Eur J Med Chem (1994) 29, 87–93

Synthesis and calcium antagonistic activity of diethyl styrylbenzylphosphonates

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(Received 22 June 1993; accepted 4 October 1993)

Summary — Twenty-three new phosphonic ester derivatives of stilbene exhibiting structural analogies with fostedil are described. Examination of calcium antagonism showed that this activity could not be increased by introducing electron-withdrawing, electron-releasing or lipophilic substituents. Only compounds containing fluorine at the 2 or 4 positions exhibited similar activity to the model.

fostedil / calcium antagonist / diethyl phosphonate / stilbene

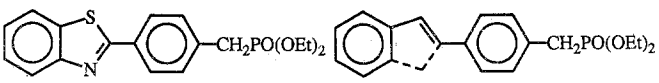
Introduction

We report here the follow-up to our studies of analogues of fostedil described in 1982 [1]. This calcium antagonist, with a simple structure, consists of 3 components: a diethyl methylphosphonate moiety, a phenyl group and a benzothiazole ring.

We have previously demonstrated the beneficial role of the phosphonate group [2]. This role is also apparent in the dihydropyridine series [3].

We have also been able to show the need for 2 independent aromatic systems to be present. If the heterocyclic benzothiazole is removed the calcium antagonistic activity disappears [4, 5]. Ring substitution with other polyheterocyclic systems such as imidazopyridine or imidazopyrimidine does not restore this activity [5]. However replacement with isosteric heterocyclic compounds (benzothiophene or benzofuran) can restore calcium antagonism [6]. In this case the introduction of a fluorine atom, previously reported to have a beneficial effect in fostedil derivatives [7], at position 5 or 6 of the benzofuran ring, maintains or even slightly increases this activity.

Our examination of a series of variously substituted diethyl benzylphosphonates showed that 2 conjugated aromatic groups separated by an optimal distance had to be present [8]. The most active compound in this series is stilbene, which may be considered as an open analogue of fostedil, with a potential cycle and with fewer conformation restrictions, and benzofuran and benzothiophene compounds, which are themselves active [6].



Fostedil

To optimise the results obtained with this initial derivative, we describe here a series of 23 diethyl phosphonate derivatives of stilbene bearing electron-withdrawing and electron-releasing substituents (the beneficial role of lipophilic substituents has also been demonstrated [9]) together with 1 or more fluorine atoms in various positions (table I).

Chemistry

We obtained our compounds by 2 different methods, 1 consisting of 3 steps, the other of a single step (scheme 1).

Method 1

Method 1 concerns compounds **5a**, **b**, **c**, **d**, **e**, **f**, **h**, **i**, **j**, **k**, **n**, **o**, **p**, **t**, **u**, **v** and **w**. The methyl compounds **3** were obtained by condensing a suitable aldehyde with 4-methyl diethyl benzylphosphonate **1** [8] in the Wittig–Horner reaction [10, 11]. For compound **3u** we con-

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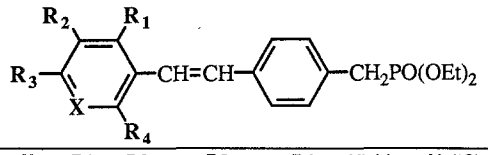
Table I. Physical properties of diethyl phosphonates **5**.



Comp N°	X	R1	R2	R3	R4	Yield (%) [a]	Mp(°C) n_D	Rf [b]
5a	CH	H	H	H	H	91	92	0.41[5]
5b	CH	O_2N	H	H	H	11	1.5205 (15°C)	0.35
5c	CH	H	H	O_2N	H	36	113	0.34
5d	CH	F	H	H	H	80	1.5833 (19°C)	0.38
5e	CH	H	F	H	H	31	70	0.36
5f	CH	H	H	F	H	63	81	0.38
5g	CH	F	H	F	H	12	1.5759 (22°C)	0.39
5h	CH	H	H	F_3C	H	60	78	0.39
5i	CH	Cl	H	H	H	24	1.5431(16°C)	0.38
5j	CH	H	H	Cl	H	80	91	0.44
5k	CH	Cl	H	Cl	H	24	1.5570 (16°C)	0.36
5m	CH	H	H	$(H_3C)_2N$	H	13	94	0.37
5n	CH	H	H	H_3C-S	H	42	99	0.49
5o	CH	H_3C-O	H	H	H	10	1.5874 (25°C)	0.44
5p	CH	H	H	H_3C-O	H	75	73	0.54
5q	CH	H_3C-O	H	H_3C-O	H	15	66	0.55
5r	CH	H_3C-O	H	H_3C-O	H_3C-O	15	1.5861 (21°C)	0.41
5s	CH	H_3C	H	H	H	15	161	0.51
5t	CH	H	H	H_3C	H	37	70	0.45
5u	CH	H	H	$(H_3C)_3C$	H	52	88	0.48
5v	CH	H	H	C_6H_5O	H	55	90	0.45
5w	CH	H	H	$(EtO)_2POCH_2$	H	64	144	0.09
5x	N	H	H	H	H	12	155	0.27

[a]The yields given refer only to the final step; [b]ethyl acetate.

densed 4-tertiobutyl diethyl benzylphosphonate with 4-methyl benzaldehyde. Sodium hydride was chosen as a strong base. Tetrahydrofuran (THF) and distilled anhydrous 1,2-dimethoxyethane (DME) were used as solvents. Better yields were obtained with DME; THF sometimes required gentle heating. The physical constants of compounds **3** are indicated in table II.

It was difficult to elucidate the stereochemistry of compounds **3a**, **b**, **d**, **e**, **f**, **j**, **n**, **t**, **u** and **v**, by proton NMR. Ethylene proton signals may sometimes be blurred with the aromatic protons and are usually apparent as a singlet. In compounds in which determination was possible, only the *E* isomer could be isolated.

The bromomethyl derivatives **4** were obtained by free-radical bromination of the methyl compounds **3**. *N*-bromosuccinimide (NBS) was used as a halogenating agent and azo-bis-isobutyronitrile (AIBN) as a generator of free radicals [12]. The physical properties of these compounds are presented in table III.

The diethyl phosphonates **5** were synthesized according to the Michaelis–Arbuzov reaction [13] by heating the bromomethyl derivatives **4** in the presence of triethylphosphite (TEP). The physical properties of these compounds are indicated in table I.

Method 2

Method 2 concerns compounds **5g**, **m**, **q**, **r**, **s**, **x**. These compounds may also be obtained by the Wittig–Horner reaction but in this case the selected aldehyde was condensed with 1,4-bis (diethoxy phosphomethyl) benzene **2** in anhydrous THF [8].

This method involves just 1 step and would thus seem more convenient than *Method 1*. However the yields remained very low and were generally lower than the overall yields obtained with *Method 1*.

A coupling constant of about 16 Hz indicated that compounds **5i**, **k**, **o**, **q** and **r** were *E* olefins. For the reasons indicated previously, the configuration of the other compounds could not be determined by proton NMR.

Pharmacology

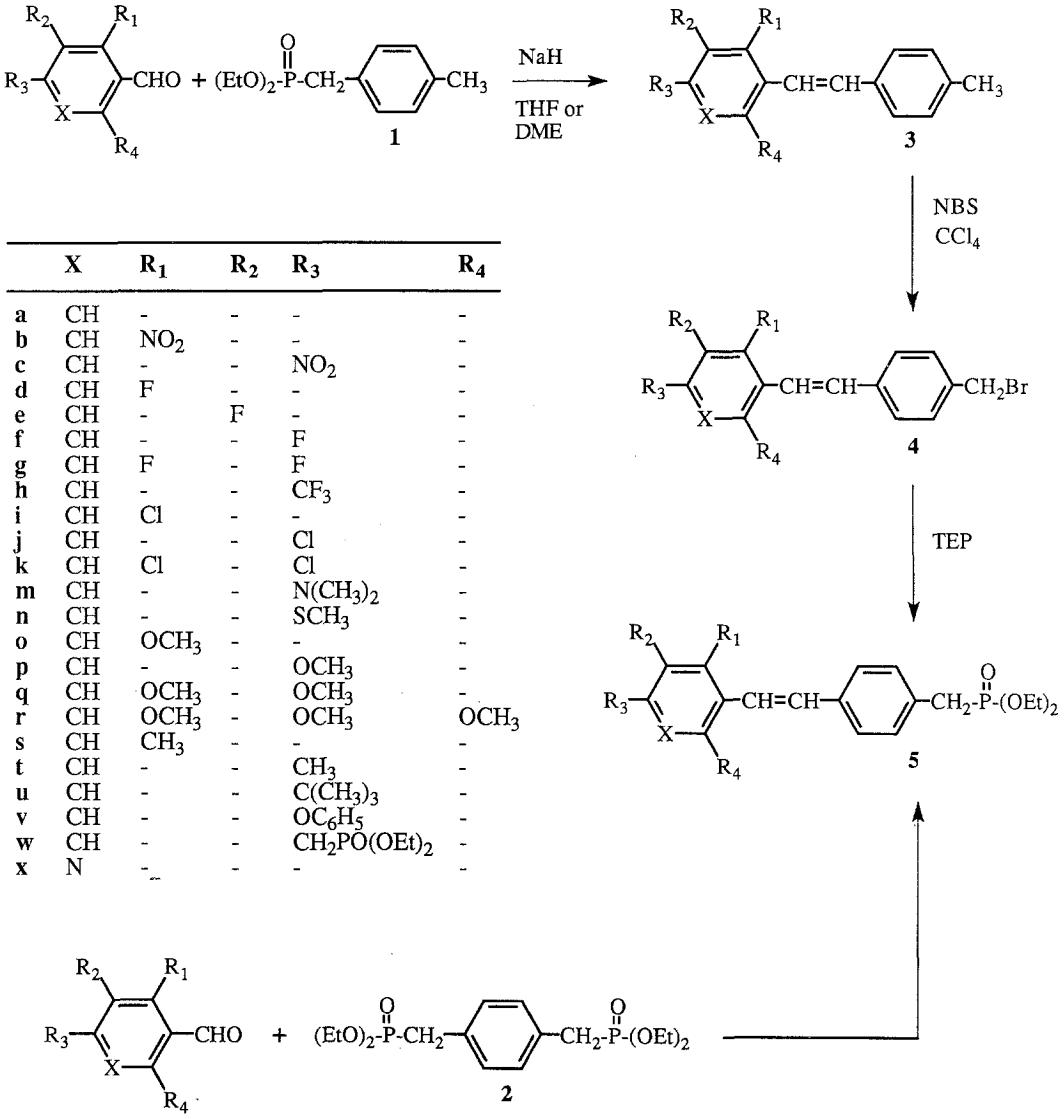
Calcium antagonism was examined *in vitro* by studying the reduced contraction of rabbit aortal fragments in the presence of calcium chloride. These results are indicated in table IV. The antagonistic effect of fostedil was determined under the same experimental conditions for comparison.

Results and discussion

Although the examined derivatives could be considered as open analogues of fostedil, most of them were totally inactive. Except for the 2 fluorine-containing compounds **5f** and **5d**, the introduction of electron-releasing lipophilic substituents as specified by Belluci [9] could not increase the calcium antagonism of the non-substituted derivative **5a**.

The introduction of a fluorine atom was described elsewhere as having a beneficial role [7], but the effect was irregular. Thus the 3-fluoro- and 2,4-difluoro-substituted compounds, **5e** (–11%) and **5g** (–12%), respectively, were much less active than **5a** (–29%). In contrast, the 4-fluoro- and 2-fluoro-substituted compounds **5f** (–47%) and **5d** (–53%) exhibited similar activity to that of fostedil (–57%). This variability in the activity of the various fluoro derivatives could not be attributed to differences in lipophilic properties or electronic charge distribution within the molecule.

Substitution of the fluorine atom in the 2 active compounds **5f** and **5d** by a chlorine atom (**5i**, **5j**), a nitro substituent (**5b**, **5c**) or a methoxy group (**5o**, **5p**) resulted in loss of activity.



	X	R_1	R_2	R_3	R_4
a	CH	-	-	-	-
b	CH	NO_2	-	-	-
c	CH	-	-	NO_2	-
d	CH	F	-	-	-
e	CH	-	F	-	-
f	CH	-	-	F	-
g	CH	F	-	F	-
h	CH	-	-	CF_3	-
i	CH	Cl	-	-	-
j	CH	-	-	Cl	-
k	CH	Cl	-	Cl	-
m	CH	-	-	$N(CH_3)_2$	-
n	CH	-	-	SCH_3	-
o	CH	OCH_3	-	-	-
p	CH	-	-	OCH_3	-
q	CH	OCH_3	-	OCH_3	-
r	CH	OCH_3	-	OCH_3	OCH_3
s	CH	CH_3	-	-	-
t	CH	-	-	CH_3	-
u	CH	-	-	$C(CH_3)_3$	-
v	CH	-	-	OC_6H_5	-
w	CH	-	-	$CH_2PO(OEt)_2$	-
x	N	-	-	-	-

Scheme 1.

These results suggest that the phenyl ring cannot tolerate bulky substituents. This fact was emphasized by Yoshino *et al*: substitution of the benzothiazolyl nucleus in fostedil with various groups other than fluorine led to a drop in activity [1].

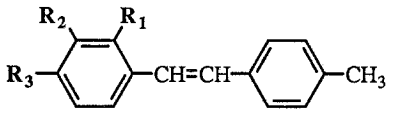
It is therefore not sufficient for a compound to be an isostere of fostedil for it to exhibit calcium antagonism. Only the *ortho* or *para* fluoro derivatives exhibited analogous activity to fostedil and greater activity than the non-substituted derivative **5a**, which is the first member of this series.

Experimental protocols

Chemistry

Product purity was systematically verified by thin-layer chromatography on silica gel 60 F 254. Melting points were determined on a Kofler apparatus and were uncorrected. Elemental analyses (C, H, N, X, P) complied with accepted standards and are not presented. The infrared (IR) spectra were measured in films (liquids) or potassium bromide (KBr) pellets (solids) and were recorded on a Perkin–Elmer spectrometer model 983G. ^{1}H-NMR spectra were recorded on a Varian T60

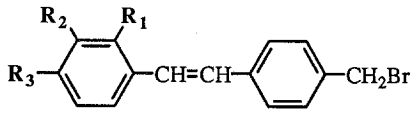
Table II. Physical properties of methyl derivatives **3**.



Comp N°	R1	R2	R3	Yield (%)	Mp (°C)	Rf [a]
3b	O_2N	H	H	18	31	0.86
3c	H	H	O_2N	27	153	0.80
3d	**F**	H	H	33	75	0.98
3e	H	**F**	H	64	106	0.83
3f	H	H	**F**	81	157	0.98
3h	H	H	F_3C	56	190	0.92
3i	**Cl**	H	H	14	45	0.86
3j	H	H	**Cl**	40	202	0.89
3k	**Cl**	H	**Cl**	33	54	0.93
3n	H	H	H_3C-S	86	175	0.49
3o	H_3C-O	H	H	64	75	0.94
3p	H	H	H_3C-O	79	180	0.41
3t	H	H	H_3C	59	195	0.95
3u	H	H	$(H_3C)_3C$	96	132	0.98
3v	H	H	C_6H_5O	91	161	0.90[b]

[a]1,2-Dichloroethane; [b]light petroleum/ethyl acetate (5:95 v/v).

Table III. Physical properties of bromomethyl derivatives **4**.



Comp N°	R1	R2	R3	Yield (%)	Mp(°C) n_D	Rf [a]
4b	O_2N	H	H	95	1.5730 (19°C)	0.43
4c	H	H	O_2N	75	112	0.20 [b]
4d	**F**	H	H	53	74	0.75
4e	H	**F**	H	79	88	0.83
4f	H	H	**F**	79	111	0.89
4h	H	H	F_3C	60	65	0.75
4i	**Cl**	H	H	18	1.6003 (19°C)	0.74
4j	H	H	**Cl**	40	165	0.85
4k	**Cl**	H	**Cl**	50	50	0.18
4	H	H	H_3C-S	45	144	0.68[b]
4o	H_3C-O	H	H	70	1.6470 (25°C)	0.58
4p	H	H	H_3C-O	57	126	0.96
4t	H	H	H_3C	36	78	0.87
4u	H	H	$(H_3C)_3C$	71	110	0.29 [b]
4v	H	H	C_6H_5O	51	144	0.89
4w	H	H	BrH_2C	17	192	0.80

[a]1,2-Dichloroethane; [b]ethyl acetate.

spectrometer at 60 MHz and (or) a Bruker FT200 spectrometer at 200.13 MHz. Tetramethylsilane (TMS) was used as an internal standard and chemical shifts were expressed in ppm.

The ^{31}P-NMR spectra were measured on a Bruker FT200 spectrometer at 81.1 MHz using orthophosphoric acid as an internal standard. The chemical shifts for all the phosphonates that we synthesized were between 20 and 25 ppm and compatible with the proposed structures.

Synthesis of the 4-styryl-substituted toluenes **3** *(**b–f**, **h–k**, **n–p**, **t–v**)*

To 200 ml distilled anhydrous DME, was added in turn 0.05 mol 50% sodium hydride in mineral oil, previously washed with cyclohexane, 0.04 mol diethyl *para*-methyl benzylphosphonate **1**, and 0.04 mol substituted aldehyde. This mixture was stirred at rt for 10 h. The excess hydride was destroyed with methanol. The obtained mixture was poured into 500 ml distilled water. After filtration and drying, the crude product was recrystallised in ethanol (for compounds **3d**, **e**, **f**, **h**, **i**, **j**, **n**, **o**, **p**, **t**, **u**, **v**) or purified by silica-gel chromatography with methylchloroform as eluent (compounds **3b**, **c**, **k**).

2-Nitro 4'-methyl stilbene ***3b***. IR (KBr) (ν cm^{-1}): 3049, 3023, 2947 (CH, CH_3); 1602 (C=C); 1518, 1345 (NO_2). ^{1}H-NMR, $CDCl_3$ (δ ppm): 2.43 (s, 3H, CH_3); 7.16–8.06 (m, 10H, CH=CH and Ar).

4-Nitro 4'-methyl stilbene ***3c***. IR (KBr) (ν cm^{-1}): 2995, 2982, 2850 (CH, CH_3); 1596 (C=C); 1500, 1346 (NO_2). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.34 (s, 3H, CH_3); 7.03–8.22 (m, 10H, CH=CH and Ar).

2-Fluoro 4'-methyl stilbene ***3d***. IR (KBr) (ν cm^{-1}): 3054, 3021, 2943 (CH, CH_3); 1570, 1509, 1481 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.32 (s, 3H, CH_3); 7.0–7.58 (m, 10H, CH=CH and Ar).

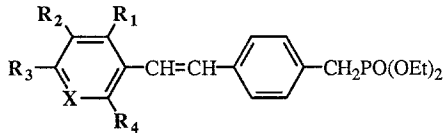
3-Fluoro 4'-methyl stilbene ***3e***. IR (KBr) (ν cm^{-1}): 3051, 3026, 2933 (CH, CH_3); 1582, 1509, 1487 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.32 (s, 3H, CH_3); 6.89–7.39 (m, 10H, CH=CH and Ar).

4-Fluoro 4'-methyl stilbene ***3f***. IR (KBr) (ν cm^{-1}): 3047, 3019, 2918 (CH, CH_3); 1597, 1510 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.33 (s, 3H, CH_3); 7.0–7.46 (m, 10H, CH=CH and Ar).

4-Methyl 4'-trifluoromethyl stilbene ***3h***. IR (KBr) (ν cm^{-1}): 3053, 3023, 2998, 2924 (CH, CH_3); 1611, 1603, 1570 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.32 (s, 3H, CH_3); 6.96 (s, 2H, CH=CH); 7.03–7.86 (m, 8H, Ar).

2-Chloro 4'-methyl stilbene ***3i***. IR (KBr) (ν cm^{-1}): 3050, 3021, 2922 (CH, CH_3); 1611 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.36 (s, 3H, CH_3); 7.13–7.83 (m, 10H, CH=CH and Ar).

Table IV. *In vitro* calcium antagonistic activity of diethyl phosphonates **5**.



Comp N°	X	R_1	R_2	R_3	R_4	% Inhibition[a]
5n	CH	-	-	H_3C-S	-	+4
5p	CH	-	-	H_3C-O	-	+4
5s	CH	H_3C	-	-	-	+1
5w	CH	-	-	$(EtO)_2POCH_2$	-	0
5b	CH	O_2N	-	-	-	-2
5h	CH	-	-	F_3C	-	-2
5q	CH	H_3C-O	-	H_3C-O	-	-3
5m	CH	-	-	$(H_3C)_2N$	-	-4
5v	CH	-	-	C_6H_5-O	-	-4
5k	CH	Cl	-	Cl	-	-4
5r	CH	H_3C-O	-	H_3C-O	H_3C-O	-5
5t	CH	-	-	H_3C	-	-5
5o	CH	H_3C-O	-	-	-	-6
5j	CH	-	-	Cl	-	-7
5x	N	-	-	-	-	-7
5i	CH	Cl	-	-	-	-10
5u	CH	-	-	$(H_3C)_3C$	-	-10
5c	CH	-	-	O_2N	-	-11
5e	CH	-	F	-	-	-11
5g	CH	F	-	F	-	-12
5a	CH	-	-	-	-	-29
5f	CH	-	-	F	-	-47
5d	CH	F	-	-	-	-53
Fostedil	/	/	/	/	/	-57

[a]Reduction in contraction of rabbit aortic fragments in the presence of calcium chloride at a concentration of 0.50 µg/ml.

4-Chloro 4'-methyl stilbene ***3j***. IR (KBr) (ν cm^{-1}): 3050, 3010, 2910 (CH, CH_3); 1600 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.2 (s, 3H, CH_3); 6.78–7.29 (m, 10H, CH=CH and Ar).

2,4-Dichloro 4'-methyl stilbene ***3k***. IR (KBr) (ν cm^{-1}): 3050, 3023, 2977 (CH, CH_3); 1627, 1605 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.36 (s, 3H, CH_3); 7.1–7.76 (m, 9H, CH=CH and Ar).

4-Methyl 4'-methylthio stilbene ***3n***. IR (KBr) (ν cm^{-1}): 3039, 3001, 2975, 2915 (CH, CH_3); 1605, 1586, 1506 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.26 (s, 3H, Ar-CH_3); 2.42 (s, 3H, S-CH_3); 6.83 (s, 2H, CH=CH); 6.83–7.46 (m, 8H, Ar).

2-Methoxy 4'-methyl stilbene ***3o***. IR (KBr) (ν cm^{-1}): 3053, 2993, 2920 (CH, CH_3); 1591 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.34 (s, 3H, CH_3); 3.87 (s, 3H, CH_3O); 6.86–7.6 (m, 10H, Ar and CH=CH).

4-Methoxy 4'-methyl stilbene ***3p***. IR (KBr) (ν cm^{-1}): 3047, 3019, 2935, 2914, 2839 (CH, CH_3); 1634, 1608, 1572 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.30 (s, 3H, H_3C-Ar); 3.93 (s, 3H, H_3C-O); 6.83–7.60 (m, 10H, CH=CH and Ar).

4,4'-Dimethyl stilbene ***3t***. IR (KBr) (ν cm^{-1}): 3025, 3010, 2932 (CH, CH_3); 1650, 1600 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.34 (s, 6H, $2CH_3$); 7.03–7.41 (m, 10H, CH=CH and Ar).

4'-Tertiobutyl 4-methyl stilbene ***3u***. IR (KBr) (ν cm^{-1}): 3043, 3019, 2948 (CH, CH_3); 1629, 1605, 1565, 1510 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.38 (s, 9H, $(CH_3)_3C$); 2.35 (s, 3H, CH_3); 7.10 (s, 2H, CH=CH); 7.18–7.53 (m, 8H, Ar).

4-Methyl 4'-phenoxy stilbene ***3v***. IR (KBr) (ν cm^{-1}): 3039, 2957, 2911 (CH, CH_3); 1656, 1587, 1502 (C=C). ^{1}H-NMR (DMSO-d_6) (δ ppm): 2.33 (s, 3H, CH_3); 6.83–7.56 (m, 15H, CH=CH and Ar).

Synthesis of bromomethyl derivatives ***4 (b–f, h–k, n–p, t–w)***
A solution of 0.05 mol of methyl derivative **3** in 150 ml carbon tetrachloride was heated for 0.5 h. NBS (9.90 g, 0.056 mol) and a catalytic amount of AIBN were added. The mixture was refluxed for ≈ 6 h. After cooling slightly, the succinimide was filtered off. The resulting solution was then further cooled to obtain the bromomethyl derivative which either crystallises or the solvent, when necessary, was evaporated. Recrystallisation was carried out, when required, in ethanol.

2-Nitro 4'-bromomethyl stilbene ***4b***. IR (film) (ν cm^{-1}): 3069, 3027, 2989 (CH, CH_2); 1604, 1559, 1521 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.49 (s, 2H, CH_2-Br); 7.07–8.11 (m, 10H, CH=CH and Ar).

4-Nitro 4'-bromomethyl stilbene ***4c***. IR (KBr) (ν cm^{-1}): 3045, 2992, 2950 (CH, CH_2); 1595, 1510 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.51 (s, 2H, CH_2-Br); 7.09–7.66 (m, 8H, CH=CH and Ar); 8.19–8.25 (m, 2H, α to NO_2).

2-Fluoro 4'-bromomethyl stilbene ***4d***. IR (KBr) (ν cm^{-1}): 3045, 3021, 2999 (CH, CH_2); 1570, 1510, 1481 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.54 (s, 2H, CH_2Br); 7.23–7.67 (m, 10H, CH=CH and Ar).

3-Fluoro 4'-bromomethyl stilbene ***4e***. IR (KBr) (ν cm^{-1}): 3031, 3021, 2975 (CH, CH_2); 1580, 1509, 1482 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.48 (s, 2H, CH_2Br); 6.95–7.64 (m, 10H, CH=CH and Ar).

4-Fluoro 4'-bromomethyl stilbene ***4f***. IR (KBr) (ν cm^{-1}): 3050, 2981 (CH, CH_2); 1599, 1506, 1467 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.46 (s, 2H, CH_2Br); 6.88–7.45 (m, 10H, CH=CH and Ar).

4-Bromomethyl 4'-trifluoromethyl stilbene ***4h***. IR (KBr) (ν cm^{-1}): 3044, 3028, 2999 (CH, CH_2); 1610, 1504 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.50 (s, 2H, CH_2Br); 7.15 (s, 2H, CH=CH); 7.40–7.80 (m, 8H, Ar).

2-Chloro 4'-bromomethyl stilbene ***4i***. IR (film) (ν cm^{-1}): 3060, 3029, 2989 (CH, CH_2); 1606 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.41 (s, 2H, CH_2Br); 7.03–7.98 (m, 10H, CH=CH and Ar).

4-Chloro 4'-bromomethyl stilbene ***4j***. IR (KBr) (ν cm^{-1}): 3125, 3010, 3009 (CH, CH_2), 1558 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.50 (s, 2H, CH_2Br); 6.72–7.84 (m, 10H, CH=CH and Ar).

2,4-Dichloro 4'-bromomethyl stilbene ***4k***. IR (KBr) (ν cm^{-1}): 3045, 3039, 2999 (CH, CH_2); 1625 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.5 (s, 2H, CH_2Br); 7.06–7.66 (m, 9H, CH=CH and Ar).

4-Methylthio 4'-bromomethyl stilbene ***4n***. IR (KBr) (ν cm^{-1}): 3069, 2970, 2935 (CH, CH_2, CH_3); 1627, 1587, 1509 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.50 (s, 3H, CH_3); 4.46 (s, 2H, CH_2Br); 7.13 (s, 2H, CH=CH); 7.16–7.67 (m, 8H, Ar).

2-Methoxy 4'-bromomethyl stilbene ***4o***. IR (film) (ν cm^{-1}): 3028, 3005, 2957 (CH, CH_2); 1600 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 3.77 (s, 3H, OCH_3); 4.4 (s, 2H, CH_2Br); 6.79–8.0 (m, 10H, CH=CH and Ar).

4-Methoxy 4'-bromomethyl stilbene ***4p***. IR (KBr) (ν cm^{-1}): 3185, 3003, 2961 (CH, CH_2, CH_3); 1589, 1573, 1512 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 3.85 (s, 3H, CH_3); 4.60 (s, 2H, CH_2Br); 6.80–7.60 (m, 10H, CH=CH and Ar).

4-Methyl 4'-bromomethyl stilbene ***4t***. IR (KBr) (ν cm^{-1}): 3012, 2995, 2961 (CH, CH_2, CH_3); 1590 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 2.35 (s, 3H, CH_3); 4.5 (s, 2H, CH_2Br); 7.03–7.50 (m, 10H, CH=CH and Ar).

4-Tertiobutyl 4'-bromomethyl stilbene ***4u***. IR (KBr) (ν cm^{-1}): 3035, 3000, 2962 (CH, CH_2, CH_3); 1600, 1511, 1459 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.33 (s, 9H, $(H_3C)_3C$); 4.50 (s, 2H, CH_2Br); 7.07 (s, 2H, CH=CH); 7.43 (m, 8H, Ar).

4-Phenoxy 4'-bromomethyl stilbene ***4v***. IR (KBr) (ν cm^{-1}): 3035, 2971, 2930 (CH, CH_2); 1588, 1500, 1485 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.43 (s, 2H, CH_2Br); 6.76–7.51 (m, 15H, CH=CH and Ar).

4,4'-Dibromomethyl stilbene ***4w***. IR (KBr) (ν cm^{-1}): 3046, 3010, 2981 (CH, CH_2); 1625 (C=C). ^{1}H-NMR ($CDCl_3$) (δ ppm): 4.51 (s, 4H, 2 CH_2Br); 7.09–7.50 (m, 10H, Ar and CH=CH).

Synthesis of diethyl phosphonates ***5***

*Method 1 (Michaelis–Arbuzov reaction) (**5b–f**, **h–k**, **n–p**, **t–w**).* A solution of 0.02 mol of the bromomethyl derivative **4** in 0.025 mol triethylphosphite (TEP) was refluxed in an oil bath at 140°C for 6 h maximum. The excess TEP was eliminated under reduced pressure. The resulting viscous oil was chromatographed on a silica-gel column, firstly with 1,2-dichloroethane then with ethyl acetate. The collected product was recrystallised in a minimum amount of ethyl acetate.

2-Nitro 4'-diethoxyphosphonomethyl stilbene ***5b***. IR (film) (ν cm^{-1}): 3063, 2984, 2933 (CH, CH_2, CH_3); 1602 (C=C); 1269 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.34 (t, 6H, CH_3); 3.17 (d, 2H, CH_2-P, J = 22 Hz); 4.11 (m, 4H, CH_2-O); 7.04–8.54 (m, 10H, CH=CH and Ar).

4-Nitro 4'-diethoxyphosphonomethyl stilbene ***5c***. IR (KBr) (ν cm^{-1}): 3074, 2978, 2922 (CH, CH_2, CH_3); 1628, 1586 (C=C); 1245 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.26 (t, 6H, CH_3); 3.17 (d, 2H, CH_2-P, J = 22 Hz); 4.08 (q, 4H, CH_2-O); 7.17 (d, 2H, CH=CH, J = 12.52 Hz); 7.29–7.64 (m, 6H, Ar); 8.16–8.23 (m, 2H, Ar α to NO_2).

2-Fluoro 4'-diethoxyphosphonomethyl stilbene ***5d***. IR (film) (ν cm^{-1}): 3038, 2983 (CH, CH_2, CH_3); 1575, 1511, 1483 (C=C); 1246 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (t, 6H, CH_3); 3.16 (d, 2H, CH_2-P, J = 22 Hz); 4.03 (m, 4H, CH_2-O); 7.31–7.5 (m, 10H, CH=CH and Ar).

3-Fluoro 4'-diethoxyphosphonomethyl stilbene ***5e***. IR (KBr) (ν cm^{-1}): 3029, 2986 (CH, CH_2, CH_3); 1581, 1512, 1486 (C=C); 1249 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (t, 6H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz); 4.02 (q, 4H, CH_2-O); 7.05 (s, 2H, CH=CH); 8.4–9.0 (m, 8H, Ar).

4-Fluoro 4'-diethoxyphosphonomethyl stilbene ***5f***. IR (KBr) (ν cm^{-1}): 3021, 2984 (CH, CH_2, CH_3); 1597, 1555, 1512 (C=C); 1242 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (t, 6H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz); 4.05 (m, 4H, CH_2-O); 6.9–7.6 (m, 10H, CH=CH and Ar).

4-Trifluoromethyl 4'-diethoxyphosphonomethyl stilbene ***5h***. IR (KBr) (ν cm^{-1}): 3042, 2985 (CH, CH_2, CH_3); 1610, 1589, 1546 (C=C); 1253 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.29 (t, 6H, CH_3, J = 7 Hz); 3.19 (d, 2H, CH_2-P, J = 22 Hz); 4.12 (m, 4H, CH_2-O, J = 7 Hz); 7.10 (s, 2H, CH=CH); 7.45– 7.75 (m, 8H, Ar).

2-Chloro 4'-diethoxyphosphonomethyl stilbene E ***5i***. IR (film) (ν cm^{-1}): 3055, 2982, 2933 (CH, CH_2, CH_3); 1606 (C=C); 1261 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (t, 6H, CH_3); 3.16 (d, 2H, CH_2-P, J = 22 Hz); 4.11 (q, 4H, CH_2-O); 7.11 (q, 2H, CH=CH, J = 16 Hz); 7.14–7.69 (m, 8H, Ar).

4-Chloro 4'-diethoxyphosphonomethyl stilbene ***5j***. IR (KBr) (ν cm^{-1}): 3033, 3010, 2958 (CH, CH_2, CH_3); 1600, 1556, 1500 (C=C); 1246 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (t, 6H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz); 4.02 (m, 4H, CH_2-O); 7.03 (s, 2H, CH=CH); 7.01–7.5 (m, 8H, Ar).

2,4-Dichloro 4'-diethoxyphosphonomethyl stilbene E ***5k***. IR (film) (ν cm^{-1}): 3057, 3027, 2983 (CH, CH_2, CH_3); 1628, 1606, 1582, 1559 (C=C); 1246 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.23 (t, 6H, CH_3); 3.14 (d, 2H, CH_2-P, J = 22 Hz); 4.09 (q, 4H, CH_2-O); 7.0 (d, 2H, CH=CH, J = 16.3 Hz); 7.19–7.59 (m, 7H, Ar).

4-Methylthio 4'-diethoxyphosphonomethyl stilbene ***5n***. IR (KBr) (ν cm^{-1}): 3020, 2981, 2927 (CH, CH_2, CH_3); 1634, 1588, 1523, 1502 (C=C); 1290, 1242 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.23 (t, 6H, CH_3, J = 7 Hz); 2.47 (s, 3H, S-CH_3); 3.10 (d, 2H, CH_2-P, J = 22 Hz); 4.03 (m, 4H, CH_2-O, J = 7 Hz); 6.90 (s, 2H, CH=CH); 7.10–7.43 (m, 8H, Ar).

2-Methoxy 4'-diethoxyphosphonomethyl stilbene E ***5o***. IR (film) (ν cm^{-1}): 3026, 2980, 2935 (CH, CH_2, CH_3); 1627 (C=C); 1245 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.22 (t, 6H, CH_3); 3.05 (d, 2H, CH_2-P, J = 22 Hz); 3.85 (s, 3H, OCH_3); 3.95 (q, 4H, CH_2-O); 6.5 (q, 2H, CH=CH, J = 16.4 Hz); 7.02–7.5 (m, 8H, Ar).

4-Methoxy 4'-diethoxyphosphonomethyl stilbene ***5p***. IR (KBr) (ν cm^{-1}): 3031, 2982, 2950 (CH, CH_2, CH_3); 1601, 1556, 1513 (C=C); 1253 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.38 (t, 6H, CH_3, J = 8 Hz); 3.20 (d, 2H, CH_2-P, J = 22 Hz); 3.90 (s, 3H, CH_3-O); 4.20 (m, 4H, CH_2-O, J = 8 Hz); 6.80–7.62 (m, 10H, CH=CH and Ar).

4-Methyl 4'-diethoxyphosphonomethyl stilbene ***5t***. IR (KBr) (ν cm^{-1}): 3048, 3025, 2949 (CH, CH_2, CH_3); 1606 (C=C); 1246 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.24 (t, 6H, CH_3); 2.34 (s, 3H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz); 4.11 (m, 4H, CH_2-O); 7.04 (s, 2H, CH=CH); 7.13–7.46 (m, 8H, Ar).

4-Tertiobutyl 4'-diethoxyphosphonomethyl stilbene ***5u***. IR (KBr) (ν cm^{-1}): 3024, 2959, 2903 (CH, CH_2, CH_3); 1607, 1565, 1510 (C=C); 1290, 1242 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.35 (t, 6H, CH_3, J = 6 Hz); 1.40 (s, 9H, $(CH_3)_3C$); 3.13 (d, 2H, CH_2-P, J = 22 Hz); 4.01 (m, 4H, CH_2-O, J = 6 Hz); 7.02 (s, 2H, CH=CH); 7.26–7.56 (m, 8H, Ar).

4-Phenoxy 4'-diethoxyphosphonomethyl stilbene ***5v***. IR (KBr) (ν cm^{-1}): 3057, 3017, 2959 (CH, CH_2, CH_3); 1605, 1585, 1500 (C=C); 1245 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.23 (t, 6H, CH_3, J = 7 Hz); 3.13 (d, 2H, CH_2-P, J = 21 Hz); 3.95 (m, 4H, CH_2-O, J = 7 Hz); 6.76–7.60 (m, 15H, CH=CH and Ar).

4,4'-Diethoxyphosphonomethyl stilbene ***5w***. IR (KBr) (ν cm^{-1}): 3002, 2978, 2948 (CH, CH_2, CH_3); 1605, 1510 (C=C); 1250 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.25 (m, 12H, CH_3); 3.10 (d, 4H, CH_2-P, J = 22 Hz); 4.02 (m, 8H, CH_2-O); 7.06 (s, 2H, CH=CH); 7.06–7.78 (m, 8H, Ar).

*Method 2 (Wittig–Horner reaction) (****5g****, ****m****, ****q****, ****r****, ****s****, ****x****).* To a solution of 7 g (0.02 mol) 1,4-bis-diethoxyphosphonomethyl benzene **2** [8] in 200 ml anhydrous THF, was added 2.4 g (0.05 mol) of 50% sodium hydride in mineral oil, previously washed with petroleum ether. After stirring for 15 min, 0.02 mol of a suitably substituted aldehyde was slowly added. This mixture was refluxed for 24 h. After neutralising the excess sodium hydride with methanol and filtration, the resulting solution was evaporated under reduced pressure. The crude product obtained was purified by silica-gel column chromatography with methylchloroform as eluent.

2,4-Difluoro 4'-diethoxyphosphonomethyl stilbene ***5g***. IR (film) (ν cm^{-1}): 3045, 2983, 2930 (CH, CH_2, CH_3); 1611, 1601, 1589 (C=C); 1249 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.31 (t, 6H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz); 4.3 (q, 4H, CH_2-O); 6.59–7.56 (m, 9H, CH=CH and Ar).

4-Dimethylamino 4'-diethoxyphosphonomethyl stilbene E ***5m***. IR (KBr) (ν cm^{-1}): 2981, 2943, 2931 (CH, CH_2, CH_3); 1608 (C=C); 1245 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.23 (t, 6H, CH_3); 2.95 (s, 6H, $2CH_3$-N); 3.13 (d, 2H, CH_2-P, J = 22 Hz); 4.00 (m, 4H, CH_2-O); 6.68 (d, 2H, α to N $(CH_3)_2$, J = 9 Hz); 6.86 (d, 1H, CH, J = 16 Hz); 7.02 (d, 1H, CH, J = 16 Hz); 7.25–7.45 (m, 6H, Ar).

2,4-Dimethoxy 4'-diethoxyphosphonomethyl stilbene E ***5q***. IR (KBr) (ν cm^{-1}): 3036, 2977, 2939 (CH, CH_2, CH_3); 1603 (C=C); 1252 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.24 (t, 6H, CH_3); 3.14 (d, 2H, CH_2-P, J = 22 Hz); 3.58–4.17 (m, 10H, OCH_3 and CH_2-O); 6.96 (d, 2H, CH=CH, J = 16.48 Hz); 7.22–7.9 (m, 7H, Ar).

2,4,6-Trimethoxy 4'-diethoxyphosphonomethyl stilbene E ***5r***. IR (film) (ν cm^{-1}): 2977, 2939, 2909 (CH, CH_2, CH_3); 1600 (C=C); 1214 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.24 (t, 6H, CH_3); 3.15 (d, 2H, CH_2-P, J = 22 Hz), 3.6 (s, 3H, OCH_3); 3.8 (s, 6H, 2 OCH_3); 4.1 (m, 4H, CH_2-O); 6.16 (s, 2H, H α to OCH_3); 7.21–7.27 (dd, 2H, Ar α to CH_2-P, J = 2.5 Hz and 8 Hz); 7.35 (d, 1H, CH, J = 16 Hz); 7.4 (d, 2H, Ar α to CH, J = 22 Hz); 7.44 (d, 1H, CH, J = 16 Hz).

2-Methyl 4'-diethoxyphosphonomethyl stilbene E ***5s***. IR (KBr) (ν cm^{-1}): 3079, 3049, 2955 (CH, CH_2, CH_3); 1597 (CH=CH); 1259 (PO). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.24 (t, 6H, CH_3); 2.42 (s, 3H, CH_3); 3.16 (d, 2H, CH_2-P, J = 22 Hz); 4.03 (q, 4H, CH_2-O); 6.94 (d, 2H, CH=CH, J = 16 Hz); 7.02–7.59 (m, 8H, Ar).

Diethyl 4-[2-(3-pyridyl) vinyl] benzyl phosphonate E ***5x***. IR (KBr) (ν cm^{-1}): 3024, 2985, 2932 (CH, CH_2, CH_3); 1562 (C=C); 1241 (P=O). ^{1}H-NMR ($CDCl_3$) (δ ppm): 1.23 (t, 6H, CH_3); 3.12 (d, 2H, CH_2-P, J = 20 Hz); 4.0 (m, 4H, CH_2-O); 7.13 (d, 2H, Ar α to CH=CH, J = 4 Hz); 7.26–7.32 (m, 3H, 2H at CH_2-P α position and pyridine H_5); 7.54 (s, 2H, CH=CH); 7.81–7.87 (m, 1H, H_4); 8.47–8.5 (dd, 1H, H_6); 8.72 (sd, 1H, H_2, J = 1.9 Hz).

Pharmacology

All compounds were assayed at a concentration of 0.50 μg/ml. The experimental protocol was identical to that described elsewhere [4] and based on that of Polster [14]. Each product was assayed on 3 different preparations. The mean values of the results, expressed as percentage relaxation are reported in increasing order of activity in table IV.

In view of the variability of the biological material only those compounds producing a relaxation percentage larger than 10% were considered to exhibit activity.

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