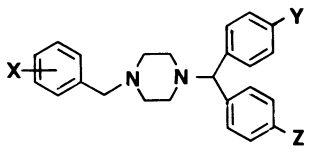
As a lead development based on the previous quantitative structure–activity relationship (QSAR) results on cerebral vasodilating activities of 1-benzyl-4-diphenylmethylpiperazines, 1-cinnamyl-4-diphenylmethylpiperazines having electron-donating groups on the cinnamyl moiety were designed. Two methods of synthesis were developed. As expected from the QSAR results, these compounds exhibited stronger potency and longer-lasting effect than cinnarizine and flunarizine.

Keywords——lead development; cinnamylpiperazine; diphenylmethylpiperazine; cinnarizine; flunarizine; cerebral vasodilating activity

In the previous paper, we described quantitative structure–activity relationships (QSAR) of 1-benzyl-4-diphenylmethylpiperazine derivatives (**1**) for cerebral vasodilating activity.[1] The results indicate that increase of the electron density on the benzylic nitrogen atom and the introduction of a sterically small substituent at the *para* position of the diphenylmethyl moiety bring about strong interaction of the molecule with the active site, resulting in high potency and prolonged action. Among the analogs, we selected 1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride (KB-2796) for clinical evaluation.

The above results prompted us to attempt a lead development. Although there may be several means to increase the electron density on the nitrogen atom, we selected the structure with a double bond between the phenyl residue and the methylene group to transmit the electronic effect of the substituents on the phenyl ring to the nitrogen atom. The substituent on the diphenylmethyl moiety was selected to be a hydrogen or a fluorine atom. Namely, 1-(substituted cinnamyl)-4-diphenylmethylpiperazines (**2**) were designed. These compounds correspond to substituted cinnarizine (**3**) or flunarizine (**4**), which were selected as references to modify the structure of trimetazidine at the beginning of this series of studies to search for a novel cerebral vasodilator.[2] In this paper, we describe the synthesis of these compounds as well as their cerebral vasodilating activities.



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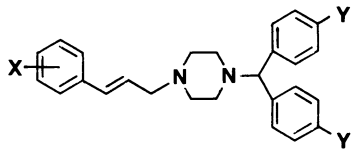

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3 (cinnarizine: X = Y = H)
4 (flunarizine: X = H, Y = F)

Chart 1

Chemistry

At first, the compounds (**2**) were synthesized by the route shown in Chart 2 (method A). Thus, a cinnamic acid derivative was converted to an acid chloride then condensed with a diphenylmethylpiperazine derivative. The product was converted to an acid addition salt and recrystallized in order to purify it (Table I). After reversion to the free base, the amide was reduced with lithium aluminum hydride in ether. The products are summarized in Table II.

As the above method gave very poor yields, other methods shown in Chart 3 (method B) were investigated. Thus, a cinnamic acid derivative was dissolved in *tert*-butanol–acetonitrile (5 : 1) in the presence of triethylamine then ethyl chloroformate was added to prepare a mixed anhydride. A diphenylmethylpiperazine derivative in the same solvent system was added to the mixed anhydride. After the reaction was completed, water was added to the mixture and

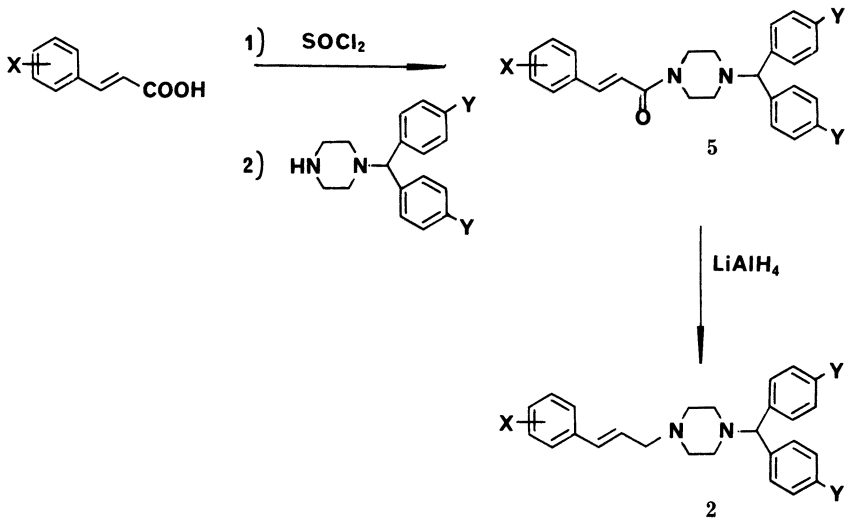
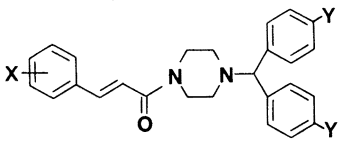


Chart 2

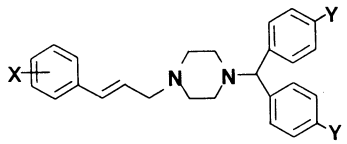
TABLE I. 1-Cinnamoyl-4-diphenylmethylpiperazines Obtained by Method A



Compd. No.	X	Y	Yield (%)	mp (°C)	Recrystn.[a] solvent	Formula[b]	Analysis (%) Calcd (Found)		
							C	H	N
5a	2,3,4-$(OMe)_3$	F	28	225—229 (dec.)	M	$C_{29}H_{30}F_2N_2O_4 \cdot HCl$	63.91 (63.69	5.73 5.89	5.14 5.08)
5b	2,3,4-$(OMe)_3$	H	44	207—209 (dec.)	E	$C_{29}H_{32}N_2O_4 \cdot HCl$	68.43 (68.32	6.53 6.60	5.50 5.56)
5c	2,4-$(OMe)_2$	F	29	195—197	C–M	$C_{28}H_{28}F_2N_2O_3 \cdot 0.5FA$	67.15 (67.11	5.64 5.68	5.22 5.27)
5d	2,4-$(OMe)_2$	H	40	239—241 (dec.)	M	$C_{28}H_{30}N_2O_3 \cdot HCl$	70.21 (70.07	6.52 6.53	5.85 5.87)

a) C = $CHCl_3$, E = EtOH, IP = iso-PrOH, M = MeOH, W = water. *b*) FA stands for fumaric acid.

TABLE II. 1-Cinnamyl-4-diphenylmethylpiperazines



Compd. No.	X	Y	Yield (%)[a] A	Yield (%)[a] B	mp (°C)	Recrystn.[b] solvent	Formula[c]	Analysis (%) Calcd (Found) C	H	N	Potency[d]
2a	2,3,4-$(OMe)_3$	F	24	56	205—212 (dec.)	E	$C_{29}H_{32}F_2N_2O_3 \cdot 2HCl$	61.38 (61.52)	6.04 (5.89)	4.94 (5.08)	1.25 (D)[e]
2b	2,3,4-$(OMe)_3$	H	20	58	230—234 (dec.)	E	$C_{29}H_{34}N_2O_3 \cdot 2HCl$	65.53 (65.35)	6.83 (6.79)	5.27 (5.42)	0.98 (D)
2c	2,4-$(OMe)_2$	F	33	51	194—195	E–W	$C_{28}H_{30}F_2N_2O_2 \cdot FA$	66.20 (66.12)	5.90 (5.91)	4.82 (4.73)	1.25 (D)
2d	2,4-$(OMe)_2$	H	26	59	192—195 (dec.)	E–W	$C_{28}H_{32}N_2O_2 \cdot FA$	70.57 (70.75)	6.66 (6.63)	5.14 (5.21)	0.99 (D)
2e	4-$N(Me)_2$	F	35[f]		186—189 (dec.)	IP	$C_{28}H_{31}F_2N_3 \cdot FA$	68.19 (68.40)	6.26 (6.29)	7.46 (7.48)	1.65 (D)
Cinnarizine											0.71
Flunarizine·2HCl											0.79 (D)

a) Yields are based on isolated amides. A and B mean method A and method B, respectively. *b*) and *c*) See footnotes *a*) and *b*) of Table I, respectively. *d*) The potency is expressed as the ratio of cerebral vasodilating activity to that of papaverine taken as 1. (D) stands for prolonged duration of action. *e*) Data obtained with a dose of 0.3 mg/kg, i.v. Other compounds were administered at a dose of 1 mg/kg, i.v. *f*) See the text.

the amide that precipitated was collected by filtration in high yield. In the case of **5b**, which is an oil, the product was extracted with ethyl acetate. The amides obtained by this procedure were pure enough to use in the next step without further purification. The amides were reduced in toluene with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) to give compounds **2a–d** in high yields (Table II).

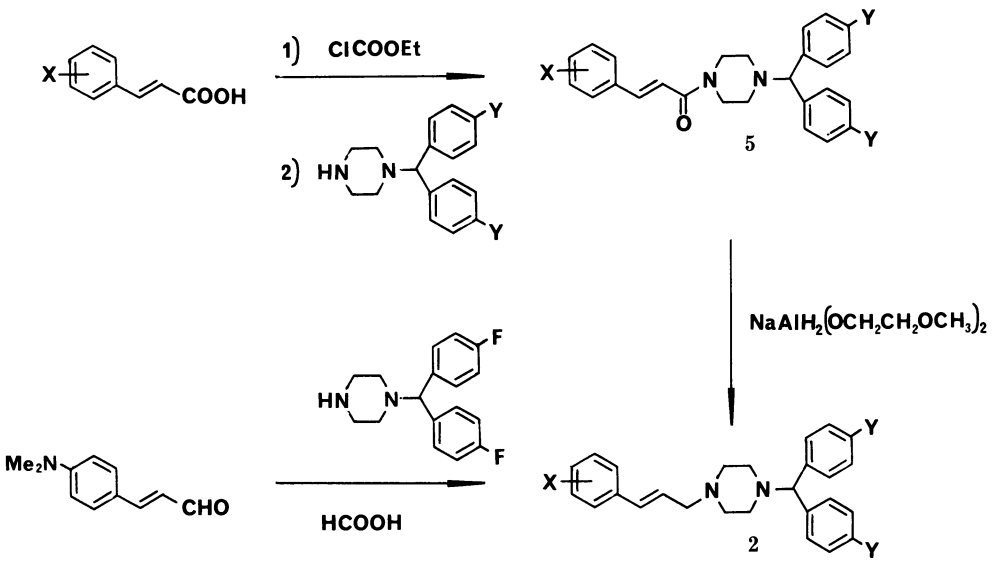


Chart 3

The *p*-dimethylamino derivative (**2e**) was obtained in a single step by using the Leuckart–Wallach reaction from the corresponding cinnamaldehyde, which was available commercially.

TABLE III. Free Base of 1-Cinnamoyl-4-diphenylmethylpiperazines Obtained by Method B

Compd. No.	X	Y	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
Free **5a**	2,3,4-$(OMe)_3$	F	80	175—177	Benzene	$C_{29}H_{30}F_2N_2O_4$	68.49	5.95	5.51
							(68.36	6.00	5.53)
Free **5b**	2,3,4-$(OMe)_3$	H	100[a]						
Free **5c**	2,4-$(OMe)_2$	F	82	171—173	Benzene	$C_{28}H_{28}F_2N_2O_3$	70.28	5.90	5.85
							(70.30	5.77	5.85)
Free **5d**	2,4-$(OMe)_2$	H	85	175—177	Benzene	$C_{28}H_{30}N_2O_3$	75.99	6.83	6.33
							(75.78	6.77	6.26)

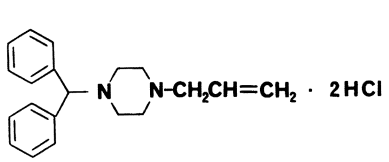
a) Free **5b** was an oil. Physical data of the HCl salt of this compound were the same as those of **5b** of Table I.

Results and Discussion

The compounds listed in Table II were tested for cerebral vasodilating activity by the method reported previously.[2] As expected from the previous QSAR results, these compounds, which have electron-donating substituents on the cinnamyl moiety, exhibited stronger activity and longer duration of action than **3** and **4**. The bis(4-fluorophenyl)methyl derivatives (**2a** and **2c**) were more potent than the corresponding diphenylmethyl analogs (**2b** and **2d**).

The *p*-dimethylamino derivative (**2e**) was one of the most active compounds, but its acute toxicity ($LD_{50} < 45$ mg/kg) was very strong. Similar results were reported for the *p*-dimethylaminobenzyl derivative previously.[3] These results suggest that 1-benzyl-4-diphenylmethylpiperazines (**1**) and 1-cinnamyl-4-diphenylmethylpiperazines (**2**) exhibit not only cerebral vasodilating activity but also toxicity through similar mechanisms. Among these derivatives, the most active **2a** was selected for further study.

Many substituted cinnarizine derivatives have been reported,[4,5] but there seems to be no compound which is more potent than **3** and **4**, because some have an electron-withdrawing group on the cinnamyl moiety and some have a bulky substituent on the diphenylmethyl residue. Aligeron[6] (**6**) and Cinepazide[7] (**7**), cerebral vasodilators containing a piperazine moiety, can be regarded as analogs of **3**. The potencies of these compounds evaluated by the same method were 0.4 for **6** and 0.04 for **7**. Thus, **2a** is thought to be one of the most potent analogs of **3**.



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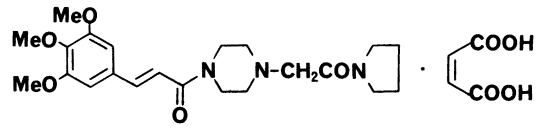

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Chart 4

Experimental

Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Hitachi R-24A NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Silica gel 60 F_{254} (Merck) TLC plates were used for thin layer chromatography (TLC). For column chromatography, Silica gel 60 (Merck) was used.

Typical Procedures of Method A——1-Diphenylmethyl-4-(2,3,4-trimethoxycinnamoyl)piperazine Hydrochloride (**5b**): 2,3,4-Trimethoxycinnamic acid (5.0 g) was suspended in $CHCl_3$ (20 ml), and $SOCl_2$ (7.0 ml) was added dropwise under ice cooling. The mixture was stirred for 0.5 h then the excess $SOCl_2$ and $CHCl_3$ were distilled off under reduced pressure. The residue was diluted with CH_2Cl_2 (40 ml) and added dropwise under ice cooling to a solution of diphenylmethylpiperazine (4.0 g) in CH_2Cl_2 (60 ml). The mixture was stirred for 0.5 h under ice cooling, 10% $NaHCO_3$ was added to the mixture, and then the organic layer was separated, washed with water and dried over $MgSO_4$. After the solvent had been distilled off, the residue was dissolved in EtOH (40 ml). Concentrated HCl (2 ml) was added to the solution and then Et_2O was added. The precipitated solid was collected by filtration and recrystallized from EtOH to give **5b** (4.4 g).

Compounds **5a, 5c** and **5d** were obtained in the same manner as described for **5b,** but **5c** was obtained as the hemifumarate. The yield, melting point and elementary analysis data are given in Table I.

1-Diphenylmethyl-4-(2,3,4-trimethoxycinnamyl)piperazine Dihydrochloride (**2b**): **5b** (3.7 g) was suspended in a mixture of AcOEt and water, and with stirring, 20% NaOH was added to adjust the pH of the aqueous layer to 9—10. The AcOEt layer was separated, washed with water, and dried over $MgSO_4$. The solvent was distilled off under reduced pressure and the resulting free base was dissolved in dry Et_2O (60 ml). Lithium aluminum hydride (0.3 g) was added portionwise to the mixture at room temperature, and the whole was stirred for 4 h at room temperature. Water was added portionwise, and then 3 N HCl was added to make the mixture nearly neutral. The organic layer was separated, washed with water, and dried over $MgSO_4$. After the solvent had been distilled off, the residue was diluted with EtOH (10 ml). Concentrated HCl (1 ml) was added to the solution and the precipitated solid was collected by filtration and recrystallized from EtOH to give **2b** (0.8 g).

Compounds **2a**,**2c** and **2d** were obtained in the same manner as described for **2b**, but **2c** and **2d** were obtained as the fumarates. The yield, melting point and elementary analysis data are given in Table II.

Typical Procedures of Method B——1-[Bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxycinnamoyl)piperazine (Free Base of **5a**): A solution of 2,3,4-trimethoxycinnamic acid (30.0 g) and triethylamine (25.5 g) in *tert*-BuOH–MeCN (5 : 1, v/v) (300 ml) was cooled in an ice-bath. A solution of ethyl chloroformate (13.7 g) in *tert*-BuOH–MeCN (5 : 1, v/v) (40 ml) was added dropwise, then the mixture was stirred for 0.5 h. A solution of 1-[bis(4-fluorophenyl)methyl]piperazine (36.3 g) in *tert*-BuOH–MeCN (5 : 1,v/v) (150 ml) was added dropwise, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice-water (450 ml) and the deposited solid was collected by filtration, washed with water (400 ml) and then dried to give the free base of **5a** (51 g).

1-[Bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxycinnamyl)piperazine Dihydrochloride (**2a**): A toluene (10 ml) solution of sodium bis(2-methoxyethoxy)aluminum hydride (70% toluene solution, Vitride, Hexcel Corporation) (8.66 g) was added to a toluene (100 ml) solution of the free base of **5a** (10.16 g) and the mixture was stirred for 0.5 h. Water (30 ml) was added and the deposited solid was filtered off. The organic layer was separated and washed with water, then dried over $MgSO_4$. After evaporation of the solvent, the residue was diluted with $ClCH_2CH_2Cl$ (100 ml) and concentrated HCl (4 ml) was added. The precipitated solid was collected by filtration and recrystallized to give **2a** (6.36 g).

Compounds **2c** and **2d** were obtained as the fumarate in the same manner as described for **2a**. In the case of **2b,** the intermediate, the free base of **5b**, was not a solid. Therefore the free base of **5b** was obtained by extraction. The reduction process was similar to that for **2a**. The results are summarized in Table II.

1-(4-Dimethylaminocinnamyl)-4-[bis(4-fluorophenyl)methyl]piperazine Fumarate (2e)——4-Dimethylaminocinnamaldehyde (1.8 g) and 1-[bis(4-fluorophenyl)methyl]piperazine (2.9 g) were melted in an oil bath at 120 °C and formic acid (0.5 ml) was added dropwise. The mixture was stirred for 1 h under heating, and then allowed to cool to room temperature. The mixture was diluted with EtOH (10 ml), a solution of fumaric acid (2.3 g) in EtOH (40 ml) was added, and the deposited solid was collected. Recrystallization from iso-PrOH gave **2e** (2.0 g). The yield, melting point and elementary analysis data are given in Table II.

Biological Testing Method[2]——The cerebral blood flow-increasing activity was measured by using the amount of vertebral blood flow as an index.[8] Mongrel dogs of either sex (body weight 11 to 18 kg) were anesthetized with sodium pentobarbital (30 mg/kg, by intravenous injection) and artificially ventilated. The right vertebral artery was isolated from the surrounding tissues and a flow probe was attached to it and led to an electromagnetic flow meter (MVF-2100, Nihon Koden Co., Ltd.). The blood flow was periodically measured.

Each of the test compounds was dissolved in a 2% tartaric acid solution containing 20% dimethylacetamide, and administered to the right femoral vein at a dose of 1 mg/kg. The potency was expressed in terms of the ratio of the maximum change of blood flow induced by the test compound to that induced by papaverine.

References and Notes

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