2-Aryl-Substituted, Benzo-anellated 5-Membered Heterocyclic Compounds as Potentially Active Substances for the Cardiovascular System: 1,3-Benzothiazolyl- and 1,3-Benzoxazolylbenzylphosphonates

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In the course of investigations on structure-activity relationships of calcium antagonists analogous to fostedil, a series of 2-aryl- and 2-arylvinyl-substituted 1,3-benzothiazoles and 1,3-benzoxazoles bearing a phosphonate group on the phenyl ring has been synthesized by cyclization, bromination, and subsequent Michaelis-Arbuzow reaction. Pharmacological investigations on isolated organs from guinea pigs revealed both negative inotropic effects and a relaxing action on smooth musculature; these activities were particularly pronounced in the 1,3-benzothiazole compound group.

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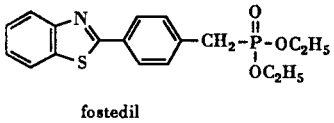
Introduction.

The modulation of calcium influx into cells of smooth and cardiac musculature by means of the chemically and physiologically heterogenous "calcium antagonistic" class of compounds has found wide application as a therapeutic concept [1-2].

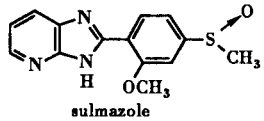
(Benzothiazolyl)benzylphosphonates of the fostedil-type (Scheme 1) represent a structurally novel group of calcium antagonists [3-4]. It is assumed that the mode of action of these compounds is based on an interaction with an enzyme capable of phosphorylating calcium channels [5-6]. The structurally related imidazopyridine sulmazole (Scheme 1), with positive inotropic principles, reveals its activities by stimulation of the transmembraneous Na^+/-Ca^{2+}-exchange [7].

In the course of investigations on structure-activity relationship of fostedil and sulmazole, numerous 1,3-benzothiazoles, 1,3-benzoxazoles [8], and 1,3-benzimidazoles [9] have been prepared and their effects on the cardiovascular system studied.

Scheme 1



fostedil



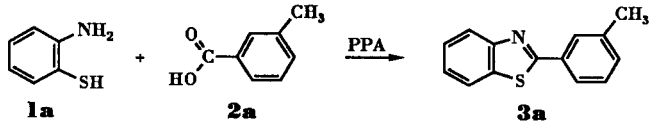
sulmazole

Chemistry.

The present work is concerned with the introduction of the phosphonate structural unit into the above mentioned ring systems for the purpose of obtaining compounds with calcium antagonistic properties. The rationale for the performed syntheses was the investigation of structure-activity relationships of compounds in which (i) the benzothiazole unit in fostedil had been replaced by other, structurally related heterocyclic systems, (ii) the aryl moiety bearing the phosphonate group was no longer directly bonded to the heterocyclic ring but rather linked to it by a vinyl bridge, and (iii) the position of the phosphonate group on the phenyl ring was varied with concomitant alternation of the chain length of the ester groups in order to ascertain the optimum combination.

The first series of experiments had the objective of preparing 2-phenyl-substituted compounds retaining the benzothiazole structure but bearing phosphonic acid diester structures with differing chain lengths at the 3-position of the aryl ring. In analogy to the methodology described [8,9], 2-aminothiophenol (**1a**) and 3-methylbenzoic acid (**2a**) were cyclized in phosphorylchloride to furnish the 2-substituted 1,3-benzothiazole **3a**. Higher yields (84%) were realized by using polyphosphoric acid (PPA) (Scheme 2).

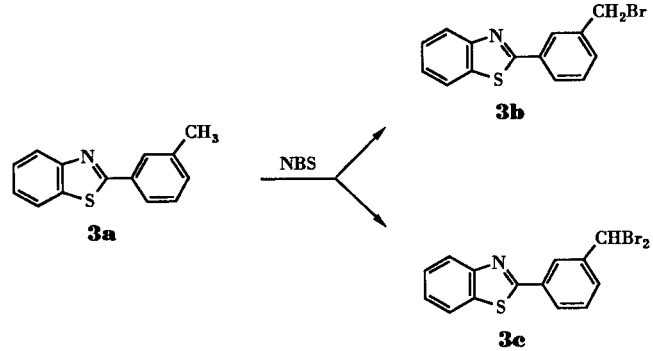
Scheme 2



1a **2a** **3a**

The reactants **1a** and **2a** were heated under nitrogen, the mixture was then hydrolysed, and the *p*H value adjusted to 5. The precipitate that separated was purified by recrystallization. Since the proposed construction of a

Scheme 3



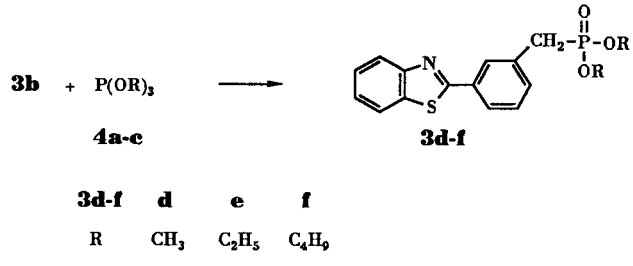
3a **3b** **3c**

phosphonic acid diester unit by the reaction of a trialkylphosphite with an alkyl halide seemed applicable [10,11], the 3'-methyl group of **3a** needed to be brominated. This halogenation to furnish **3b** was achieved using *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide as catalyst (Scheme 3).

When the optimal reaction conditions are not followed exactly, *e.g.* by use of a larger than necessary amount of brominating reagent, a double bromination of the methyl group can take place. Such a case can be readily detected by nmr spectroscopy on the basis of the chemical shift of the brominated methyl group and its signal integration. The desired subsequent reaction is not possible under these circumstances.

The final products, **3d-f**, of this reaction sequence can be generated according to Michaelis-Arbuzow from **3b** and the trialkyl phosphites **4a-c** under alkali metal iodide-catalysis [12] (Scheme 4). The product yields after flash chromatographic purification or recrystallization are in the range 50-70%.

Scheme 4



3d-f	**d**	**e**	**f**
R	CH_3	C_2H_5	C_4H_9

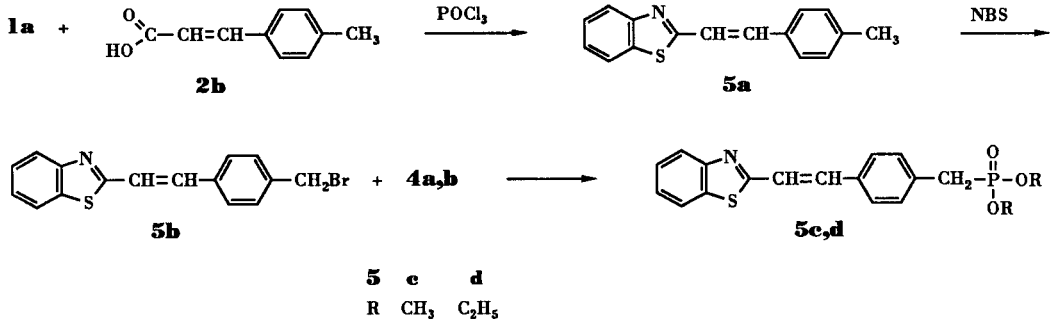
Derivatives of the structural type **5** in which the phenyl group is bonded to the heterocyclic ring through a vinyl bridge are accessible by analogous reactions. The initial step comprised cyclization of **1a** with 4-methylcinnamic acid (**2b**) to furnish the 1,3-benzothiazole **5a**. Bromination of **5a** as described above and subsequent reaction of **5b** with trimethyl or triethyl phosphite then provided the desired final products **5c** and **d** (Scheme 5).

The already mentioned modifications of the heterocyclic unit were realized by application of the above concept to systems able to generate the 1,3-benzoxazole basic unit, corresponding in principle to the syntheses of the structural types **3** and **5**. Starting material was 2-aminophenol (**1b**) which was cyclized with the corresponding carboxylic acid in phosphoryl chloride or PPA and then brominated to furnish the desired intermediate. Subsequent Michaelis-Arbusow reaction gave rise to phosphonates of the structural type **6**. Dibromination can also be observed here as a side reaction. The reaction sequence is summarized in Scheme 6.

Structural Confirmation.

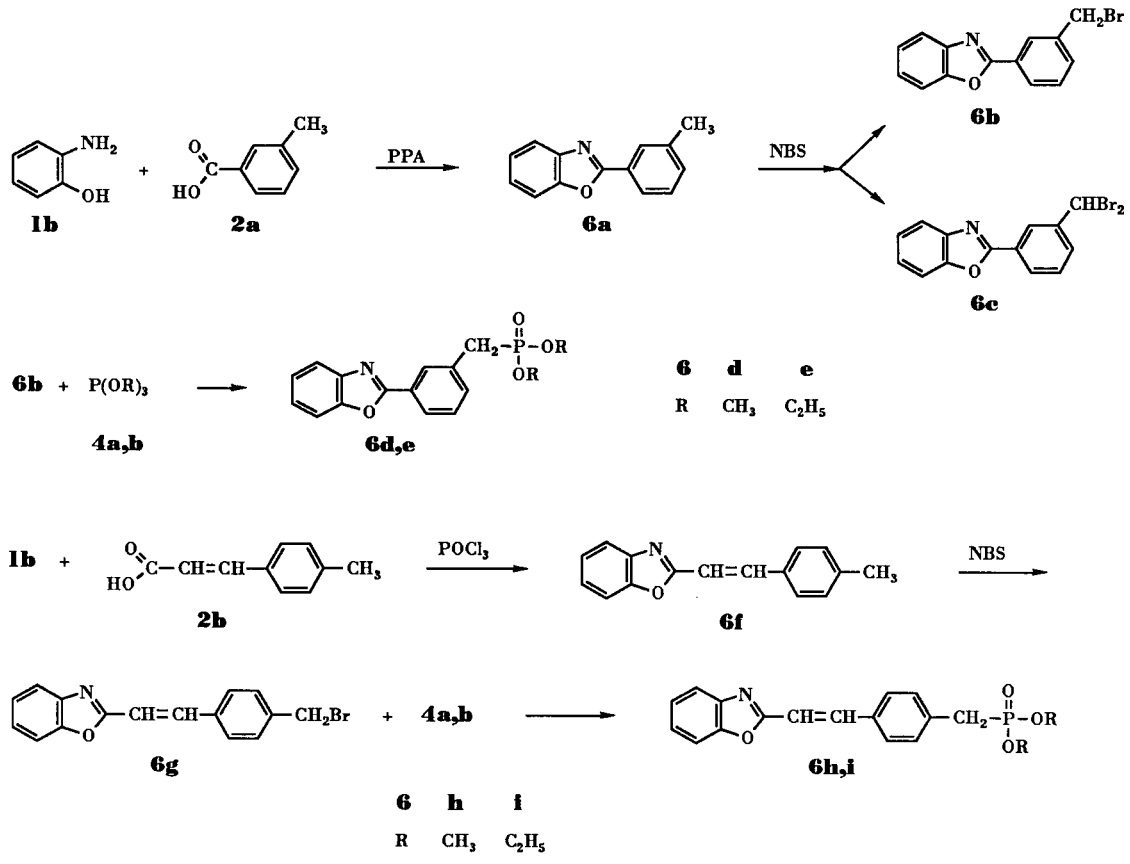
The postulated structures were substantiated by analysis of infrared, ^{1}H nmr, and mass spectroscopic data. Characteristic features were observed in the ^{1}H nmr spectrum as a consequence of the presence of the phosphonate group since, in addition to the usual H,H spin couplings, H,P couplings also influence the splitting patterns of the proton resonance. The terminal methyl groups of the phosphonate diester **5d** give rise to a triplet at δ = 1.22 ppm with an alkane coupling constant of ^3J = 7 Hz as a result of coupling with neighbouring methylene protons. On account of the spatial separation, an influence of the ^{31}P atom on these resonances cannot be observed. The signal of the benzylic methylene protons (δ = 3.18 ppm), on the other hand, experiences a noticeable splitting with a coupling constant of ^2J (H,P) = 22 Hz through H,P interaction. The vicinal H,P coupling over three bonds can still be observed in this spectrum although it is markedly weaker. Thus, the methylene protons of the phosphonate unit $P(OCH_2CH_3)_2$ are responsible for the formation of a multiplet between δ = 3.9 and 4.1 ppm; this multiplet is made up of two slightly shifted quadruplets resulting from H,P coupling. A non-analysable multiplet between δ = 7.3 and 7.5 ppm integrating for eight protons can be assigned to the protons of the substituted phenyl ring, H-5 and H-6 of the anellated phenyl ring, and the protons of the vinyl group. As observed previously [8], H-7 and H-4 of the ben-

Scheme 5



5	**c**	**d**
R	CH_3	C_2H_5

Scheme 6



zothiazole give rise to doublets with ^3J = 8 Hz appearing at δ = 7.83 and 7.97 ppm, respectively.

Pharmacological Section.

1. Material and Methods.

The methodology of the pharmacological investigations on isolated organs of the guinea pig (ileum, aorta, electrically stimulated left atria) have been described in detail in refs [13-15]. EC_{50} value: the dose which brings about 50% of the maximum effect.

Relative activity: the ratio of the maximum effect of each substance to the maximum effect of nifedipine or fostedil.

The experiments on Langendorff hearts and the *in vivo* vascular investigations on the rat were performed by the Hoechst AG, Frankfurt am Main, FRG, for which I here express my since thanks.

2. Results.

Compounds of the structural types **3**, **5**, and **6** exert relaxing effects on both smooth musculature and on cardiac muscles. All substances tested in experiments on electrically stimulated left atria exhibited a dose-dependent inhibition of contractility. The results and experimental data are shown in Table 1.

Table 1
Investigations on Electrically Stimulated Guinea Pig Left Atria, EC_{50} Values, Realtive Activities

Compound	EC_{50} [mol/l]	Max Effect (%) [a]	Rel Activity [b]	n [c]
Fostedil	$4{,}0 \times 10^{-7}$	79±3.0	1	(Belluci *et al.* 1987)
3d	$2{,}8 \times 10^{-5}$	53±1.4	0.67	3
3e	$2{,}8 \times 10^{-5}$	68±2.3	0.86	4
5d	$4{,}0 \times 10^{-5}$	39±8.4	0.49	3
6d	$5{,}6 \times 10^{-5}$	61±4.2	0.77	3
6i	6.3×10^{-5}	28±3.2	0.35	3

[a] Inhibition of contractility $\bar{x}$±S.E.M. [b] Fostedil = 1. [c] Number of experiments.

In comparison with the standard fostedil, good relative degrees of activity were observed although the EC_{50} values were higher than that of fostedil (4.0×10^{-7} mol/l). A shift of the phosphonate group from the 4-position in fostedil to the 3-position in structural type **3** was, therefore, accompanied by a loss of activity in such a way that higher doses were required to achieve the desired effect. Coupling of the aryl unit to the heterocyclic ring through a vinyl bridge (structures **5**) led to a reduction of activity both in terms of the maximum degree of activity and of the EC_{50} value. In the group of benzoxazoles **6** highest activity was found with **6d** with a relative activity of 0.77.

Relaxing effects on barium chloride-stimulated ileum preparations were observed for all substances and the maximum was found at a relative degree of activity of 0.8 to 0.9 (**3d, e, 5d**) in comparison to the standard nifedipine. Nifedipine was used as comparator drug in the experiments on smooth musculature. The results of these investigations are summarized in Table 2.

Table 2
Investigations on Barium Chloride-Stimulated Ileum of Guinea Pigs, EC_{50} Values, Realtive Activities

Compound	EC_{50} [mol/l]	Max Effect (%) [a]	Rel Activity [b]	n [c]
Nifedipine	$2{,}0 \times 10^{-8}$	95±2.8	1	9
3d	$3{,}8 \times 10^{-5}$	80±7.1	0.84	3
3e	$2{,}2 \times 10^{-5}$	77±3.0	0.81	3
3f	$6{,}3 \times 10^{-5}$	49±9.1	0.52	3
5c	$5{,}6 \times 10^{-5}$	29±2.3	0.31	3
5d	$4{,}5 \times 10^{-5}$	84±9.1	0.88	3
6d	$5{,}6 \times 10^{-5}$	34±1.4	0.36	3
6e	$5{,}6 \times 10^{-5}$	67±5.0	0.71	3
6h	$5{,}6 \times 10^{-5}$	48±5.0	0.51	6
6l	$3{,}5 \times 10^{-5}$	55±10.4	0.58	3

[a] Contraction inhibition $\bar{x}$±S.E.M. [b] Nifedipine = 1. [c] Number of experiments.

Highest activities were found for the benzothiazoles, including also **5d** in which the phenyl ring is connected to the heterocyclic moiety through a vinyl bridge.

The results of the experiments on ileum samples were confirmed by the results of investigations on potassium chloride-stimulated aortic strips from guinea pigs. The derivatives **3e** and **5c** were examplarily tested for their contractility inhibiting effects and were found to possess comparable degrees of activity with nifedipine (1.1 for **3e**, 0.86 for **5c**), although the EC_{50} values were noticeable higher (Table 3).

In addition, the benzothiazole **5c** and the benzoxazole **6h** were also tested for their cardiac acitivity on Langendorff hearts and on anesthetized rats.

At a dose of 10 mg/kg on anesthetized Wistar rats, compound **5c** effected a 10% reduction of systolic and diastolic pressures and concomitantly reduced the heart rate by 10%. On Langendorff hearts, the injection of 5 μg of **5c** (solvent: propane-1,2-diol) effected a 91% increase of coronary flow (segontin standard in a comparative experiments: 67%). Accordingly, it has a higher coronary dilating action than the standard but an inotropic activity could not be detected in this case.

Table 3
Investigations on Potassium Chloride-Stimulated Aortic Strips of Guinea Pigs, EC_{50} Values, Realtive Activities

Compound	EC_{50} [mol/l]	Max Effect (%) [a]	Rel Activity [b]	n [c]
Nifedipine	$8{,}9 \times 10^{-9}$	70±6.6	1	4
3e	$1{,}8 \times 10^{-5}$	74±3.4	1.1	3
5c	$3{,}0 \times 10^{-5}$	60±2.2	0.86	3

[a] Contraction inhibition $\bar{x}$±S.E.M. [b] Nifedipine = 1. [c] Number of experiments.

In the same experimental system, **6h** effected a 10% reduction of systolic and diastolic pressures; a chronotropic activity was not observed. **6h** did not exhibt any activity on Langendorff experiments.

Discussion.

The introduction of the phosphonate group into the molecules of 2-aryl-substituted 1,3-benzothiazoles and 1,3-benzoxazoles was realized by bromination and subsequent Michaelis-Arbuzow reaction with a trialkyl phosphite. Whereas analogous structures with varying substitution on the aryl ring but without a phosphonate moiety did not show any appreciable effects on the cardiovascular system [8], the structural types investigated in the present work exerted calcium antagonistic effects which could be observed both as a cardiac activity in the sense of a negative inotropic action and as an effect on smooth musculature. The most pronounced activity was found in the group of 1,3-benzothiazoles with relative degrees of activity being in the same order of magnitude as those of the comparator drugs fostedil and nifedipine (Tables 1-3) whereas EC_{50} values were significantly higher.

EXPERIMENTAL

Melting points were taken with a Büchi SMP 20 melting point apparatus according to Dr. Tottoli and are not corrected. The ir spectra were taken on Beckmann spectrophotometers IR-33 and IR-4220. The ^{1}H nmr spectra were taken on Varian EM 360 and Bruker AM 400 spectrometers, TMS as internal standard. The mass spectra were observed on a Varian MAT CH 7a (Bremen/-FRG). The tlc, cc, and pcc were taken on silica gel (Merck) of various activity grades.

General Procedure for the Syntheses of the Structural Types **3**, **5**, and **6**.

Equimolar amounts (150 mmoles) of the respective carboxylic acid and 2-aminothiophenol (**1a**) or 2-aminophenol (**1b**) were suspended in polyphosphoric acid and the mixture was heated at 200° under nitrogen for 2 hours. After the mixture had been allowed to cool to 100°, the crude product was taken up in water (500 ml), and the *p*H value of the mixture was adjusted 5.0 by addition of sodium hydroxide pellets. The separated precipitate was filtered under suction and then repeatedly recrystallized from ethanol/water. For bromination, the intermediate was suspended in tetrachloromethane, an equimolar amount of *N*-bromosuccinimide together with a spatula-tip of benzoyl peroxide were added, and the mixture was heated to boiling for 4 hours. After being allowed to cool, the resultant mixture was filtered, the filtrate was concentrated and the residue was repeatedly recrystallized from ligroin. Subsequent introduction of the phosphonate group was achieved by heating the brominated compound to boiling in the presence of the appropriate trialkyl phosphite (12 fold excess) and potassium iodide in the absence of a solvent. The desired product was purified by concentration of the reaction mixture and either recrystallization from ethanol/water of flash chromatography on silica gel with dichloromethane/acetone, 2:1.

The following intermediates had previously been reported in the literature: **3a** [16], **3b** [17], **5a** [18], **5b** [19], **6a** [20], **6f** [21], **6g** [22].

2-(3-Methylphenyl)-1,3-benzothiazole (**3a**).

This compound was obtained as colorless platelets (ethanol/water), mp 72°, yield 28.3 g (84%); ir (potassium bromide): 3050 (aromatic CH stretch), 2850 (aliphatic CH stretch), 1550, 1510 (phenyl C=C stretch), 760, 730, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 2.45 (s, 3 H, C*H*$_3$), 7.15-7.5 (m, 4 H, *H* of the substituted phenyl ring), 7.75-7.85 (m, 4 H, *H* of the anellated phenyl ring); ms: (90 eV) m/z = 226 (26%, M^++H), 225 (100%, M^+), 224 (24%, M^+-H), 210 (3%, M^+-CH_3), 108 (13%, $C_6H_4S^+$), 91 (4%, $C_7H_7^+$).

Anal. Calcd. for $C_{14}H_{11}NS$ (225.2): C, 74.7; H, 4.9; N, 6.1. Found: C, 74.3; H, 4.9; N, 6.1.

2-[3-(Bromomethyl)phenyl]-1,3-benzothiazole (**3b**).

This compound was obtained in colorless platelets (ligroin), mp 104°, yield 44%; ir (potassium bromide): 3060 (aromatic CH stretch), 1510 (phenyl CH stretch), 760, 730, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 4.56 (s, 2 H, C*H*$_2$Br), 7.3-7.6 (m, 4 H, *H* of the substituted phenyl ring), 7.8-8.2 (m, 4 H, *H* of the anellated pheny ring); ms: (90 eV) m/z = 305 (23%, M^+), 303 (23%, M^+), 225 (48%, 305-Br), 224 (100%, M^+-Br), 108 (10%, $C_6H_4S^+$).

Anal. Calcd. for $C_{14}H_{10}BrNS$ (304.2): C, 55.3; H, 3.3; N, 4.6. Found: C, 55.5; H, 3.6; N, 4.3.

2-[3-(Dibromomethyl)phenyl]-1,3-benzothiazole (**3c**).

This compound was obtained as colorless platelets (ligroin), mp 104°, yield 14%; ir (potassium bromide): 3020 (aromatic CH stretch), 1480 (phenyl C=C stretch), 760, 740, 690 cm^{-1} (aromatic CH stretch); ^1H nmr (deuteriochloroform): δ (ppm) = 6.7 (s, 1 H, C*H*Br$_2$), 7.35-7.6 (m, 3 H, *H*-4, *H*-5, *H*-6 of the substituted phenyl ring), 7.7-8.15 (m, 4 H, *H* of the anellated phenyl ring), 8.3 (s, 1 H, *H*-2 of the substituted phenyl ring); ms: (90 eV) m/z = 383 (25%, M^+), 303 (75%, M^+-Br), 222 (100%, 303-HBr).

Anal. Calcd. for $C_{14}H_9Br_2NS$ (383.2): C, 43.9; H, 2.3; N, 3.7. Found: C, 44.1; H, 2.2; N, 3.9.

2-[3-(Dimethylphosphonatomethyl)phenyl]-1,3-benzothiazole (**3d**).

This compound was obtained as colorless needles (ethanol/water) from 2.0 g (6.6 mmoles) of **3b** and 10.0 g (81 mmoles) of trimethylphosphite (**4a**) to give 1.57 g (71%) **3d**, mp 98°; ir (potassium bromide): 3060 (aromatic CH stretch), 2920, 2850 (aliphatic CH stretch), 1250 (P=O stretch), 760, 730, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.22 (d, C*H*$_2$P, ^2J (H,P) = 22 Hz), 3.68 (d, 6 H, OC*H*$_3$, ^3J (H,P) = 11 Hz), 7.3-7.55 (m, 4 H, *H* of the substituted phenyl ring), 7.85-8.1 (m, 4 H, *H* of the anellated phenyl ring); ms: (90 eV) m/z = 334 (18%, M^++H), 333 (92%, M^+), 318 (7%, M^+-CH_3), 240 (22%, M^+-HP(OCH$_3$)$_2$), 224 (100%, M^+-PO(OCH$_3$)$_2$), 109 (59%, PO(OCH$_3$)$_2^+$), 108 (13%, $C_6H_4S^+$), 93 (15%, P(OCH$_3$)$_2^+$).

Anal. Calcd. for $C_{16}H_{16}NO_3PS$ (333.3): C, 57.7; H, 4.8; N, 4.2. Found: C, 57.4; H, 4.7; N, 4.1.

2-[3-(Diethylphosphonatomethyl)phenyl]-1,3-benzothiazole (**3e**).

This compound was obtained as colorless needles (ethanol/water) from 2.95 g (9.7 mmoles) of **3b** and 20.0 g (120 mmoles) triethylphosphite (**4b**) to give 1.75 g (50%) of **3d**, mp 106°; ir (potassium bromide): 3040 (aromatic CH stretch), 2980, 2900 (aliphatic CH stretch), 1245 (P=O stretch), 760, 730, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.3 (t, 6 H, CH$_2$C*H*$_3$, ^3J = 7 Hz), 3.25 (d, 2 H, C*H*$_2$-P, ^2J (H,P) = 24 Hz), 3.86-4.26 (m, 4 H, C*H*$_2$-CH$_3$), 7.3-7.5 (m, 4 H, *H* of the substituted phenyl ring), 7.8-8.16 (m, 4 H, *H* of the anellated phenyl ring); ms: (90 eV) m/z = 362 (16%, M^++H), 361 (80%, M^+), 332 (10%, M^+-C_2H_5), 239 (23%, M^+-HP(OC$_2$H$_5$)$_2$), 224 (100%, M^+-PO(OC$_2$H$_5$)$_2$), 108 (17%, $C_6H_4S^+$).

Anal. Calcd. for $C_{18}H_{20}NO_3PS$ (361.4): C, 59.8; H, 5.6; N, 3.9. Found: C, 59.9; H, 5.5; N, 3.7.

2-[3-(Dibutylphosphonatomethyl)phenyl]-1,3-benzothiazole (**3f**).

This compound was obtained as colorless oil (flash chromatographic purification) from 2.9 g (9.5 mmoles) of **3b** and 20.0 g (91 mmoles) of tributylphosphite (**4c**) to give 2.7 g (71%) of **3f**, n_D^{20} = 1.585; ir: 2960, 2880 (aliphatic CH stretch), 1250 (P=O stretch), 760, 739, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 0.74-1.8 (m, 14 H, OCH$_2$C$_3$*H*$_7$), 3.24 (d, 2 H, C*H*$_2$P, ^2J (H,P) = 24 Hz), 3.82-4.16 (m, 4 H, OC*H*$_2$-C$_3$H$_7$), 7.3-7.6 (m, 4 H, *H* of the substituted phenyl ring), 7.8-8.16 (m, 4 H, *H* of the anellated phenyl ring); ms: (90 eV) m/z = 417 (100%, M^+).

Anal. Calcd. for $C_{22}H_{28}NO_3PS \cdot H_2O$ (435.5): C, 60.7; H, 6.9; N, 3.2. Found: C, 61.1; H, 7.1; N, 3.3.

2-[2-(4-Methylphenyl)ethenyl]-1,3-benzothiazole (**5a**).

This compound was obtained as colorless needles (ethanol/water) from 6.3 g (50 mmoles) of **1a** and 8.1 g (50 mmoles) of 4-methyl cinnamic acid (**2b**) to give 12.4 g (98%) of **5a**, mp 138°; ir (potassium bromide): 3060 (aromatic CH stretch), 1630 (aliphatic CH stretch), 1600, 1510 (phenyl C=C stretch), 800, 760, 730 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform) δ (ppm) = 2.38 (s, 3 H, C*H*$_3$), 7.1-7.58 (m, 8 H, *H* of the substituted phenyl ring, *H*-5 and *H*-6 of the anellated phenyl ring, *H* of the ethenyl group), 7.74-8.04 (m, 2 H, *H*-4 and *H*-7 of the anellated phenyl ring); ms: (90 eV) m/z = 252 (46%, M^+), 251 (100%, M^+-H), 237 (8%, M^+-CH_3), 115 (9%, C_9H_7).

Anal. Calcd. for $C_{16}H_{13}NS$ (252.2): C, 76.6; H, 5.2; N, 5.6. Found: C, 76.4; H, 5.4; N, 5.7.

2-{2-[4-(Bromomethyl)phenyl]ethenyl}-1,3-benzothiazole (**5b**).

This compound was obtained as colorless powder (ethanol/water) from 16.6 g (66 mmoles) of **5a** and 11.8 g (66 mmoles) *N*-bromosuccinimide to give 6.3 g of **5b** (29%), mp 154°; ir (potassium bromide): 3040 (aromatic CH stretch), 1630 (C=C stretch), 760, 730 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 4.48 (s, 2 H, CH_2Br), 7.2-7.56 (m, 8 H, *H* of the substituted phenyl ring, *H*-5 and *H*-6 of the anellated phenyl ring, *H* of the ethenyl group), 7.78-8.06 (m, 2 H, *H*-4 and *H*-7 of the anellated phenyl ring); ms: (90 eV) m/z = 331 (9%, M^+), 329 (9%, M^+), 250 (100%, M^+-Br), 115 (26%, $C_9H_7^+$).

Anal. Calcd. for $C_{16}H_{12}BrNS$ (330.2): C, 58.2; H, 3.7; N, 4.2. Found: C, 58.0; H, 3.8; N, 4.2.

2-{2-[4-(Dimethylphosphonatomethyl)phenyl]ethenyl}-1,3-benzothiazole (**5c**).

This compound was obtained as yellow platelets (ethanol/water) from 2.9 g (8.8 mmoles) of **5b** and 10.0 g (81 mmoles) of **4a** to give 1.2 g (38%) of **5c**, mp 115°; ir (potassium bromide): 3050, (aromatic CH stretch), 2960, 2900 (aliphatic CH stretch), 1630 (aliphatic C=C stretch), 1250 (P=O stretch), 825, 760 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.17 (d, 2 H, CH_2P, ^2J (H,P) = 24 Hz), 3.68 (d, 6 H, OCH_3, ^3J (H,P) = 12 Hz), 7.25-7.62 (m, 8 H, *H* of the substituted phenyl ring, *H*-5 and *H*-6 of the anellated phenyl ring, *H* of the ethenyl group), 7.74-8.04 (m, 2 H, *H*-4 and *H*-7 of the anellated phenyl ring); ms: (90 eV) m/z = 359 (32%, M^+), 358 (71%, M^+-H), 295 (45%, M-POOH); 294 (81%, 358-POOH), 281 (45%, M^+-$POOCH_3$), 280 (82%, 358-$POOCH_3$), 250 (77%, M^+-$PO(OCH_3)_2$), 249 (65%, M^+-$HPO(OCH_3)_2$), 236 (34%, 281-CH_2OCH_3), 123 (15%, $CH_2PO(OCH_3)_2$), 115 (33%, C_9H_7), 109 (27%, $PO(OCH_3)_2^+$), 57 (100%).

Anal. Calcd. for $C_{18}H_{18}NO_3PS$ (359.0): C, 60.2; H, 5.1; N, 3.9. Found: C, 60.6; H, 5.1; N, 3.9.

2-{2-[4-(Diethylphosphonatomethyl)phenyl]ethenyl}-1,3-benzothiazole (**5d**).

This compound was obtained as yellow needles (ethanol/water) from 1.3 g (3.9 mmoles) of **5b** and 20.0 g (120 mmoles) of **4b** to give 0.4 g (26%) of **5d**, mp 84°; ir (potassium bromide): 3030 (aromatic CH stretch), 2980, 2880 (aliphatic CH stretch), 1620 (aliphatic CH stretch), 1240 (P=O stretch), 770 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.22 (t, 6 H, CH_2CH_3, ^3J = 7 Hz), 3.18 (d, 2 H, CH_2-P, ^2J (H,P) = 22 Hz), 3.9-4.1 (m, 4 H, CH_2CH_3), 7.3-7.53 (m, 8 H, *H* of the substituted phenyl ring, *H*-5 and *H*-6 of the anellated phenyl ring, *H* of the ethenyl group), 7.83 (d, 1 H, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 7.97 (d, 1 H, *H*-4 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 387 (35%, M^+), 386 (100%, M^+-H), 250 (52%, M^+-$PO(OC_2H_5)_2$), 115 (29%, $C_9H_7^+$).

Anal. for $C_{20}H_{22}NO_3PS$ (387.4): C, 62.0; H, 5.7; N, 3.6. Found: C, 61.8; H, 5.5; N, 3.5.

2-(3-Methylphenyl)-1,3-benzoxazole (**6a**).

This compound was obtained as colorless platelets (ethanol/water) from 13.6 g (100 mmoles) of **2a** and 10.9 g (100 mmoles) of **1b** to give 10.9 g (52%) of **6a**, mp 87°; ir (potassium bromide): 3040 (aromatic CH stretch), 2920 (aliphatic CH stretch), 1550 (phenyl C=C stretch), 740, 720, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 2.44 (s, 3 H, CH_3), 7.25-7.45 (m, 4 H, *H* of the substituted phenyl ring), 7.46-8.15 (m, 4 H, *H* of the anellated phenyl ring); ms: (90 eV) m/z = 210 (15%, M^++H), 209 (100%, M^+).

Anal. Calcd. for $C_{14}H_{11}NO$ (209.1): C, 80.4; H, 5.3; N, 6.7. Found: C, 80.3; H, 5.4; N, 6.8.

2-[3-(Bromomethyl)phenyl]-1,3-benzoxazole (**6b**).

The compound was obtained as colorless needles (ethanol/water), mp 91°, yield 57%; ir (potassium bromide): 3060 (aromatic CH stretch), 1550 (phenyl C=C stretch), 750, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 4.56 (s, 2 H, CH_2Br), 7.26-7.84 (m, 6 H, *H*-4 and *H*-5 of the substituted phenyl ring, *H* of the anellated phenyl ring), 8.1-8.34 (m, 2 H, *H*-2 and *H*-6 of the substituted phenyl ring); ms: (90 eV) m/z = 289 (25%, M^+), 287 (26%, M^+), 208 (100%, M^+-Br).

Anal. Calcd. for $C_{14}H_{10}BrNO \cdot 0.5H_2O$ (297.1): C, 56.6; H, 3.7; N, 4.7. Found: C, 56.8; H, 3.5; N, 4.4.

2-[3-(Dibromomethyl)phenyl]-1,3-benzoxazole (**6c**).

This compound was obtained from the above described reaction by flash chromatographic separation, yellow powder, mp 100°, yield 1%; ir (potassium bromide): 3020 (aromatic CH stretch), 1550 (phenyl C=C stretch), 750, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.7 (s, 1 H, $CHBR_2$), 7.3-7.42 (m, 2 H, *H*-4 and *H*-5 of the substituted phenyl ring), 7.5-7.62 (m, 2 H, *H*-5 and *H*-6 of the anellated phenyl ring), 7.7-7.85 (m, 2 H, *H*-4 and *H*-7 of the anellated phenyl ring), 8.2 (d, split, 1 H, *H*-6 of the substituted phenyl ring, ^3J = 8 Hz), 8.43 (s, split, 1 H, *H*-2 of the substituted phenyl ring); ms: (90 eV) m/z = 367 (18%, M^+), 288 (99%, M^+-Br), 286 (100%, M^+-Br), 206 (72%, 286-HBr), 89 (29%, $C_7H_5^+$).

Anal. Calcd. for $C_{14}H_9BR_2NO$ (367.1): C, 45.8; H, 2.5; N, 3.8. Found: C, 45.8; H, 2.1; N, 3.4.

2-[3-(Dimethylphosphonatomethyl)phenyl]-1,3-benzoxazole (**6d**).

This compound was obtained as colorless powder (ethanol/water) from 2.1 g (7.3 mmoles) of **6b** and 15.0 g (120 mmoles) of **4a** to give 0.52 g (22%) of **6d**, mp 84°; ir (potassium bromide): 3070 (aromatic CH stretch), 2960, 2939, 2860 (aliphatic CH stretch), 1550 (phenyl C=C stretch), 1250 (P=O stretch), 760, 720, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.26 (d, 2 H, CH_2P, ^2J (H,P) = 24 Hz), 3.72 (d, 6 H, OCH_3, ^3J (H,P) = 13 Hz), 7.24-7.84 (m, 6 H, *H*-4 and *H*-5 of the substituted phenyl ring, *H* of the anellated phenyl ring), 8.08-8.24 (m, 2 H, *H*-2 and *H*-6 of the substituted phenyl ring); ms: (90 eV) m/z = 317 (97%, M^+), 302 (10%, M^+-CH_3), 223 (27%, 317-$HP(OCH_3)_2$), 208 (100%, M^+-$PO(OCH_3)_2$), 109 (27%, $PO(OCH_3)_2^+$), 93 (12%, $P(OCH_3)_2^+$).

Anal. Calcd. for $C_{16}H_{16}NO_4P$ (317.2): C, 60.6; H, 5.1; N, 4.4. Found: C, 60.5; H, 5.2; N, 3.9.

2-[3-(Diethylphosphonatomethyl)phenyl]-1,3-benzoxazole (**6e**).

This compound was obtained as colorless platelets (ethanol/water) from 2.2 g (7.8 mmoles) of **6b** and 15.0 g (90 mmoles) of **4b** to give 1.64 g (61%) of **6e**, mp 87°; ir (potassium bromide): 3050 (aromatic CH stretch), 2990, 2920 (aliphatic CH stretch), 1560 (phenyl C=C stretch), 1250 (P=O stretch), 750, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.26 (t, 6 H, CH_2CH_3 ^3J = 7 Hz), 3.24 (d, 2 H, CH_2P, ^2J (H,P) = 24 Hz), 3.84-4.22 (m, 4 H, CH_2CH_3), 7.24-7.84 (m, 6 H, *H*-4 and *H*-5 of the substituted phenyl ring, *H* of the anellated ring), 8.04-8.14 (m, 2 H, *H*-2 and *H*-6 of the substituted phenyl ring); ms: (90 eV) m/z =

345 (85%, M^+), 316 (13%, $M^+-C_2H_5$), 223 (38%, $M^+-HP(OC_2H_5)_2$), 208 (100%, $M^+-PO(OC_2H_5)_2$).

Anal. Calcd. for $C_{18}H_{20}NO_4P$ (345.3): C, 62.6; H, 5.8; N, 4.1. Found: C, 62.7; H, 6.1; N, 3.8.

2-[2-(4-Methylphenyl)ethenyl]-1,3-benzoxazole (**6f**).

This compound was obtained as colorless powder (ethanol/-water) from 13.3 g (100 mmoles) of **1b** and 17.2 g (100 mmoles) of **2b** in a yield of 18.5 g (79%), mp 127°; ir (potassium bromide): 3010 (aromatic CH stretch), 1635 (aliphatic CH stretch), 1560, 1530 (phenyl C=C stretch), 810, 740 cm^{-1} (aromatic CH wagging); ^1H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.5 (s, 3 H, CH_3), 6.9-7.9 (m, 10 H, aromatic *H* and *H* of the ethenyl group); ms: (90 eV) m/z = 235 (6%, M^+), 234 (15%, M^+-H), 142 (11%, $234-C_7H_8$), 117 (21%, $C_9H_9^+$), 115 (79%, $C_9H_7^+$), 63 (100%).

Anal. Calcd. for $C_{16}H_{13}NO$ (235.3): C, 81.7; H, 5.6; N, 6.0. Found: C, 81.5; H, 5.4; N, 6.0.

2-{2-[4-(Bromomethyl)phenyl]ethenyl}-1,3-benzoxazole (**6g**).

This compound was obtained as colorless powder from 1.4 g (5.9 mmoles) of **6f** and 1.1 g (5.9 mmoles) of *N*-bromosuccinimide, mp 173°, yield 1.1 g (59%); ir (potassium bromide): 1640 (aliphatic C=C stretch), 1530 (phenyl C=C stretch), 820, 750 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 4.5 (s, 2 H, CH_2Br), 7.05 (d, 1 H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 18 Hz), 7.25-7.8 (m, 9 H, aromatic *H*, and *H*-2 of the ethenyl group); ms: (90 eV) m/z = 314 (13%, M^+), 234 (100%, M^+-Br), 115 (15%, $C_9H_7^+$).

Anal. Calcd. for $C_{16}H_{12}BrNO$ (314.2): C, 61.2; H, 3.9; N, 4.5. Found: C, 61.3; H, 4.0; N, 4.2.

2-{2-[4-(Dimethylphosphonatomethyl)phenyl]ethenyl}-1,3-benzoxazole (**6h**).

This compound was obtained as pale yellow platelets from 3.0 g (9.5 mmoles) of **6g** and 20.0 g (161 mmoles) of **4a**, yield 2.36 g (72%), mp 124°; ir (potassium bromide): 3030 (aromatic CH stretch), 2950, 2900, 2840 (aliphatic CH stretch), 1635 (aliphatic C=C stretch), 1530 (phenyl C=C stretch), 1250 (P=O stretch), 820, 750, cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.16 (d, 2 H, CH_2-O, ^2J (H,P) = 24 Hz), 3.68 (d, 6 H, OCH_3, ^3J (H,P) = 12 Hz), 6.98 (d, 1 H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 18 Hz), 7.25-7.86 (m, 9 H, aromatic *H*, *H*-2 of the ethenyl group); ms: (90 eV) m/z = 343 (13%, M^+), 342 (100%, M^+-H), 278 (27%, 342-POOH), 233 (12%, $M^+-HPO(OCH_3)_2$).

Anal. Calcd. for $C_{18}H_{18}NO_4P$ (343.3): C, 63.0; H, 5.3; N, 4.1. Found: C, 62.7; H, 5.5; N, 4.0.

2-{2-[4-(Diethylphosphonatomethyl)phenyl]ethenyl}-1,3-benzoxazole (**6i**).

This compound was obtained as pale yellow powder from 2.28 g (7.3 mmoles) of **6g** and 20.0 g (120 mmoles) of **4b**, yield 2.2 g (81%), mp 59°; ir (potassium bromide): 2980, 2940, 2900 (aliphatic CH stretch), 1635 (aliphatic C=C stretch), 1530 (phenyl C=C stretch), 1250 (P=O stretch), 820, 750, cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.24 (t, 6 H, CH_2CH_3, ^3J = 7 Hz), 3.15 (d, 2 H, CH_2-P, ^2J (H,P) = 24 Hz), 3.8-4.2 (m, 4 H, CH_2-CH_3), 7.01 (d, 1 H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 18 Hz), 7.25-7.86 (m, 9 H, aromatic *H* and *H*-2 of the ethenyl group); ms: (90 eV) m/z = 371 (40%, M^+), 370 (100%, M^+-H), 342 (6%, $M^+-C_2H_5$), 234 (46%, $M^+-PO(OC_2H_5)_2$), 233 (59%, $370-PO(OC_2H_5)_2$), 115 (24%, $C_9H_7^+$).

Anal. Calcd. for $C_{20}H_{22}NO_4P$ (371.4): C, 64.7; H, 6.0; N, 3.8. Found: C, 64.7; H, 5.9; N, 3.5.

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