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Synthesis and calcium antagonistic activity of a series of diethyl benzofuryl, benzothienyl and benzogammapyronyl benzylphosphonates

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Summary — In this work we present about 15 original heterocyclic diethyl benzylphosphonate analogues of fostedil, in which we have varied the nature of the heterocycle, the substituents or the phosphonic group, or even the position of this latter. Three diethyl 4-(2-benzofuryl) benzyl phosphonates exhibited slightly higher calcium antagonism than the control. Solely substitution with a fluorine atom was able to maintain activity, whereas the other modifications always decreased it .

calcium antagonist / fostedil /phosphonate / chromone / benzofuran / benzothiophene

Introduction

Fostedil was described as a new calcium antagonist in 1982 [1–3]. This compound consists of a diethyl benzylphosphonate group with a 2-benzothiazolyl radical attached in the *para* position on the latter.

A hypothesis has been put forward in which the phosphonic methane moiety would be mainly responsible for the induction of calcium antagonism, and as a result, numerous phosphonates have been synthesized in the search for other calcium antagonists, with varying degrees of success [4–7].

Thus the calcium antagonistic activity of dihydropyridines has been enhanced by the addition of a phosphonate group [8, 9]. However, when this same moiety was fixed directly onto oxygenated heterocyclic compounds (chromone, benzofurane, etc), which are widely acknowledged to exhibit cardiovascular tropism, no derivative was found to be active [10].

When the phenyl in fostedil was replaced by aromatic heterocyclic compounds (furan, thiophene, pyridine) or the distance between the phosphonate and this moiety was modified, the calcium antagonistic activity was reduced [11, 12].

In these studies, in an attempt to enhance the calcium antagonism of oxygenated heterocyclic compounds, we inserted a phenyl group between the latter and the phosphonic moiety so as to come closer to the fostedil structure. At the same time we varied the position of the diethyl phosphonate which also modified the distance. The benzofuran derivative, which is the most active in the series, was substituted with various groups. Finally the diethyl phosphonate of the fluorinated benzofuran derivative was replaced by a lactam amidophosphonate, as replacement of the diethyl phosphonate of fostedil by other functional groups (particularly the amidophosphonates or the lactam amidophosphonates), has been reported to bring about a significant increase in calcium antagonism [13, 14].

Three types of heterocyclic compounds, *ie* benzothiophenes, benzofurans and chromones, were prepared, the structures of which are shown in tables I and II.

Chemistry

Phosphonate synthesis was carried out according to scheme 1. The bromomethyl derivatives **IIIa–IIIk**, **IIIm** and **IIIn** were obtained by free radical bromination [15] of the methyl compounds **IIa–IIk**, **IIm** and

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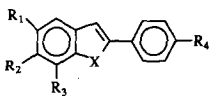
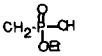
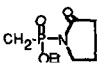
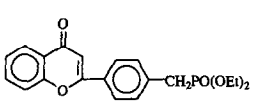
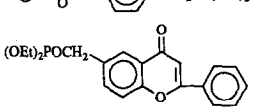
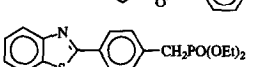
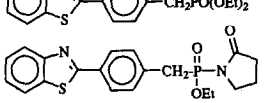
Table I. *In vitro* calcium antagonistic activity of compounds **IIa, IVa–VIk, VII** and **VIII**.



Compd	*X*	*R1*	*R2*	*R3*	*R4*	*% Inhibition*[a]
IIa	O	H	H	H	CH_3	-3
IVa	O	H	H	H	$CH_2PO(OEt)_2$	-62
IVb	O	F	H	H	$CH_2PO(OEt)_2$	-69
IVc	O	H	F	H	$CH_2PO(OEt)_2$	-62
IVd	O	H	H	F	$CH_2PO(OEt)_2$	-25
IVe	O	Cl	H	H	$CH_2PO(OEt)_2$	-16
IVf	O	Br	H	H	$CH_2PO(OEt)_2$	+2
IVg	O	Me O	H	H	$CH_2PO(OEt)_2$	-1
IVh	O	$CH_2PO(OEt)_2$	H	H	H	-11
IVi	O	H	$CH_2PO(OEt)_2$	H	H	-5
IVj	S	H	H	H	$CH_2PO(OEt)_2$	-43
IVk	S	$CH_2PO(OEt)_2$	H	H	H	-10
VII	O	F	H	H		-17
VIII	O	F	H	H		-49

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

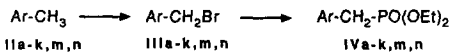
Table II. *In vitro* calcium antagonistic activity of compounds **IVm** and **IVn**.

Compd	*Structure*	*% Inhibition*[a]
IVm		0
IVn		0
Fostedil [1]		-57
Type Sample [14]		-57

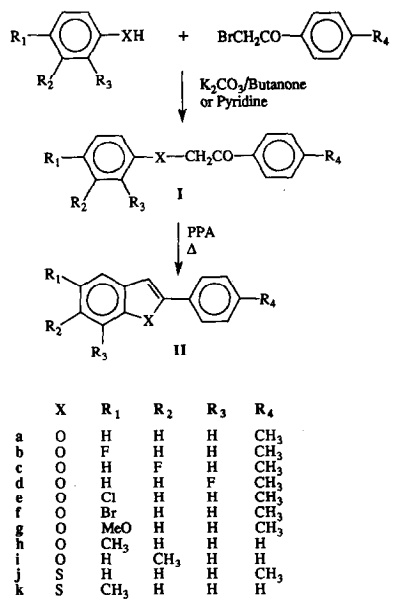
[a]Reduction in contraction of rabbit aortic fragments in the presence of calcium chloride at a concentration of 0.50 μg/ml.

IIn. These bromomethyl derivatives were heated in the presence of triethylphosphite according to the Michaelis–Arbuzov reaction [16] to produce the desired diethyl phosphonates **IVa–IVk, IVm** and **IVn**.

The methyl benzofuran and benzothiophene derivatives were prepared as in scheme 2.



Scheme 1.



	X	R_1	R_2	R_3	R_4
a	O	H	H	H	CH_3
b	O	F	H	H	CH_3
c	O	H	F	H	CH_3
d	O	H	H	F	CH_3
e	O	Cl	H	H	CH_3
f	O	Br	H	H	CH_3
g	O	MeO	H	H	CH_3
h	O	CH_3	H	H	H
i	O	H	CH_3	H	H
j	S	H	H	H	CH_3
k	S	CH_3	H	H	H

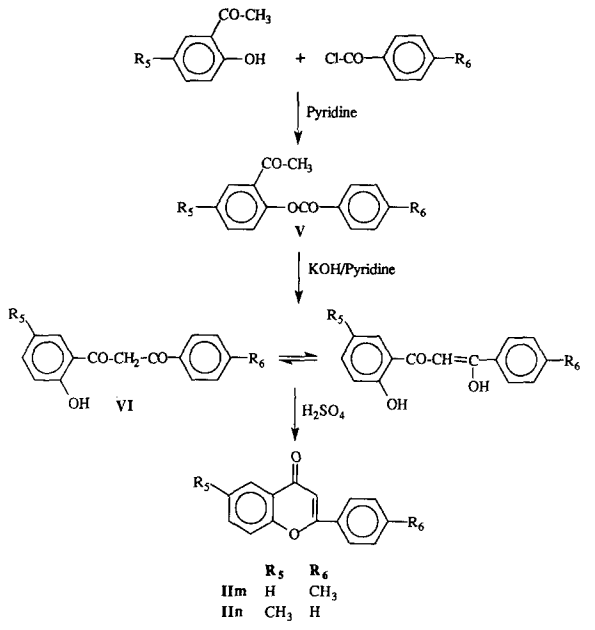
Scheme 2.

The suitably substituted phenol or thiophenol was condensed with 4-alkyl bromoacetophenone [17, 18]. The reaction took place in butanone in the presence of potassium carbonate in the case of the phenol derivatives, and in pyridine for the thiophenol derivatives [19, 20]. This gave the ω-phenoxyacetophenones **Ia–Ii** and the ω-phenylthioacetophenones **Ij** and **Ik**. When these compounds were heated in polyphosphoric acid (PPA) according to the Davies method [19, 20], they gave rise to the 2-paratolyl benzofurans **IIa–IIi** and the 2-paratolyl benzothiophenes **IIj** and **IIk**.

The methyl flavone derivatives were synthesized according to a previously described method [21] (scheme 3).

A suitably substituted orthohydroxyacetophenone was condensed with 4-alkyl benzoyl chloride in pyridine [22]. The **Vm** and **Vn** esters [23] thus obtained gave rise by Baker–Venkataraman transposition [24, 25] to the diketone derivatives **VIm** and **VIn** [23]. The enol forms were cyclized into the flavone derivatives **IIm** [26] and **IIn** [22] by sulphuric dehydration.

Partial hydrolysis of diethyl 4-(5-fluoro-2-benzofuryl) benzylphosphonate **IVb** produced the hemiphosphonate **VII**. The latter when treated with thionyl



Scheme 3.

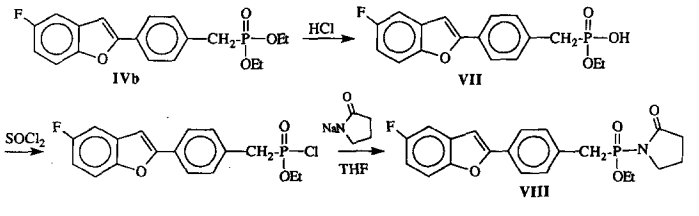
chloride produced the phosphonochloridate which reacted with the lactam sodium salt in anhydrous tetrahydrofuran to produce lactam amidophosphonate **VIII**, according to the method already described [14] (scheme 4).

Pharmacology

The degree of calcium antagonism was detected *in vitro* by examining the reduction in contraction of rabbit aortic fragments in the presence of calcium chloride. The results were expressed as percentage relaxation and are reported in tables I and II.

The antagonistic effects of fostedil, piprofurol, nifedipine and diltiazem were determined under the same experimental conditions for comparison (table III).

For a product to be considered to exhibit some activity, a dose of 0.5 µg/ml has to inhibit aortic contraction by at least 10%.



Scheme 4.

Table III. Comparative activity of compounds **IVa–c**, **VIII** and various calcium antagonists.

Compd	*% Inhibition*			
	0.50 (µg/ml)	*0.10 (µg/ml)*	*0.05 (µg/ml)*	*IC_{50} (µg/ml)*
IVa	– 62	–30	–25	0.240
IVb	– 69	–20	–	–
IVc	– 62	–22	–	–
VIII	– 49	–21	–	–
Fostedil	– 57	–18	–	0.370
Ditiazem	–	–	–	0.100
Piprofurol	–	–	–	0.024
Nifedipine	–	–	–	0.009

Results and discussion

By replacing the benzothiazole ring in fostedil with a benzofuran or benzothiophene ring (compounds **IVa**, **IVj**) we were able to obtain certain compounds that exhibited the same degree of activity as the control. Activity disappeared when the diethyl phosphonate group (compound **IIa**) was removed, thus confirming the beneficial influence of this group [27].

Despite the frequently reported analogy between chromone and benzofuran, the **IVm** derivative was totally inactive.

Changing the position of the diethyl phosphonate also caused the activity to disappear. This phenomenon was even more marked in the case of benzofuran (**IVa** *vs* **IVh**) and benzothiophene (**IVj** *vs* **IVk**). The position of the diethyl phosphonate in chromone did not influence the activity, both compounds being inactive.

Activity was maintained if fluorine was substituted on the benzofuran nucleus at positions 5 and 6, whereas it was reduced if the substitution took place at position 7. Chlorine, bromine and methoxy groups if attached to the heterocyclic compound at position 5 also led to the disappearance of activity.

According to Yoshino *et al* [14] the replacement of one ethyl in the phosphonate group with a lactam amidophosphonate increases the activity of fostedil. In our studies this modification to the phosphonate reduced activity (**IVb**: –69% *vs* **VIII**: –49%).

We therefore measured the calcium antagonism of the modified fostedil previously described and were unable, with our method of screening, to detect the claimed enhancement.

Although certain compounds (**IVa–c**) were more active than the control it has to be concluded that none of our benzylphosphonates exhibited the profile of a true calcium antagonist. The IC_{50} of the molecules used therapeutically (nifedipine, verapamil, diltiazem) are all well below 0.1 µg/ml. The IC_{50} of the most active of our compounds (table III) was 0.24 µg/ml.

Experimental protocols

Chemistry

R_f were determined by allowing the compounds to migrate on silica gel 60 F254 chromoplates over a distance of 10 cm using the solvent indicated for each compound. Melting points were measured with a Maquenne electric unit and are not corrected. The microanalyses complied with the accepted standards and have not been published.

Infrared spectra were measured with a Perkin–Elmer 983G apparatus. The potassium bromide pellet technique was used for solid products, while liquids were examined as a film between optically polished sodium chloride plates.

^{1}H-NMR spectra were measured either on a Varian A60 spectrometer at 60 MHz or with a Bruker 250 MHz apparatus (Fourier transformation) with TMS as internal standard.

We have only described here the physico-chemical and spectral characteristics of compounds not already described in the literature.

*ω-Aryloxy acetophenones **Ia–Ii***

To 0.11 mol potassium carbonate, was added 0.10 mol phenol dissolved in 200 ml anhydrous butanone. After heating for ≈ 20 min, 0.11 mol 4-alkyl bromoacetophenone was added. The resulting mixture was refluxed for 3 h, then cooled, filtered and the solvent evaporated under reduced pressure. The resulting product was recrystallised in ethanol.

The physical characteristics of compounds **Ia** [28], **Ie–Ig** [29], **Ih** and **Ii** [19] complied with those already described in the literature.

*ω-(Phenylthio) alkyl acetophenones **Ij** and **Ik***

0.10 mol ω-bromoacetophenone was added to 0.10 mol 4-alkyl thiophenol dissolved in 200 ml pyridine. The mixture was refluxed for 4 h. It was then cooled and the pyridinium hydrobromide filtered. The collected solution was evaporated under reduced pressure. The resulting residue was taken up in water. The precipitate was filtered and recrystallised in ethanol. The characteristics of compound **Ik** have already been described [20] and are not reported here.

*2-Tolyl benzofurans and 2-tolyl benzothiophenes **IIa–IIk***

Forty g polyphosphoric acid were heated in an oil bath to a temperature of 140–160°C for 30 min. 0.05 mol of either 4-alkyl ω-aryloxyacetophenone **Ia–Ii** or 4-alkyl ω-arylthio acetophenone **Ij** and **Ik** was then added. The reaction mixture was heated for ≈ 6 h. After cooling the obtained product was taken up in cold water. The precipitate was filtered, dried, then recrystallised in ethanol. Compounds **IIa** [28], **IIe–IIh** [29], **IIi**

Table IV. Physical properties of compounds **I** and **II**.

Compd	Formula	Yield (%)	Mp (°C)	R_f[a]	IR (KBr) (cm^{-1})	^{1}H-NMR ($CDCl_3$) (δ ppm)
Ib	$C_{15}H_{13}FO_2$	76	98	0,61	3113 , 3062 , 3017, 2902 , 2842 (CH_3, CH_2, CH); 1702 (CO) ; 1617,1559,1546 (C=C).	2.40 (s, 3H, CH_3); 5.10 (s, 2H, CH_2); 6.85-7.20 (m, 4H, arom.) ;7.35 (d, 2H , $H_{2'}$, $H_{6'}$; J = 8Hz); 7.85 (d, 2H, H_2, H_6; J = 8Hz).
Ic	$C_{15}H_{13}FO_2$	80	101	0.65	3105 , 3070 , 3053, 2956 , 2842 (CH_3, CH_2, CH), 1705 (CO); 1607,1570,1556 (C=C).	2.45 (s, 3H, CH_3); 5.20 (s, 2H, CH_2); 6.90-7.20 (m, 4H, aromatiques) ; 7.39 (d, 2H , $H_{2'}$,$H_{6'}$; J = 8Hz); 7.95 (d, 2H, H_2, H_6; J = 8Hz).
Id	$C_{15}H_{13}FO_2$	69	93	0.75	3124, 3071, 3044, 2971, 2949, 2929 (CH_3, CH_2, CH); 1689 (CO); 1606,1593,1570 (C=C).	2.45 (s, 3H, CH_3); 5.20 (s, 2H, CH_2); 6.80-7.20 (m, 6H, arom.); 8.10 (d, 2H, H_2, H_6 ; J = 8Hz).
Ij	$C_{15}H_{14}OS$	93	69	0.76	3147, 3070, 3053, 3031, 3014, 2999,2938, 2904 (CH_3, CH_2, CH); 1670 (CO); 1602, 1577, 1477 (C=C)	2.50 (s, 3H, CH_3); 4.33 (s, 2H, CH_2); 7.20-7.53 (m, 7H, arom.); 7.90 (dd, 2H, H_2, H_6; J = 8.0, 2.0 Hz).
IIb	$C_{15}H_{11}FO$	70	155	0.90	3115, 3078, 3024, 2917 (CH_3, CH); 1621, 1590 (C=C).	2.35 (s, 3H, CH_3); 6.92 (s, 1H, H_3); 7.01 (ddd, 1H, H_6; J = 2.7, 8.6, 8.9 Hz); 7.18 (dd, 1H, H_4, J = 2.7, 8.6 Hz); 7.37 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8 Hz); 7.38 (dd, 1H, H_7; J = 4.0, 8.9 Hz); 7.76 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8 Hz).
IIc	$C_{15}H_{11}FO$	81	162	0.83	3074, 3058, 3002, 2987, 2957 (CH_3, CH); 1607, 1589 (C=C).	2.35 (s, 3H, CH_3); 6.85 (s, 1H, H_3); 6.90-7.00 (m,1H, H_5); 7.16-7.21 (m, 3H, H_7, $H_{3'}$, $H_{5'}$); 7.36-7.44 (m, 1H, H_4); 7.64-7.69 (m, 2H, $H_{2'}$, $H_{6'}$).
IId	$C_{15}H_{11}FO$	47	126	0.72	3115, 3101, 3077, 3023, 2993, 2963, 2920, 2861 (CH_3, CH); 1628, 1594, 1541, 1504, 1482 (C=C).	2.30 (s, 3H, CH_3); 6.90-7.75 (m, 8H, arom.).
IIj	$C_{15}H_{12}S$	64	163	0.46	3151, 3054, 3039, 3033, 3022, 2913, 2859 (CH_3, CH); 1556, 1537, 1497, 1431 (C=C)	2.34 (s, 3H, CH_3); 7.12 (d, 2H, $H_{3'}$, $H_{5'}$; J = 8Hz); 7.29-7.33 (m, 2H, H_5, H_6); 7.44 (s, 1H, H_3); 7.56 (d, 2H, $H_{2'}$, $H_{6'}$; J = 8 Hz); 7.74 (dd, 1H, H_4; J = 1.0, 7.5 Hz); 7.87 (dd, 1H, H_7; J=1.5, 7.5Hz).

[a] 1,2-Dichloroethane.

[19], **IIk** [20] have already been described. The physical properties of compounds **I** and **II** are reported in table IV.

*Bromomethyl derivatives **IIIa–IIIk**, **IIIm** and **IIIn***

0.05 mol of the methyl derivative was dissolved in 150 ml carbon tetrachloride. This mixture was heated for ≈ 30 min. 9.90 g (0.056 mol) *N*-bromosuccinimide and a catalytic amount (0.5 g) of azo bis isobutyronitrile was then added. The mixture was refluxed for ≈ 6 h. After cooling, the succinimide was filtered. The resulting solution was concentrated. The residue was chromatographed on a silica gel column using either cyclohexane (**IIIa**, **IIIh**, **IIIi**), a mixture of cyclohexane

Table V. Physical properties of compounds **III**.

Compd	*Formula*	*Yield (%)*	*Mp (°C)*	*R_f*[a]	*IR (KBr) (cm^{-1})*	*^{1}H-NMR ($CDCl_3$) (δ ppm)*
IIIb	$C_{15}H_{10}BrFO$	56	112	0,92	3144, 2955, 2929 (CH_2, CH); 1620,1592,1556 (C=C)	4.60 (s, 2H, CH_2Br); 6,99 (ddd, 1H, H_6, J = 2.7, 8.7, 8.9 Hz); 7.25 (dd, 1H, H_4, J = 2,7; 8,7 Hz); 7,32 (s, 1H, H_3); 7.33 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8Hz); 7.40 (dd, 1H, H_7, J = 4.1, 8.9 Hz); 7.49 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8Hz).
IIIc	$C_{15}H_{10}BrFO$	49	109	0,93	3095, 3089, 3063, 3036, 2978, 2951, 2920, 2885 (CH_2, CH); 1603, 1594,1567,1509 (C=C).	4.40 (s, 2H, CH_2Br); 6.97-7.75 (m, 8H,arom.).
IIId	$C_{15}H_{10}BrFO$	53	97	0,83	3105, 3089, 3063, 3031,2958, 2931, 2920, 2865 (CH_3, CH_2, CH);1606,1584,1557,1500(C=C).	4.43 (s, 2H, CH_2Br); 6.87-7.79 (m, 8H, arom).
IIIe	$C_{15}H_{10}BrClO$	59	132	0,80	3107, 3089, 3060, 3051, 3036, 3013, 2961, 2929, 2859 (CH_2, CH); 1606,1584,1559,1500 (C=C).	4.51 (s, 2H, CH_2Br); 6.85 (s,1H, H_3); 7.18 (dd, 1H, H_6; J=2.5, 7.5Hz); 7.20 (d, 2H , $H_{3'}$, $H_{5'}$; J=8Hz); 7.35 (d, 1H, H_7; J=7.5Hz); 7.48 (d,1H, H_4; J=2.5Hz); 7.72 (d, 2H, $H_{2'}$,$H_{6'}$; J=8Hz).
IIIf	$C_{15}H_{10}Br_2O$	63	156	0,89	3181, 3103, 3083 (CH_2, CH); 1603,1582,1555 (C=C).	4.60 (s, 2H, CH_2Br); 6.60-7.80 (m, 8H, arom.).
IIIg	$C_{16}H_{13}BrO_2$	63	111	0,89	3107, 3089, 3033, 2959, 2832 (CH_3, CH_2, CH); 1610, 1597, 1558,1518 (C=C).	3.82 (s, 3H, CH_3); 4.45 (s, 2H, CH_2Br); 6.86 (dd,1H, H_6; J = 9.0, 3.0 Hz); 6.92 (s, 1H, H_3); 7.01 (d, 1H, H_4; J = 3Hz); 7.37 (m, 3H, H_7, $H_{3'}$, $H_{5'}$); 7.77 (m, 2H, $H_{2'}$, $H_{6'}$).
IIIh	$C_{15}H_{11}BrO$	58	124	0,79[b]	3059, 2967, 2931, 2899 (CH_2, CH); 1592,1488 (C=C).	4.60 (s, 2H, CH_2Br); 6.94 (s,1H, H_3); 7,07 (dd,1H, H_6; J = 2.0, 8.0 Hz); 7.28-7.47 (m, 5H, H_4, H_7, $H_{3'}$, $H_{4'}$, H_5); 7.81-7.87 (m, 2H, $H_{2'}$, $H_{6'}$).
IIIi	$C_{15}H_{11}BrO$	65	112	0,51	3199, 3051, 2995, 2945, 2826, 2802 (CH_2, CH); 1554 (C=C).	4.59 (s, 2H, CH_2Br); 6.94 (s, 1H, H_3); 7.05 (dd, 1H, H_5; J = 2.0, 8.0 Hz); 7.31 (m, 1H, $H_{4'}$); 7.35 (dd, 2H, $H_{3'}$, $H_{5'}$; J = 2.0, 7.0 Hz); 7.40 (d,1H, H_7; J = 2Hz); 7.45 (d, 1H, H_4; J = 8 Hz); 7.81 (dd, 2H, $H_{2'}$, $H_{6'}$; J = 2.0, 7.0 Hz).
IIIj	$C_{15}H_{11}BrS$	55	173	0,68	3050, 3022, 3006, 2979, 2848 (CH_2, CH); 1597, 1557, 1527, 1495, 1452 (C=C).	4.51 (s, 2H, CH_2Br); 7.17 (d, 2H, $H_{3'}$, $H_{5'}$; J=8Hz); 7.24 (dd, 1H, H_5 or H_6; J = 2.0, 5.0 Hz); 7.29 (dd, 1H, H_5 or H_6; J = 2.0, 5.0 Hz); 7.44 (s,1H, H_3); 7.56 (d, 2H, $H_{2'}$, $H_{6'}$; J=8Hz); 7.74 (dd, 1H, H_4; J=1, 7.5 Hz); 7.87 (dd, 1H, H_7; J=1.5, 7.5 Hz).
IIIk	$C_{15}H_{11}BrS$	60	163	0,59	3030, 3012, 3002, 2989, 2898 (CH_2, CH); 1593, 1567, 1537, 1499, 1452 (C=C).	4.45 (s, 2H, CH_2Br); 7.12 (dd,1H, H_6; J = 3.0, 8.0 Hz); 7.22 (s, 1H, H_3); 7.26-7.45 (m, 4H, H_7, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.54 (d, 1H, H_4; J = 2.5Hz); 7.69 (dd, 2H, $H_{2'}$, $H_{6'}$; J = 1.5, 8.0 Hz).
IIIm	$C_{16}H_{11}BrO_2$	36	135	0,77[b]	3057, 2986 (CH_2, CH); 1635 (C=O); 1603,1564 (C=C).	4.51 (s, 2H, CH_2Br); 6.77 (s, 1H, H_3); 7.40 (m, 1H, H_6); 7.48-7.54 (m, 2H, H_7, H_8); 7.64-7.71 (m, 2H, $H_{3'}$, $H_{5'}$); 7.82-7.89 (m, 2H $H_{2'}$, $H_{6'}$); 8.18 (d,1H, H_5).
IIIn	$C_{16}H_{11}BrO_2$	47	128	0,23	3061, 3008, 2924, 2845 (CH_2, CH); 1642 (C=O); 1611, 1568, 1483 (C=C).	4.60 (s, 2H, CH_2Br); 6.80 (s, 1H, H_3); 7.36-8.40 (m, 8H, arom.).

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

Table VI. Physical properties of compounds **IV**.

Compd	Formula	Yield (%)	Mp (°C)	R_f[a]	IR (KBr) (cm^{-1})	^1H-NMR ($CDCl_3$) (δ ppm)
IVb	$C_{19}H_{20}FO_4P$	72	117	0,41	3180, 3111, 3067, 3045, 3033, 2985, 2951, 2910 (CH_3, CH_2, CH); 1609,1593,1559,1501 (C=C); 1239 (P=O).	1.25 (t, 6H, CH_3; J=7Hz); 3.18 (d, 2H, CH_2-P; J=22 Hz); 4.03 (m, 4H, CH_2-O; J=7Hz); 6.92 (s, 1H, H_3); 6,98 (ddd, 1H, H_6, J = 2.6, 8.6, 8.9 Hz); 7.18 (dd, 1H, H_4, J = 2.6, 8.6 Hz); 7.39 (m, 3H, $H_{2'}$, $H_{6'}$ et H_7); 7.76 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8Hz).
IVc	$C_{19}H_{20}FO_4P$	51	85	0,32	3058, 3042, 3014, 2985, 2972, 2956 (CH_3, CH_2, CH); 1587, 1546, 1515, 1509 (C=C);1260 (P=O).	1.40 (t, 6H, CH_3; J=8Hz); 3.33 (d, 2H, CH_2-P; J=22Hz); 4.20 (m, 4H, CH_2-O; J=8Hz); 7.05-7.89 (m, 8H, arom.).
IVd	$C_{19}H_{20}FO_4P$	45	86	0,53	3105, 2997, 2956, 2943, 2904, 2896 (CH_3, CH_2, CH);1568,1549, 1523,1506 (C=C);1257,1237 (P=O)	1.36 (t, 6H, CH_3, J=8Hz); 1.36 (t, 6H, CH_3, J=8Hz); 3.30 (d, 2H, CH_2-P; J=22Hz); 4.16 (m, 4H, CH_2-O; J = 8Hz); 7.16-7.89 (m, 8H, arom.).
IVe	$C_{19}H_{20}ClO_4P$	69	140	0,48	3139, 3051, 2981, 2953, 2931, 2904 (CH_3, CH_2, CH); 1606,1585,1555,1536,1501 (C=C); 1274,1237 (P=O).	1.24 (t, 6H, CH_3; J=8Hz); 3.15 (d, 2H, CH_2-P; J=22Hz); 4.03 (m, 4H, CH_2-O; J = 8Hz); 6.85 (s,1H, H_2); 7.18 (dd, 1H, H_6; J=2.5, 7.5 Hz); 7.20 (d, 2H, $H_{2'}$, $H_{6'}$; J = 8Hz); 7.35 (d, 1H, H_7; J=7.5Hz); 7.48 (d,1H, H_4; J=2.5Hz); 7.72 (d, 2H, $H_{3'}$,$H_{5'}$; J=8Hz).
IVf	$C_{19}H_{20}BrO_4P$	67	131	0,33	3106, 2983, 2907 (CH_3, CH_2, CH); 1604,1584,1555 (C=C); 1241 (P=O).	1.40 (t, 6H, CH_3; J = 7Hz); 3.25 (d, 2H, CH_2-P; J=22Hz); 4.30 (m, 4H, CH_2-O; J = 7Hz); 6.82-8.15 (m, 8H, arom.).
IVg	$C_{20}H_{23}O_5P$	82	129	0,41	3111, 3059, 2979, 2954, 2837 (CH_3, CH_2, CH); 1608, 1595, 1557,1500 (C=C); 1240 (P=O).	1.25 (t, 6H, CH_3; J=7Hz); 3.17 (d, 2H, CH_2-P; J=22Hz); 3.83 (s, 3H, CH_3-O); 4.03 (m, 4H, CH_2-O; J=7Hz); 6.86 (dd, 1H, H_6; J = 9.0, ,3.0 Hz); 6.92 (s, 1H, H_3); 7.01 (d, 1H, H_4; J = 3 Hz); 7.37 (m, 3H, H_7, $H_{2'}$, $H_{6'}$); 7.77 (m, 2H, $H_{3'}$, $H_{5'}$).
IVh	$C_{19}H_{21}O_4P$	59	112	0,55	3063, 2963, 2919, 2907, 2885 (CH_3, CH_2, CH); 1611,1583 (C=C); 1276, 1239 (P=O).	1.25 (t, 6H, CH_3; J=8Hz); 3.20 (d, 2H, CH_2-P; J=21Hz); 4.15 (m, 4H, CH_2-O); 6.94 (s,1H, H_3); 7,07 (dd,1H, H_6; J = 8.0, 2.0 Hz); 7.28-7.47 (m, 5H, H_4, H_7, $H_{3'}$, $H_{4'}$, H_5); 7.81-7.87 (m, 2H, $H_{2'}$, $H_{6'}$).
IVi	$C_{19}H_{21}O_4P$	62	58	0,62	3045, 3033, 2985, 2954, 2920 (CH_3 ,CH_2, CH); 1646, 1621, 1604, 1595, 1586 (C=C); 1249 (P=O).	1.31 (t, 6H, CH_3; J=7Hz); 3.49 (d, 2H, CH_2-P; J=21Hz); 4.05 (m, 4H, CH_2-O; J = 7 Hz); 6.94 (s, 1H, H_3); 7.05 (dd, 1H, H_5; J = 2.0, 8.0 Hz); 7.31 (m, 1H, $H_{4'}$); 7.35(dd, 2H, $H_{3'}$,$H_{5'}$; J=2.0,7.0 Hz);7.40(d,1H, H_7; J=2Hz); 7.45(d,1H,H_4; J=8Hz); 7.81(dd, 2H, $H_{2'}$, $H_{6'}$;J=7.0,2.0 Hz).
IVj	$C_{19}H_{21}O_3PS$	65	143	0,64	3047, 3027, 2981, 2935, 2903 (CH_3, CH_2, CH); 1652, 1646, 1635, 1627, 1623, 1617, 1606, 1586, 1559 (C=C); 1254, 1238 (P=O).	1.24 (t, 6H, CH_3; J=7Hz); 3.15 (d, 2H, CH_2-P; J=22Hz); 1.24 (t, 6H, CH_3; J=7Hz); 3.15 (d, 2H, CH_2-P; J=22Hz); 4.02 (m, 4H, CH_2-O; J=7Hz); 7.17 (d, 2H, $H_{2'}$, $H_{6'}$; J=8Hz); 7.24 (dd, 1H, H_5 or H_6; J = 2, 5Hz); 7.29 (dd, 1H, H_5 or H_6; J=2.0, 5.0 Hz); 7.44 (s, H_3); 7.56 (d, 2H, $H_{3'}$, $H_{5'}$; J=8Hz); 7.74 (dd, 1H, H_4; J=1.0, 7.5Hz); 7.87 (dd, 1H, H_7; J= 1.5, 7.5 Hz).
IVk	$C_{19}H_{21}O_3PS$	59	77	0,54	3053, 3049, 3008, 2954, 2933, 2905 (CH_3, CH_2, CH); 1634, 1628, 1616, 1609, 1589 (C=C); 1258 (P=O).	1.21 (t, 6H, CH_3; J=7Hz); 3.20 (d, 2H, CH_2-P; J=22Hz); 3.95 (m, 4H, CH_2-O; J=7Hz); 7.12 (dd,1H, H_6; J=8, 3Hz); 7.22 (s, 1H, H_3); 7.26-7.45 (m, 4H, H_7, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.54 (d,1H, H_4; J = 2.5Hz); 7.69 (dd, 2H,$H_{2'}$,$H_{6'}$; J = 8.0, 1.5 Hz).
IVm	$C_{20}H_{21}O_5P$	78	162	0,14	3191, 3068, 2977 (CH_3, CH_2, CH); 1630 (C=O); 1579 (C=C);1249 (P=O).	1.30 (t, 6H, CH_3; J=7Hz); 3.41 (d, 2H, CH_2-P; J=22Hz); 4.10 (m, 4H, CH_2; J=7Hz); 6.83 (s, 1H, H_3); 7.43 (d, 2H, $H_{2'}$, $H_{6'}$; J=8Hz); 7.56 (m, 3H, H_6, H_7, H_8); 7.87 (d, 2H, $H_{3'}$, $H_{5'}$; J=8Hz); 8.20 (d, 1H, H_5, J=8Hz).
IVn	$C_{20}H_{21}O_5P$	47	127	0,17	3075, 3056, 3033, 2987 (CH_3, CH_2, CH); 1678 (C=O);1635 (C=C); 1242 (P=O).	2.20 (t, 6H, CH_3); 3.07 (d, 2H, CH_2-P; J=21Hz); 4.25 (m, 4H, CH_2-O); 6.80 (m, 9H, arom.).

[a]Ethyl acetate.

Table VII. Physical properties of compounds **VII** and **VIII**.

Compd	*Formula*	*Yield (%)*	*Mp (°C)*	*R_f*	*IR (KBr) (cm^{-1})*	*^{1}H-NMR ($CDCl_3$) (δ ppm)*
VII	$C_{17}H_{16}FO_4P$	70	242	0.31[a]	3600-2250 (OH); 3110, 3073, 3044, 2981, 2931, 2910 (CH_3, CH_2, CH); 1617, 1590, 1558, 1543, 1503 (C=C); 1290, 1255 (PO)	[c]1.18 (t, 3H, CH_3; J=7Hz); 3.16 (d, 2H, CH_2-P; J=22 Hz); 4.03 (m, 2H, CH_2-O; J=7Hz); 7.08 (ddd, 1H, H_6, J = 2.7, 8.9, 9.2 Hz); 7,32 (s, 1H, H_3); 7.40 (m, 3H, H_4, $H_{2'}$, $H_{6'}$); 7.58 (dd, 1H, H_7, J = 4.1, 8.9 Hz); 7.76 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8Hz); 8,25 (s, 1H, OH).
VIII	$C_{21}H_{21}FNO_4P$	25	122	0.18[b]	3119, 3073, 3039, 3025, 2987, 2904 (CH_3, CH_2, CH); 1683,1646 (CO); 1622, 1617, 1596, 1569, 1555 (C=C); 1284, 1253 (PO).	1.97 (t, 3H, CH_3); 2.44 (m, 2H, CH_2); 3.19 (m, 2H, CH_2); 3.49-3.61 (m, 4H, CH_2, CH_2P); 4.03 (m, 2H, CH_2O); 7.04 (m, 1H, H_6); 7,32 (s, 1H, H_3); 7.40 (m, 3H, H_4, $H_{2'}$, $H_{6'}$); 7.6 (dd, 1H, H_7, J = 4.0, 9.0 Hz); 7.76 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8 Hz).

[a]Ethanol; [b]ethyl acetate; [c]DMSO.

and 1,2-dichloro ethane (**IIIg**, **IIIj**, **IIIm**, **IIIn**) or 1,2-dichloro ethane (**IIIb–IIIf**) as eluent. Recrystallization could be carried out in ethanol if cooled to a low temperature. The physical properties of the bromomethyl compounds are reported in table V. Those of compound **IIIa** comply with the information in the literature [30].

*Diethyl phosphonates **IVa–IVk**, **IVm** and **IVn***

0.02 mol of the bromomethyl derivative was dissolved in 4.15 g (0.025 mol) triethylphosphite (TEP). This reaction mixture was refluxed in an oil bath at 140°C for at most 6 h. The excess triethylphosphite was eliminated under reduced pressure. The residue was chromatographed on a silica gel column with 1,2-dichloro ethane as eluent and the collected product recrystallised in a minimum of ethyl acetate. The physical characteristics of the phosphonates are indicated in table VI. Those of compound **IVa** comply with the information in the literature [30].

*Ethyl 4-(5-fluoro 2-benzofuryl) benzyl (2-oxopyrrolidino) phosphinate **VIII** (scheme 4)*

*Ethyl 4-(5-fluoro 2-benzofuryl) benzyl hemiphosphonate **VII**.* 10 g (0.028 mol) diethyl 4-(5-fluoro 2-benzofuryl) benzylphosphonate **IVb** was dissolved in 40 ml concentrated hydrochloric acid. After refluxing for 3 h the precipitate was washed thoroughly in water then dried.

Ethyl 4-(5-fluoro 2-benzofuryl) benzylphosphonate chloride. Six g (0.018 mol) of hemiphosphonate **VII** was dissolved in 40 ml thionyl chloride and a catalytic amount of dimethylformamide added. The mixture was refluxed for 3 h. After evaporating the excess thionyl chloride, 6.28 g of phosphonochloridate was collected as a yellow powder and used without prior purification.

2-Pyrrolidone sodium salt. To 50 ml anhydrous tetrahydrofuran was added 3.4 g (0.02 mol) of 2-pyrrolidone and 0.92 g (0.02 mol) of 50% sodium hydride. The mixture was refluxed for 1 h. The milky solution obtained was cooled and used as such.

*Ethyl 4-(5-Fluoro 2-benzofuryl) benzyl (2-oxopyrrolidino) phosphinate **VIII**.* 6.28 g (0.02 mol) of phosphonohydrochloridate was put into suspension in 60 ml tetrahydrofuran (THF). Ten g triethylamine was then added. The mixture was cooled to 0°C. The 2-pyrrolidone sodium salt solution was added. After agitating for 3 h, it was evaporated under reduced pressure and the residue chromatographed on a silica gel column with ethyl acetate as eluent to obtain product **VIII**. This was recrystallised in a minimum of ethyl acetate.

The physical characteristics of compounds **VII** and **VIII** are indicated in table VII.

Pharmacology

All the compounds were tested on 3 aortic fragments at a concentration of 0.50 µg/ml. Doses of 0.10 and 0.05 µg/ml of the most active compounds were also examined. The 50% inhibitory concentrations (IC_{50}) of the model (fostedil), one of our benzofuran compounds, piprofurol and other calcium antagonists such as diltiazem and nifedipine were also determined for comparison. Semi-logarithmic plots of the IC_{50} were produced. The *Experimental protocols* were identical to those already described [10] and based on those of Polster [31].

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