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Synthesis and pharmacological study of new calcium antagonists, analogues of cinnarizine and flunarizine

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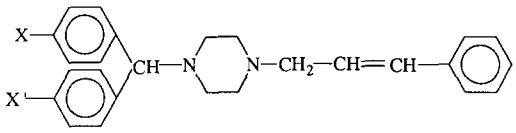
Summary — Several phosphonic diethyl esters were synthesized and their calcium antagonistic activity evaluated *in vitro*. The diethyl phosphonate group was condensed on substituted [diphenylmethyl], [(2-benzofuranyl)phenylmethyl], [(4-(diphenylmethyl-1-piperazinyl) methyl], [4-(4-diphenylmethyl-1-piperazinyl methyl) phenylmethyl], and [4-(3-phenyl-2-propenyl)-1-piperazinyl methyl] groups. Despite the presence of the diethyl phosphonate moiety and the benzhydrylpiperazinyl group, both present in potent calcium antagonist structures, only 1 of the 19 synthesized compounds exhibited a calcium antagonistic profile.

diethyl phosphonate / benzhydryl piperazine / calcium antagonist

Introduction

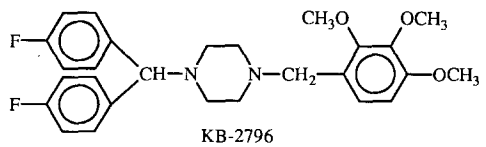
The benefit of a diethyl phosphonate moiety in conferring calcium antagonistic activity has been demonstrated in the Fostedil series [1], described in 1982 as a new calcium antagonist, and in the dihydropyridines [2, 3] already used in therapy. To potentiate calcium antagonism we envisaged the insertion of a diethoxy phosphono methyl group into analogues of cinnarizine and flunarizine (scheme 1) which are already in therapeutic use on account of their calcium antagonistic properties.



X = X' = H Cinnarizine
X = X' = F Flunarizine

Scheme 1.

These molecules can be considered as cinnamyl piperazines or benzhydrylpiperazines. The diethyl phosphonate group was incorporated into different substituted benzhydryl moieties (series I) and the diethyl methyl phosphonate group into substituted benzhydrylpiperazines or into cinnamyl piperazines (series II). In the first series one phenyl group was also replaced by a benzofuranic group. This situation is, in fact, already found in the calcium antagonist piprofurol, and the equivalent activity of some benzofuranic compounds to fostedil has been shown [4]. Due to the presence of fluorine in flunarizine and its positive role in calcium antagonism [5], this substituent was also introduced into some of our compounds. To further approach the basic model, the diethyl methyl benzylphosphonate group was also incorporated into benzhydrylpiperazines or into cinnamyl piperazines (series III). This gave us a very similar structure to that of KB-2796 (scheme 2), also described as a calcium antagonist [6].



KB-2796

Scheme 2.

*Correspondence and reprints

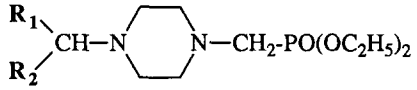
The structures of the selected products have been reported in table I.

Table I. The 3 phosphonates series.

Series I

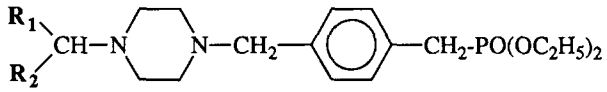
4 : a, b, c, d, e, f, g .

Series II



7 : a, b, c, d, e, h.

Series III



8 : a, b, c, d, e, h.

	a	b	c	d	e
R_1	C_6H_5	*p* F-C_6H_4	*p* Cl-C_6H_4	*p* Cl-C_6H_4	*p* CH_3O-C_6H_4
R_2	C_6H_5	*p* F-C_6H_4	C_6H_5	*p* Cl-C_6H_4	*p* CH_3O-C_6H_4

	f	g	h
R_1	Benzofuran-2-yl	Benzofuran-2-yl	C_6H_5-CH=CH-
R_2	C_6H_5	*p* F-C_6H_4	H

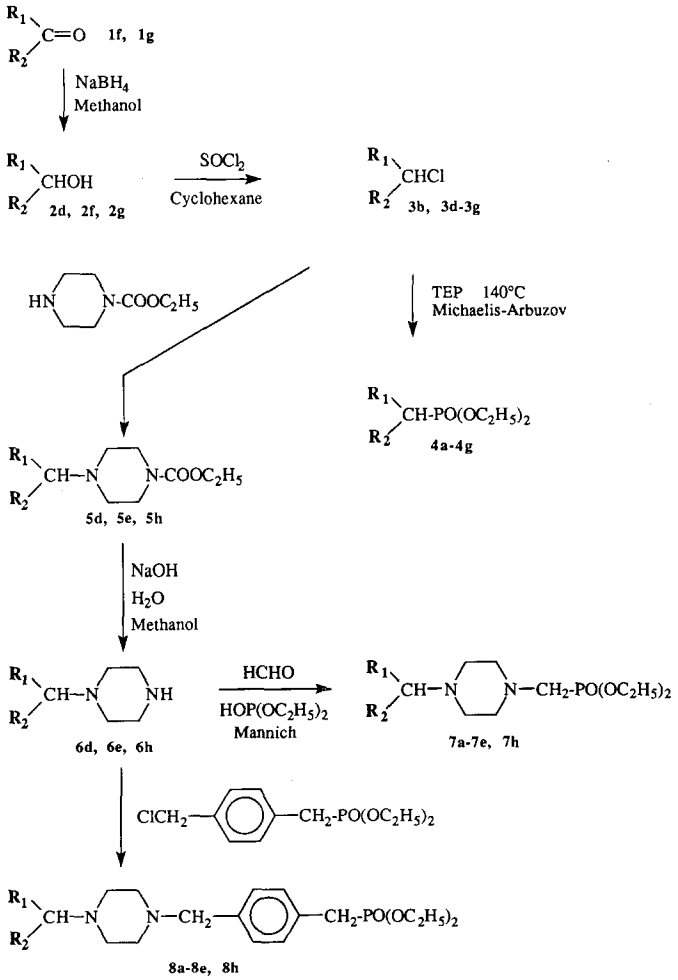
Table II. Chemical and physical data of derivatives **4**.

Compd	*Formula*	*M.W.*	*Yield (%)*	*Mp(°C) / n_D*	R_f*
4a [11]	$C_{17}H_{21}O_3P$	304	30	1.5525(19°C)	0.92
4b	$C_{17}H_{19}F_2O_3P$	340	74	1.5110(19°C)	0.66
4c [12]	$C_{17}H_{20}ClO_3P$	338.5	11	1.5425(18°C)	0.73
4d [12]	$C_{17}H_{19}Cl_2O_3P$	373	11	1.5515(18°C)	0.76
4e	$C_{19}H_{25}O_5P$	364	91	68	0.64
4f	$C_{19}H_{21}O_4P$	344	53	1.5630(25°C)	0.87
4g	$C_{19}H_{20}FO_4P$	362	66	1.5539(19°C)	0.66

*Ethyl acetate.

Chemistry

The syntheses of diethyl phosphonates **4**, **7** and **8** were conducted by the sequence shown in scheme 3 starting from the alcohols **2**. The alcohols **2a**, **2b**, **2c** and **2e** are commercially available. Alcohol **2d** [7] was obtained by reduction of 4,4'-dichlorobenzophenone with sodium borohydride. The alcohols **2f** [8] and **2g** [9] were prepared from 2-benzofurancarboxylic acid as starting material. Treatment of the carboxylic acid with thionyl chloride yielded 2-benzofurancarbonyl chloride which was condensed with benzene or fluorobenzene respectively to give 2-benzoyl benzofuranes **1f** [8] and **1g** [10]. Reduction of the ketones with sodium borohydride afforded the corresponding alcohols **2f** and **2g**.



Scheme 3.

Table III. Chemical and physical data of derivatives **7**.

Compd	Formula	M.W.	Yield (%)	Mp(°C) $/n_D$	R_f*
7a	$C_{22}H_{31}N_2O_3P$	402	9	1.5515(22°C)	0.40
7b	$C_{22}H_{29}F_2N_2O_3P$	438	11	1.5112(19°C)	0.61
7c	$C_{22}H_{30}ClN_2O_3P$	436.5	16	53	0.60
7d	$C_{22}H_{29}Cl_2N_2O_3P$	471	33	135	0.58
7e	$C_{24}H_{35}N_2O_5P$	462	87	1.5409(19°C)	0.36
7h	$C_{18}H_{29}N_2O_3P$	352	56	1.5119(21°C)	0.60**

*Ethyl acetate; **ethanol.

Table IV. Chemical and physical data of derivatives **8**.

Compd	Formula	M.W.	Yield (%)	Mp(°C) $/n_D$	R_f*
8a	$C_{29}H_{37}N_2O_3P$	492	12	89	0.27
8b	$C_{29}H_{35}F_2N_2O_3P$	528	50	1.5339(22°C)	0.24
8c	$C_{29}H_{36}ClN_2O_3P$	526.5	50	1.5509(22°C)	0.32
8d	$C_{29}H_{35}Cl_2N_2O_3P$	561	23	1.5419(20°C)	0.26
8e	$C_{31}H_{41}N_2O_5P$	552	40	89	0.20
8h	$C_{25}H_{35}N_2O_3P$	442	33	1.5350(22°C)	0.59**

*Ethyl acetate; **ethanol.

The halogen derivatives **3a**, **3b** and **3c** are commercially available. The desired halogen derivatives **3d**, **3e**, **3f** and **3g** could be obtained by chlorination of the corresponding alcohols **2** with thionyl chloride. The diethylphosphonates **4a** [11], **4b**, **4c** [12], **4d** [12], **4e**, **4f**, and **4g** were prepared *via* the Arbuzov–Michaelis reaction [13], by heating the halogen derivatives **3** with triethyl phosphite (TEP). *N*-Alkylation of ethyl 1-piperazinecarboxylate with the halides **3d**, **3e** or **3h** in anhydrous tetrahydrofuran (THF) in the presence of potassium carbonate yielded the ethoxycarbonylpiperazines **5**, which were hydrolyzed by sodium hydroxide to provide the key piperazines **6d**, **6e**, and **6h** respectively; the piperazines **6a**, **6b**, and **6c** are commercially available.

The diethyl piperazinylmethyl phosphonate derivatives **7a**, **7b**, **7c**, **7d**, **7e** and **7h** could be synthesized *via* the Mannich reaction [14, 15] by reaction of the piperazines **6** with formaldehyde and diethyl phosphite.

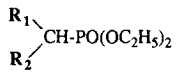
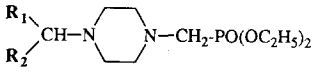
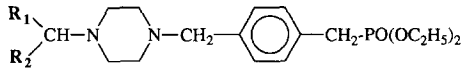
Finally, the benzhydryl piperazinylmethyl phosphonates **8a**, **8b**, **8c**, **8d**, **8e** and the cinnamyl piperazinylmethyl phosphonate **8h** were prepared by alkylation of the corresponding piperazines **6** with diethyl [4-(chloromethyl)benzyl]phosphonate [16] in anhydrous THF.

The chemical and physical data of compounds **4**, **7** and **8** have been listed in tables II–IV.

Pharmacology

In vitro calcium antagonism was detected by examining the reduction of the contraction of rabbit aortal strips in the presence of calcium chloride. For comparison, the calcium antagonistic effects of cinnarizine and flunarizine together with those of cyclizine and chlorcyclizine (methyl analogues of compounds **7a** and **7c**), were assayed under the same experimental conditions. The results are given as percentage relaxation and are reported in table V.

Table V. *In vitro* calcium antagonistic activity: reduction of the contraction of rabbit aortal strips at 0.5 µg/ml in the presence of calcium chloride.

Compd	R_1	R_2	% Inhibition
			
4a	C_6H_5	C_6H_5	-1
4b	*p* F-C_6H_4	*p* F-C_6H_4	-12
4c	*p* Cl-C_6H_4	C_6H_5	-6
4d	*p* Cl-C_6H_4	*p* Cl-C_6H_4	-1
4e	*p* $CH_3OC_6H_4$	*p* $CH_3OC_6H_4$	-7
4f	Benzofuran-2-yl	C_6H_5	+2
4g	Benzofuran-2-yl	*p* F-C_6H_4	-8
			
7a	C_6H_5	C_6H_5	-17
7b	*p* F-C_6H_4	*p* F-C_6H_4	-6
7c	*p* Cl-C_6H_4	C_6H_5	-1
7d	*p* Cl-C_6H_4	*p* Cl-C_6H_4	-12
7e	*p* $CH_3OC_6H_4$	*p* $CH_3OC_6H_4$	-20
7h	C_6H_5-CH=CH-	H	0
			
8a	C_6H_5	C_6H_5	-23
8b	*p* F-C_6H_4	*p* F-C_6H_4	-44
8c	*p* Cl-C_6H_4	C_6H_5	-14
8d	*p* Cl-C_6H_4	*p* Cl-C_6H_4	-18
8e	*p* $CH_3OC_6H_4$	*p* $CH_3OC_6H_4$	-20
8h	C_6H_5-CH=CH-	H	-17
Cinnarizine			-48
Flunarizine			-39
Cyclizine			-19
Chlorcyclizine			-11

Results and discussion

Only 10 compounds exhibited slight calcium antagonism. For a product to be considered as having activity it must in fact inhibit aortic contraction by at least 10%. Only compound **8b** exhibited activity of the same order of magnitude as cinnarizine and flunarizine.

In general, the presence of a benzylphosphonate group (compounds of structure **8**) seemed to slightly improve activity.

In contrast, the introduction of a diethyl phosphonate group – contrary to observations in other series [1–3] – did not increase calcium antagonism. Thus compounds **7a** and **7c** were not more active than cyclizine or chlorcyclizine respectively, from which they only differ in the additional phosphonate group.

The frequently reported beneficial effect of fluorine [5] was not always apparent: thus flunarizine was not more active than cinnarizine, compound **4b** was slightly more active than **4a**, and compound **7b** was less active than **7a**. In conclusion, **8b** remained the most active compound.

Experimental protocols

The purity of compounds was systematically checked by TLC on Merck 60 F 254 silica gel. Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were obtained on a Perkin–Elmer 983 G apparatus using films for liquids or inclusion in KBr pellets for solids. ^{1}H-NMR spectra were recorded with a Bruker 200 Mz spectrometer; chemical shifts have been reported in δ units (ppm) relative to TMS as internal standard. Elemental analyses are in agreement with the accepted norms and have not been reported.

Preparation of chloromethyl derivatives ***3***

To a solution of alcohol **2** (0.02 mol) in cyclohexane (100 ml) was added thionyl chloride (10 ml). The mixture was refluxed for 24 h, then the solvent was removed by evaporating *in vacuo* and the residue recrystallized from cyclohexane or used as crude product.

Bis (4-chlorophenyl) methyl chloride ***3d***
$C_{13}H_9Cl_3$, mw: 271.5, yield: 98%, mp: 56°C, R_f (1,2-dichloroethane): 0.67. IR, KBr, ν cm^{-1}: 3153, 3027, 2983 (CH); 1589 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 6.1 (s, 1H, CH); 7.4 (m, 8H, Ar).

Bis (4-methoxyphenyl) methyl chloride ***3e***
$C_{15}H_{15}ClO_2$, mw: 262.5, yield: 95%, mp: 78°C, R_f (1,2-dichloroethane): 0.47. IR, KBr, ν cm^{-1}: 3170, 3098, 3069, 2998 (CH, CH_3); 1601 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 3.83 (s, 6H, 2 CH_3-O); 6.16 (s, 1H, CH); 7.0–7.4 (m, 8H, Ar).

2-(Chlorophenylmethyl) benzofuran ***3f***
$C_{15}H_{11}ClO$, mw: 242.5, yield: 89%, n_D (24°C): 1.6180, R_f (1,2-dichloroethane): 0.83. IR, film, ν cm^{-1}: 3085, 3064 (CH); 1612, 1493 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 7.2 (s, 1H, CH); 7.7 (s, 1H, H_3); 8.4–9.2 (m, 9H, Ar).

2-[Chloro-(4-fluorophenyl) methyl] benzofuran ***3g***
$C_{15}H_{10}ClFO$, mw: 260.5, yield: 99%, n_D (25°C): 1.6050, R_f (1,2-dichloroethane): 0.86. IR, film, ν cm^{-1}: 3069, 3043 (CH); 1612 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 7.3 (s, 1H, CH); 7.9 (s, 1H, H_3); 8.2–9.2 (m, 8H, Ar).

Preparation of diethyl phosphonates ***4***

A mixture of halogen compound **3** (0.01 mol) and triethyl phosphite (3.32 g, 0.02 mol) was heated at 140°C in an oil-bath for 6 h. After evaporation *in vacuo* of the excess triethylphosphite, the product was purified by column chromatography on silica gel with 1,1,1-trichloroethane as eluent.

Diethyl (diphenylmethyl) phosphonate ***4a***
IR, film, ν cm^{-1}: 3087, 3062, 2981, 2929, 2905 (CH, CH_2, CH_3); 1595 (C=C); 1249 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.0 (t, 6H, CH_2-CH_3); 3.9 (m, 4H, CH_2-CH_3); 4.4 (d, 1H, CH, J = 25 Hz); 6.9–7.3 (m, 10H, Ar).

Diethyl [bis (4-fluorophenyl) methyl] phosphonate ***4b***
IR, film, ν cm^{-1}: 2985, 2931, 2908 (CH, CH_2, CH_3); 1602 (C=C); 1226 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.3 (t, 6H, CH_2-CH_3); 4.0 (m, 4H, CH_2-CH_3); 4.4 (d, 1H, CH, J = 24 Hz); 7.1–7.5 (m, 8H, Ar).

Diethyl [(4-chlorophenyl) phenylmethyl] phosphonate ***4c***
IR, film, ν cm^{-1}: 3029, 2980, 2930, 2906 (CH, CH_2, CH_3); 1599 (C=C); 1248 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.16 (t, 6H, CH_2-CH_3); 3.93 (m, 4H, CH_2-CH_3); 4.38 (d, 1H, CH, J = 25 Hz); 7.2–7.4 (m, 9H, Ar).

Diethyl [bis (4-chlorophenyl) methyl] phosphonate ***4d***
IR, film, ν cm^{-1}: 3087, 3065, 3029, 2983, 2930, 2866 (CH, CH_2, CH_3); 1592 (C=C); 1247 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.14 (t, 6H, CH_2-CH_3); 4.03 (m, 4H, CH_2-CH_3); 4.4 (d, 1H, CH, J = 25 Hz); 7.2–7.5 (m, 8H, Ar).

Diethyl [bis (4-methoxyphenyl) methyl] phosphonate ***4e***
IR, KBr, ν cm^{-1}: 3059, 2977, 2931, 2903 (CH, CH_2, CH_3); 1607 (C=C); 1249 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.12 (t, 6H, CH_2-CH_3); 4.0 (m, 10H, CH_3O and CH_2-CH_3); 4.3 (d, 1H, CH, J = 25 Hz); 6.8–7.4 (m, 8H, Ar).

Diethyl [(2-benzofuranyl) phenylmethyl] phosphonate ***4f***
IR, film, ν cm^{-1}: 3086, 3063 (CH, CH_2, CH_3); 1580, 1493 (C=C); 1253 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.5 (m, 6H, CH_2-CH_3); 4.9 (m, 4H, CH_2-CH_3); 5.5 (d, 1H, CH, J = 25 Hz); 7.8 (s, 1H, H_3), 8.4–9.2 (m, 9H, Ar).

Diethyl [(2-benzofuranyl) (4-fluorophenyl) methyl] phosphonate ***4g***
IR, film, ν cm^{-1}: 3070, 2980 (CH, CH_2, CH_3); 1600 (C=C); 1250 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.45 (m, 6H, CH_2-CH_3); 4.65 (m, 4H, CH_2-CH_3); 5.2 (d, 1H, CH, J = 25 Hz); 8.2–9.1 (m, 9H, Ar).

Preparation of ethoxycarbonylpiperazines ***5***

A mixture of halogen compound **3** (0.04 mol) and ethyl piperazinecarboxylate (6.32 g, 0.04 mol) in anhydrous THF (200 ml) was heated to reflux for 2 h. Then potassium carbonate (5.52 g, 0.04 mol) was added and the mixture refluxed for a further 12 h. The reaction mixture was taken up in chloroform. After filtration, the organic phase was evaporated and the product purified by column chromatography on silica gel with 1,2-dichloroethane as eluent.

Ethyl [4-(bis (4-chlorophenyl) methyl)-1-piperazinyl] carboxylate ***5d***

$C_{20}H_{22}N_2Cl_2O_2$, mw: 393, yield: 19%, mp: 150°C, R_f (1,2-dichloroethane): 0.26. IR, KBr, ν cm^{-1}: 3025, 3000, 2995, 2800 (CH, CH_2, CH_3); 1700 (CO); 1598 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.23 (t, 3H, CH_2-CH_3); 2.31 (m, 4H, CH_2N); 3.46 (m, 4H, CH_2N); 4.13 (q, 2H, CH_2-CH_3); 4.19 (s, 1H, CH); 7.3–7.4 (m, 8H, Ar).

Ethyl [4-(bis (4-methoxyphenyl) methyl)-1-piperazinyl] carboxylate ***5e***

$C_{22}H_{28}N_2O_4$, mw: 384.5, yield: 39%, mp: 93°C, R_f (1,1,1-trichloroethane): 0.88. IR, KBr, ν cm^{-1}: 3013, 2998, 2987, 2950 (CH, CH_2, CH_3); 1700 (CO), 1602 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.21 (t, 3H, CH_2-CH_3); 2.32 (m, 4H, CH_2N); 3.45 (m, 4H, CH_2N); 3.75 (s, 6H, CH_3O); 4.12 (m, 3H, CH_2-CH_3 and CH); 6.8–7.2 (m, 8H, Ar).

Ethyl [4-(3-phenyl-2-propenyl)-1-piperazinyl] carboxylate ***5h***

$C_{16}H_{22}N_2O_2$, mw: 274, yield: quantitative, n_D (27°C): 1.5705, R_f (ethylacetate): 0.44. IR, film, ν cm^{-1}: 3127, 3101, 2990 (CH, CH_2, CH_3); 1699 (CO); 1600 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.25 (t, 3H, CH_2-CH_3); 2.72 (m, 4H, CH_2N); 3.43 (d, 2H, CH=CH-CH_2); 3.66 (m, 4H, CH_2N); 4.14 (q, 2H, CH_2-CH_3); 6.58 (m, 2H, CH=CH), 7.1–7.5 (m, 5H, Ar).

Preparation of benzhydryl and cinnamyl piperazines ***6***

To a solution of 1-carbethoxy-piperazine **5** (0.007 mol) in 50 ml methanol was added 100 ml 10% sodium hydroxide. The mixture was refluxed for 72 h as hydrolysis is very slow. After extraction with chloroform and evaporation under reduced pressure, the product was isolated by column chromatography on silica gel with ethanol as eluent.

1-[Bis (4-chlorophenyl) methyl] piperazine ***6d***

$C_{17}H_{18}N_2Cl_2$, mw: 321, yield: 96%, n_D (21°C): 1.5391, R_f (ethanol): 0.13. IR, film, ν cm^{-1}: 3285 (NH); 3026, 2957, 2937, 2875 (CH, CH_2); 1591 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 2.32 (m, 4H, CH_2N); 2.87 (m, 4H, CH_2N); 4.17 (s, 1H, CH); 7.2–7.3 (m, 9H, Ar and NH).

1-[Bis (4-methoxyphenyl) methyl] piperazine ***6e***

$C_{19}H_{24}N_2O_2$, mw: 312, yield: 71%, mp: 133°C, R_f (ethanol): 0.06. IR, KBr, ν cm^{-1}: 3215 (NH); 3030, 3025, 2991 (CH, CH_2, CH_3); 1600 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 2.33 (m, 4H, CH_2N); 2.86 (m, 4H, CH_2N); 3.75 (s, 6H, 2 OCH_3); 4.12 (s, 1H, CH); 6.8–7.3 (m, 9H, NH and Ar).

1-(3-phenyl-2-propenyl) piperazine ***6h***

$C_{13}H_{18}N_2$, mw: 202, yield: 16%, n_D (28°C): 1.5725, R_f (ethanol): 0.08. IR, film, ν cm^{-1}: 3271 (NH); 3024, 2937, 2910 (CH, CH_2); 1617 (C=C). ^{1}H-NMR, $CDCl_3$, δ ppm: 2.06 (s, 1H, NH); 2.47–2.88 (m, 8H, CH_2-N); 3.13 (d, 2H, CH=CH-CH_2); 6.3 (m, 2H, CH=CH); 7.1–7.4 (m, 5H, Ar).

Preparation of diethyl benzhydryl and cinnamyl piperazinyl-methyl phosphonates 7

Piperazine **6** (0.03 mol) was mixed with 2 ml of a 10% solution of formaldehyde in water. Then, diethyl phosphite (4.4 ml) was immediately added, and the mixture was stirred for 12 h in a hot water-bath. The order of addition of the compounds must be respected to avoid the formation of by-products [12].

After extraction with 1,1,1-trichloroethane and drying with magnesium sulfate, the organic phase was evaporated. The resulting crude product was purified by column chromatography on silica gel using a mixture of 80% ethyl acetate and 20% ethanol as eluent.

Diethyl [(4-(diphenylmethyl)-1-piperazinyl) methyl] phosphonate ***7a***

IR, film, ν cm^{-1}: 3060, 3025, 2977, 2932, 2907 (CH, CH_2, CH_3); 1596 (C=C); 1245 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.3 (t, 6H, CH_2-CH_3); 2.5 (m, 8H, CH_2-N); 2.74 (d, 2H, CH_2-P, J = 13 Hz); 4.1 (m, 5H, CH_2-CH_3 and CH); 7.2–7.4 (m, 10H, Ar).

Diethyl [(4- (bis (4-fluorophenyl) methyl)-1-piperazinyl) methyl] phosphonate ***7b***

IR, film, ν cm^{-1}: 2975, 2928, 2814 (CH, CH_2, CH_3); 1602 (C=C); 1245 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.31 (t, 6H, CH_2-CH_3); 2.4 (m, 4H, CH_2N); 2.69 (m, 4H, CH_2N); 2.80 (d, 2H, CH_2-P, J = 11 Hz); 4.12 (m, 5H, CH_2-CH_3 and CH); 6.8–7.4 (m, 8H, Ar).

Diethyl [(4-((4-chlorophenyl) phenylmethyl)-1-piperazinyl) methyl] phosphonate ***7c***

IR, KBr, ν cm^{-1}: 2980, 2931, 2908, 2808 (CH, CH_2, CH_3); 1645 (C=C); 1240 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.3 (t, 6H, CH_2-CH_3); 2.39 (m, 4H, CH_2N); 2.68 (m, 4H, CH_2N); 2.81 (d, 2H, CH_2-P, J = 11 Hz); 4.12 (m, 5H, CH_2-CH_3 and CH); 7.1–7.5 (m, 9H, Ar).

Diethyl [(4- (bis (4-chlorophenyl) methyl)-1-piperazinyl) methyl] phosphonate ***7d***

IR, KBr, ν cm^{-1}: 3090, 3051, 2989, 2959 (CH, CH_2, CH_3); 1559 (C=C); 1240 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.31 (t, 6H, CH_2-CH_3); 2.38 (m, 4H, CH_2N); 2.66 (m, 4H, CH_2N); 2.78 (d, 2H, CH_2-P, J = 11.6 Hz); 4.16 (m, 5H, CH_2-CH_3 and CH); 7.2–7.3 (m, 8H, Ar).

Diethyl [(4-(bis (4-methoxyphenyl) methyl)-1-piperazinyl) methyl] phosphonate ***7e***

IR, film, ν cm^{-1}: 3096, 3061, 3030, 2960 (CH, CH_2, CH_3); 1607 (C=C); 1245 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.31 (t, 6H, CH_2-CH_3); 2.26 (m, 4H, CH_2N); 2.39 (m, 4H, CH_2N); 2.78 (d, 2H, CH_2-P, J = 11.6 Hz); 3.74 (s, 6H, CH_3O); 4.12 (m, 5H, CH_2-CH_3 and CH); 6.8–7.3 (m, 8H, Ar).

Diethyl [(4-(3-phenyl-2-propenyl)-1-piperazinyl) methyl] phosphonate ***7h***

IR, film, ν cm^{-1}: 3081, 3059, 3025, 2979 (CH, CH_2, CH_3); 1652 (C=C); 1232 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.33 (t, 6H, CH_2-CH_3); 2.54 (m, 4H, CH_2N); 2.7 (m, 4H, CH_2N); 2.79 (d, 2H, CH_2P, J = 11.6 Hz); 2.96 (dd, 2H, CH_2-N); 4.14 (q, 4H, CH_2-CH_3); 6.3–6.5 (m, 2H, CH=CH); 7.2–7.4 (m, 5H, Ar).

Preparation of diethyl piperazinylmethylbenzyl phosphonates ***8***

To a solution of diethyl [4-(chloromethyl) benzyl] phosphonate (1.66 g, 0.006 mol) [16] in anhydrous THF (150 ml) was added piperazine **6** (0.006 mol). After refluxing for 12 h, potassium carbonate (1 g, 0.007 mol) was added, and the mixture further refluxed for 6 h. After filtration and evaporation, the residue was chromatographed on silica gel with ethyl acetate and ethanol as successive eluents.

Diethyl [4-((4-diphenylmethyl) 1-piperazinyl) methyl) phenyl-methyl] phosphonate ***8a***

IR, KBr, ν cm^{-1}: 3057, 3033, 2977, 2953 (CH, CH_2, CH_3); 1608 (C=C); 1245 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.21 (t, 6H,

CH_2-CH_3); 2.46 (m, 8H, CH_2-N); 3.11 (d, 2H, CH_2-P, J = 22 Hz); 3.51 (s, 2H, N-CH_2-Ar); 3.99 (q, 4H, CH_2-CH_3); 4.22 (s, 1H, CH); 7.1–7.8 (m, 14 H, Ar).

Diethyl [4-((4-(bis (4-fluorophenyl) methyl)-1-piperazinyl) methyl) phenylmethyl] phosphonate ***8b***
IR, film, ν cm^{-1}: 3050, 2981, 2933, 2907 (CH, CH_2, CH_3); 1601 (C=C); 1246 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.19 (t, 6H, CH_2-CH_3); 2.39 (m, 8H, CH_2-N); 3.05 (d, 2H, CH_2-P, J = 22 Hz); 3.5 (s, 2H, N-CH_2-Ar); 4.0 (m, 4H, CH_2-CH_3); 4.21 (s, 1H, CH); 6.9–7.4 (m, 12H, Ar).

Diethyl [4-((4-(4-chlorophenyl) phenylmethyl)-1-piperazinyl methyl) phenylmethyl] phosphonate ***8c***
IR, film, ν cm^{-1}: 3058, 3028, 2981, 2979, 2931 (CH, CH_2, CH_3); 1645, 1599 (C=C); 1249 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.21 (t, 6H, CH_2-CH_3); 2.45 (m, 8H, (CH_2-N); 3.11 (d, 2H, CH_2-P, J = 22 Hz); 3.50 (s, 2H, N-CH_2-Ar); 4.0 (q, 4H, CH_2-CH_3); 4.13 (s, 1H, CH); 7.1–7.4 (m, 13H, Ar).

Diethyl [4-((4-(bis (4-chlorophenyl) methyl)-1-piperazinyl) methyl) phenylmethyl] phosphonate ***8d***
IR, film, ν cm^{-1}: 2991, 2936, 2910 (CH, CH_2, CH_3); 1592 (C=C); 1216 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.22 (t, 6H, CH_2-CH_3); 2.43 (m, 8H, CH_2-N); 3.11 (d, 2H, CH_2-P, J = 22 Hz); 3.47 (s, 2H, N-CH_2-Ar); 4.03 (q, 4H, CH_2-CH_3); 4.18 (s, 1H, CH); 7.2–7.4 (m, 12 H, Ar).

Diethyl [4-((4-(bis (4-methoxyphenyl) methyl)-1-piperazinyl) methyl) phenylmethyl] phosphonate ***8e***
IR, KBr, ν cm^{-1}: 3020, 2995, 2930, 2853 (CH, CH_2, CH_3); 1602 (C=C); 1246 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.21 (t, 6H, CH_2-CH_3); 2.43 (m, 8H, CH_2-N); 3,11 (d, 2H, CH_2-P, J = 22 Hz); 3.48 (s, 2H, N-CH_2-Ar); 3.72 (s, 6H, 2 OCH_3); 4.0 (q, 4H, CH_2-CH_3); 4.13 (s, 1H, CH); 6.8–7.2 (m, 12H, Ar).

Diethyl [4-((4-(3-phenyl-2-propenyl)-1-piperazinyl) methyl) phenylmethyl] phosphonate ***8h***
IR, film, ν cm^{-1}: 3080, 3057, 3025, 2980, 2935 (CH, CH_2, CH_3); 1597 (C=C); 1240 (PO). ^{1}H-NMR, $CDCl_3$, δ ppm: 1.23 (t, 6H, CH_2-CH_3); 2.53 (m, 8H, CH_2-N); 3.12 (d, 2H, CH_2-P, J = 22 Hz); 3.19 (s, 2H, N-CH_2-Ar); 3.5 (s, 2H, CH=CH-CH_2); 4.0 (q, 4H, CH_2-CH_3); 6.31 (m, 2H, CH=CH); 7.2–7.4 (m, 9H, Ar).

Pharmacology

All the compounds were assayed at 0.5 μg/ml according to the protocol already described [17] from Polster [18]. Three preparations were used for each compound; the mean values of the percentage reduction of relaxation are reported in table V. The calcium antagonistic effects of flunarizine, cinnarizine, cyclizine and chlorcyclizine were estimated as a reference.

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