2-Aryl-Substituted 4*H*-3,1-Benzoxazin-4-ones as Novel Active Substances for the Cardiovascular System

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4*H*-3,1-Benzoxazin-4-ones of the structural types **3** and **4** are accessible by cyclization reactions. The introduction of the phosphonate group was achieved by way of Wohl-Ziegler bromination and subsequent Michaelis-Arbuzow reaction with a trialkyl phosphite. Pharmacological investigations on isolated left atria, ileum specimens, and Langendorff hearts as well as *in vivo* circulatory studies on anesthetized rats revealed that the phosphonates **4** exert calcium antagonistic effects. Whereas 2-(arylvinyl)benzoxazinones gave rise to pronounced negative inotropic effects, compound **3e** exhibited relaxing effects on smooth musculature in particular and markedly increased the coronary flow through Langendorff hearts.

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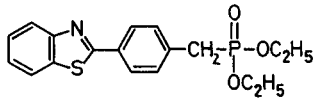
Introduction.

Calcium channel blockers have attained major significance in the therapy for cardiovascular diseases during the past few years [1-3]. (Benzothiazolyl)benzylphosphonates of the KB 944-type (Fostedil, Scheme I) represent a novel structural type of calcium antagonists [4,5], and their mechanism of action is presumably based on an interaction with a calcium channel-phosphorylating enzyme [6,7].

Scheme I



Fostedil

For investigations on structure-activity relationships, our previous work has involved the synthesis and pharmacological testing of numerous 2-aryl-substituted 1,3-benzothiazoles, 1,3-benzoxazoles, and 1,3-benzimidazoles [8-10]. With the exception of the 1,3-benzimidazoles [9], only those products carrying a phosphonate ester group on the aromatic substituent exhibited calcium antagonistic properties [10]. By variation of the position of the phosphonic acid ester group and introduction of a vinyl chain between the heterocyclic ring and the aryl group, it was possible to attain the maximal degree of activity of Fostedil while the EC_{50} values were higher.

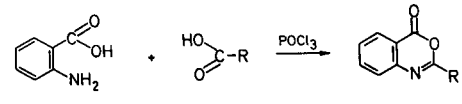
In the present work, investigations on compounds in which the annelated 5-membered heterocyclic ring has been replaced by ring-enlarged units will be reported.

Chemistry.

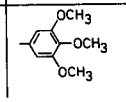
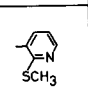
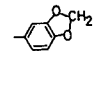
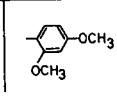
The objective of the present syntheses was the construction of systems with the 4*H*-3,1-benzoxazin-4-one skeleton bearing an aromatic substituent at the 2-position. The nature and position of substituents on the aromatic rings can be varied by the selection of suitable starting materials; furthermore, heteroaromatic structures were also employed as substituents at the 2-position. 4*H*-3,1-Benzoxazin-4-ones with similar structures but with non-aromatic substituents at the 2-position have recently attracted interest as inhibitors of human leukocytes elastase [11]. However, this is not the topic of the present work. 4*H*-3,1-Benzoxazin-4-ones have not previously been recognized as active substances for the cardiovascular system.

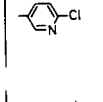
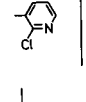
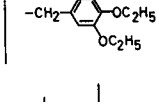
The proposed construction of the heterocyclic system involved a suitable cyclization reaction. Starting materials for these reactions were 2-aminobenzoic acid (**1**) on the one hand and the aromatic carboxylic acids **2a-o** on the

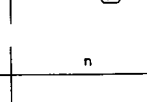
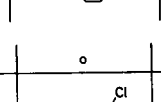
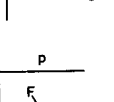
Scheme II



1 2 3 a-p

3	a	c	d	e
R				

3	f	g	h	i
R				

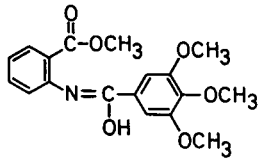
3	j	k	l	m
R				

3	n	o	p
R			

other. Under suitable reaction conditions, these compounds should be able to undergo ring closure by a double condensation. The previously reported methods for the synthesis of such compounds either employ acid chlorides [12] or, in the case of phenylvinyl-benzoxazinones, 2-methyl-3,1-benzoxazin-4-one and aromatic aldehydes [13] as starting materials. The preliminary chlorination to furnish the acid chloride is not necessary when the reaction to yield a final product of the type **3** is performed in phosphoryl chloride under a nitrogen atmosphere (Scheme II).

The yields of the desired products can be increased by warming the residue remaining after distillation of phosphoryl chloride in acetone/pyridine because cyclization of the *in situ* generated acid chloride is favored under these conditions. The thus formed benzoxazinone products are sensitive to hydrolysis and alcoholysis; hence, an attempt to recrystallize **3a** from methanol gave rise to the formation of the open chain ester **3b** (Scheme III).

Scheme III



3b

When the residue is warmed in water, the expected decomposition can also be detected by tlc monitoring.

For an investigation of the influence of the phosphonate grouping on the pharmacological properties, potential calcium antagonists possessing the 3,1-benzoxazin-4-one skeleton but bearing a phosphonic acid ester functionality on the aromatic ring at the 2-position of the heterocyclic system were prepared in a second series of experiments. These syntheses were based primarily on the construction of the benzoxazinone skeleton according to the methodology described above using appropriate starting materials for the provision of a methylphenyl or a methylphenylvinyl group at the 2-position. Subsequent bromination of the methyl group with *N*-bromosuccinimide often resulted in a double bromination. Alternatively, bromomethylbenzoic acid can be employed directly as a starting material. Subsequent introduction of the phosphonic acid diester was achieved by Michaelis-Arbuzow reaction with trialkyl phosphites [14,15]. The desired final products of this three-step process were obtained in high yields (60-90%) in the last step (Scheme IV).

The postulated structures of all compounds are in full agreement with the ir, ^{1}H-nmr, and mass spectral data (Experimental).

Pharmacology.

The pharmacological tests were performed on isolated organs such as electrically stimulated left atria of guinea pigs, barium chloride-stimulated ileum specimens (of guinea pigs), Langendorff hearts (rabbits) as well as in *in vivo* circulatory experiments on rats. The results of tests on atria are summarized in Table 1 for those compounds where an activity was observed.

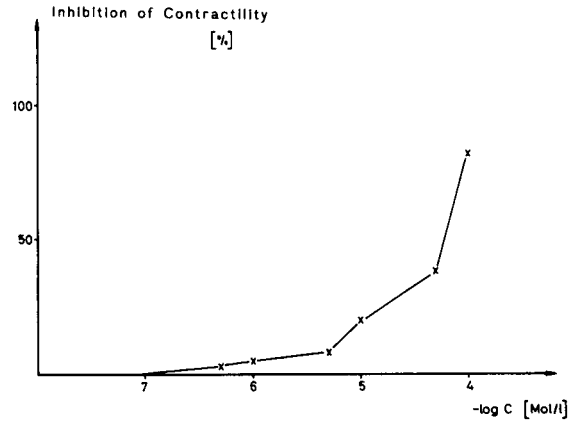


Figure 1. Dose-activity curve for the action of **3f** on electrically stimulated left atria of guinea pigs.

Table 1
Experiments on Electrically Stimulated Left Atria of Guinea Pigs; EC_{50} Values and Relative Degrees of Activity

Compound	EC_{50} [mol/l]	Maximum Effect [%] [a]	Relative Activity [b]	n [c]
Nifedipine	$2{,}8 \cdot 10^{-7}$	87±2.1	1	3
Fostedil	$4{,}0 \cdot 10^{-7}$	79±3.0	0.9	Ref [7]
3f	$2{,}6 \cdot 10^{-5}$	82±4.2	0.94	4
3j	$8{,}9 \cdot 10^{-7}$	35±3.8	0.4	3
3l	$1{,}7 \cdot 10^{-5}$	40±10.0	0.46	3
3o	$5{,}0 \cdot 10^{-5}$	74±6.4	0.85	4
4c	$2{,}0 \cdot 10^{-5}$	60±9.9	0.69	3

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

Scheme IV

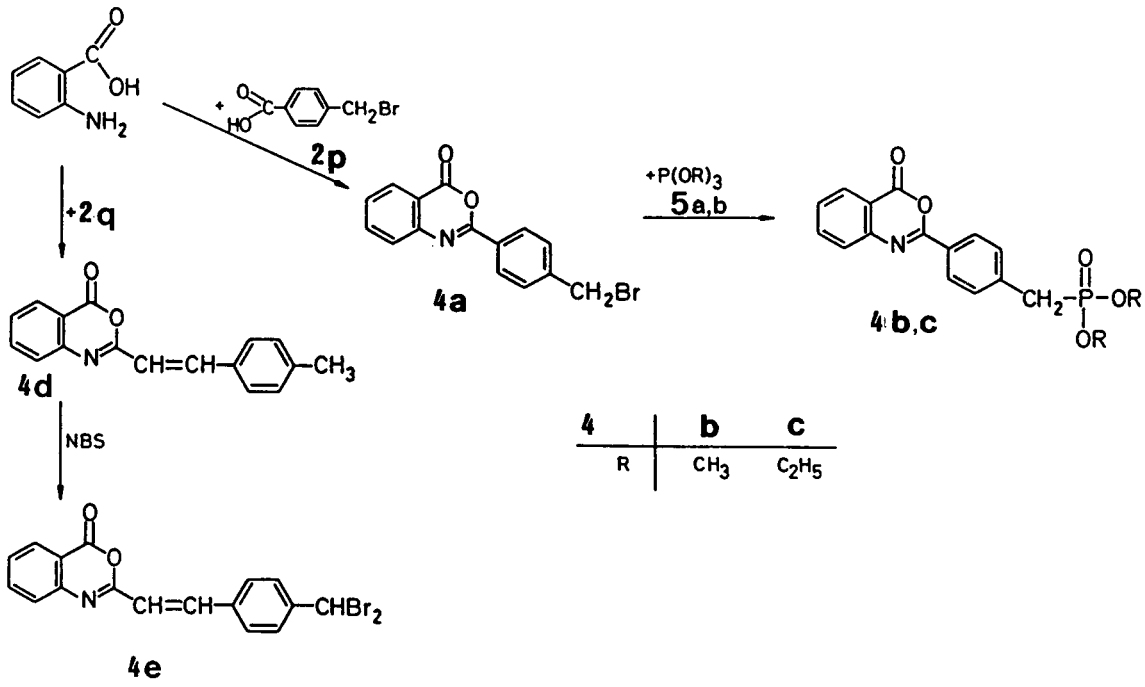


Table 2
Investigations on Barium Chloride-Ileum, EC_{50} Values and Relative Degrees of Activity

Compound	EC_{50} [mol/l]	Maximum Effect [%] [a]	Relative Activity [b]	n [c]
Nifedipine	$2{,}0 \cdot 10^{-8}$	95±2.8	1	9
3a	–	31±3.6	0.33	3
3c	–	10	0.1	2
3d	–	10	0.1	2
3e	$2{,}5 \cdot 10^{-5}$	85±8.5	0.89	3
3l	–	28±5.1	0.29	3
3n	–	20±1.2	0.21	3
3o	–	10	0.1	2
3p	–	10	0.1	2
4b	–	30±2.1	0.32	3
4c	$1{,}8 \cdot 10^{-5}$	76±5.6	0.8	4

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

Among those compounds in which the aromatic ring is directly linked to the benzoxazinone skeleton, only **3f** was found to exhibit a contractility-inhibiting activity and this effect was comparable to that of Nifedipine. Maximum activities of over 80% were recorded in several experiments. The dose-activity curve of this unexpected activity of **3f** is shown in Figure 1.

In all other cases, inhibition of contractility forces was observed only for those benzoxazinones in which the aromatic ring is linked to the heterocyclic system *via* a vinyl chain, *i.e.* **3j**, **3l**, and **3o**. In general, the relaxing action was only operative at higher dosage ranges (10^{-5} mol/l), but then with a high intensity.

As expected, compound **4c**, bearing a diethyl phosphonate group on the aromatic ring, also exhibited a contractility-inhibiting effect which probably results from an inhibition of the calcium influx, in analogy to the mode of action of Fostedil. The causes of the effects of the other 3,1-benzoxazinones have not yet been clarified. It is interesting to note that the corresponding dimethyl phosphonate does not exert any inhibitory action on atria and that its inhibitory action on barium chloride-induced contractions of guinea pig ileum is only weakly expressed (Table 2).

Contraction experiments of ileum represent a suitable test model for the verification of calcium antagonistic effects on smooth musculature [16]. Most of the other compounds of the types **3** and **4** also exhibited only weak or no activity on smooth ileum musculature in spite of their obvious effects on atria.

Compound **4c**, in accordance with the results from experiments on atria, also exhibited a marked antagonistic activity in this model with a relative activity of 0.8 in comparison to the standard Nifedipine. The strongest inhibitory action on barium chloride-stimulated ileum, however, was exerted by **3e** with a relative activity of 0.89. This result is surprising and unexpected since compound **3e** does not possess a phosphonate group.

In vascular experiments on the rat, compound **3e** effected a 20% lowering of the diastolic blood pressure after 30 minutes and a 8% negative chronotropic action, each at a dosage of 10 μg/kg.

On isolated, perfused Langendorff hearts, compound **3e** was observed to be a powerful coronary vasodilator and increased the coronary flow by 105% (in comparison to the standard Segontin: 91%; dose of each 5 μg, solvent propane-1,2-diol).

Surprisingly, compound **3f** caused a 15% increase in the systolic blood pressure and a 25% increase in the diastolic blood pressure with a concomitant increase in the heart rate from 360 beats/min to 430 beats/min, *i.e.* an increase of 20%, in the above described circulatory experiments. At the same time, compound **3f** effected a 59% increase in the coronary flow through Langendorff hearts (dosage 5 μg; standard Segontin: 88% in this experiment). Blood pressure increases are thus accompanied by a dilatation of the coronary vessels. This is an unusual phenomenon for substances with an activity on the cardiovascular system and is indicative of a dual mechanism of action.

Finally, compound **4b** did not exhibit any action in the vascular experiments but did effect a 61% increase in the coronary flow through isolated, perfused Langendorff hearts (standard segontin: 88%).

Discussion.

The 4*H*-3,1-benzoxazin-4-ones described here are accessible by simple cyclization reactions; their effects on the cardiovascular system were previously unknown. The introduction of a phosphonic acid diester partial structure on the aromatic ring in the 2-position of the heterocyclic system was achieved by Wohl-Ziegler bromination and subsequent Michaelis-Arbuzow reaction with a trialkyl phosphite.

While the phosphonate **4c** exerted respectively relaxing and contractility-inhibiting effects on left atria and ileum preparations as well as on Langendorff hearts, these actions presumably being based on calcium antagonism, compounds of the structural type **3**, above all the arylvinyl-benzoxazinones, exhibited pronounced inotropic activities. The latter effects are apparently organ-specific: at the most, slight relaxations of barium chloride-induced contractions in smooth musculature were realized. Surprisingly, one compound without a phosphonate structure was found to be the strongest "antagonist" on smooth musculature, namely **3e**. In addition to this inhibition of ileum contractions, a relaxation of potassium chloride-stimulated aortic musculature was detected as was also a marked increase in the coronary flow through isolated, perfused Langendorff hearts.

The clarification of the causes of these previously unknown activities will the subject of further investigations.

EXPERIMENTAL

1. Pharmacology.

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 [16-19].

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.

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 sincere thanks.

2. Chemistry.

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

2-(3,4,5-Trimethoxyphenyl)-4*H*-3,1-benzoxazin-4-one (**3a**) [20].

In 100 ml of phosphoryl chloride were dissolved 4.1 g (30 mmoles) of 2-aminobenzoic acid (**1**) and 6.4 g (30 mmoles) of trimethoxybenzoic acid (**2a**). The resultant mixture was heated to boiling for 5 hours under a nitrogen atmosphere. The phosphoryl chloride was then removed by distillation under vacuum, the brown, oily residue was taken up in acetone, 40 ml of pyridine were added, and the mixture was warmed gently for 15 minutes. After evaporation of the solvents, the residue was recrystallized from acetone to furnish colorless needles with mp 185°, yield 2.74 g (29%); ir (potassium bromide): 2940, 2820 (aliphatic CH stretch), 1750 (C=O stretch), 1510 (phenyl C=C stretch), 770, 690 cm^{-1} (aromatic CH wagging); ^{1}H nmr (deuteriochloroform): δ (ppm) = 3.92 (s, 3H, OCH_3 in 4-position of the phenyl ring), 3.96 (s, 6H, OCH_3 in 3- and 5-position of the phenyl ring), 7.48 (pt, 1H, *H*-6 of the anellated phenyl ring, ^{3}J = 8 Hz), 7.52 (s, 2H, *H* of the substituted phenyl ring), 7.65 (d, 1H, *H*-8 of the anellated phenyl ring, ^{3}J = 8 Hz), 7.8 (pt, 1H, *H*-7 of the anellated phenyl ring, ^{3}J = 8 Hz), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^{3}J = 8 Hz); ms: (90 eV) m/z = 314 (20%, M^+ +H), 313 (100%, M^+).

Anal. Calcd. for $C_{17}H_{15}NO_5$ (313.3): C, 65.2; H, 4.8; N, 4.5. Found: C, 65.2; H, 5.0; N, 4.4.

Methyl 2-[(3,4,5-Trimethoxybenzoyl)amino]benzoate (**3b**) [21].

After reaction of 6.9 g (50 mmoles) of 2-aminobenzoic acid (**1**) and 10.6 g (50 mmoles) of **2a** for 2 hours in boiling phosphoryl chloride under nitrogen, the solvent was evaporated. The residue was taken up in methanol and recrystallized several times to furnish colorless plates with mp 132°, yield 1.53 g (9%); ir (potassium bromide): 3500 (OH stretch), 2940, 2840 (aliphatic CH stretch), 1675 (C=O stretch), 1580, 1530, 1500 (phenyl C=C, C=N stretch), 750, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.11 (pt, 1H, *H*-5 of the ester phenyl ring, ^3J = 8 Hz), 7.3 (s, 2H, *H* of the substituted phenyl ring), 7.6 (pt, 1H, *H*-4 of the ester phenyl ring, ^3J = 8 Hz), 8.07 (d, 1H, *H*-3 of the ester phenyl ring, ^3J = 8 Hz), 8.07 (d, 1H, *H*-3 of the ester phenyl ring, ^3J = 8 Hz), 8.87 (d, 1H, *H*-6 of the ester phenyl ring, ^3J = 8 Hz), 12.06 (s, 1H, O*H*, exchangeable with deuterium oxide); ms: (90 eV) m/z = 345 (21%, M^+), 314 (3%, M^+-OCH_3•), 286 (3%, M^+-$COOCH_3$), 195 (100%, $C_{10}H_{11}O_4^+$).

Anal. Calcd. for $C_{18}H_{19}NO_6$ (345.2): C, 62.6; H, 5.5; N, 4.1. Found: C, 62.7; H, 5.5; N, 3.8.

2-[(2-Methylthio)-3-pyridyl]-4*H*-3,1-benzoxazin-4-one (**3c**).

Compound **3c** was prepared by reaction of 2.3 g (13.7 mmoles) of 2-methylthionicotinic acid (**2b**) with 1.9 g (13.7 mmoles) of 2-aminobenzoic acid (**1**) in analogy to the procedure for **3a**. The product **3c** was obtained as colorless platelets from acetone with mp 185°, yield 0.75 g (20%); ir (potassium bromide): 1750 (C=O stretch), 1600, 1570, 1540 (phenyl, pyridine C=C, C=N stretch), 770, 750 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 2.6 (s, 3H, SCH_3), 7.15 (dd, 1H, *H*-5 of the pyridine ring, ^3J = 8 Hz), 7.55 (m, 1H, *H*-6 of the anellated phenyl ring), 7.75-7.9 (m, 2H, *H*-7 and *H*-8 of the anellated phenyl ring), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz), 8.38 (dd, 1H, *H*-6 of the pyridine ring, ^3J = 8 Hz, ^4J = 2 Hz), 8.6 (dd, 1H, *H*-4 of the pyridine ring, ^3J = 5 Hz, ^4J = 2 Hz); ms: (90 eV) m/z = 270 (40%, M^+), 255 (100%, M^+-CH_3).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S$ (270.2): C, 62.2; H, 3.7 N, 10.4. Found: C, 62.4; H, 3.9; N, 10.6.

2-[3,4-Methylenedioxy)phenyl]-4*H*-benzoxazin-4-one (**3d**).

Prepared from 2.7 g (19.7 mmoles) of **1** and 3.3 g (19.7 mmoles) of 3,4-(methylenedioxy)benzoic acid (**2c**) in analogy to the procedure for **3a**, colorless needles with mp 197°, yield 0.83 g (16%); ir (potassium bromide): 3020 (aromatic CH stretch), 2930 (aliphatic CH stretch), 1760 (C=O stretch), 1600, 1570, 1500 (phenyl C=C, C=N stretch), 780, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.06 (s, 2H, CH_2 of the methylenedioxy group), 6.9 (d, 1H, *H*-4 of the substituted phenyl ring, ^3J = 8 Hz), 7.48 (pt, 1H, *H*-6 of the anellated phenyl ring, ^3J = 8 Hz), 7.62 (d, 1H, *H*-8 of the anellated phenyl ring, ^3J = 8 Hz), 7.7-7.95 (m, 3H, *H*-2 and *H*-6 of the substituted phenyl ring, *H*-7 of the anellated phenyl ring), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring); ms: (90 eV) m/z = 267 (92%, M^+), 149 (100%, $C_8H_5O_3^+$).

Anal. Calcd. for $C_{15}H_9NO_4$ (267.2): C, 67.4; H, 3.4; N, 5.2. Found: C, 67.1; H, 3.4; N, 5.4.

2-(2,4-Dimethoxyphenyl)-4*H*-3,1-benzoxazin-4-one (**3e**).

Prepared in analogy to the procedure for **3a** by reacting 6.9 g (50 mmoles) of **1** with 9.1 g (50 mmoles) of 2,4-dimethoxybenzoic acid (**2d**) in phosphoryl chloride for 3 hours and subsequent warming of the residue in acetone/pyridine. The crude product was recrystallized several times from ligroin to furnish colorless needles with mp 132°, yield 1.4 g (10%); ir (potassium bromide): 3060 (aromatic CH stretch), 2950, 2840 (aliphatic CH stretch), 1760 (C=O stretch), 1590, 1560, 1500 (phenyl C=C, C=N stretch), 770, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.87 (s, 3H, OCH_3 in 4 position of the phenyl ring), 3.92 (s, 3H, OCH_3 in 2-position of the phenyl ring), 6.5-6.67 (m, 2H, *H*-3 and *H*-5 of the substituted phenyl ring), 7.48 (pt, 1H, *H*-6 of the anellated phenyl ring, ^3J = 8 Hz), 7.65 (d, 1H, *H*-8 of the anellated phenyl ring, ^3J = 8 Hz), 7.78 (pt, 1H, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 7.92 (d, 1H, *H*-6 of the substituted phenyl ring, ^3J = 8 Hz), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 283 (45%, M^+), 119 (100%, $C_7H_5NO^+$).

Anal. Calcd. for $C_{16}H_{13}NO_4$ (283.2): C, 67.8; H, 4.6; N, 4.9. Found: C, 67.3; H, 4.5; N, 4.4.

2-(4-Chloro-3-pyridyl)-4*H*-3,1-benzoxazin-4-one (**3f**).

Prepared by reaction of 4.1 g (30 mmoles) of **1** with 4.7 g (30 mmoles) 6-chloronicotinic acid (**2e**) as described for **3a**, colorless needles with mp 245°, yield 0.6 g (8%); ir (potassium bromide): 3080 (aromatic CH stretch), 1770 (C=O stretch), 1610, 1590 (phenyl, pyridine C=C, C=N stretch), 780, 760, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 7.4-7.62 (m, 2H, *H*-5 of the pyridine ring, *H*-6 of the phenyl ring), 7.7 (d, 1H, *H*-8 of the phenyl ring, ^3J = 8 Hz), 7.88 (pt, split, 1H, *H*-7 of the phenyl ring, ^3J = 8 Hz), 8.25 (d, 1H, *H*-5 of the phenyl ring, ^3J = 8 Hz), 8.5 (dd, 1H, *H*-6 of the pyridine ring, ^3J = 8 Hz, ^4J = 2 Hz), 9.28 (d, 1H, *H*-2 of the pyridine ring, ^4J = 2 Hz); ms: (90 eV) m/z = 258 (100%, M^+).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$ (258.7): C, 60.4; H, 2.7; N, 10.8. Found: C, 59.8; H, 2.5; N, 10.7.

2-(2-Chloro-3-pyridyl)-4*H*-3,1-benzoxazin-4-one (**3g**).

Prepared in analogy to **3a** from 6.9 g (50 mmoles) of **1** and 7.9 g (50 mmoles) of 2-chloronicotinic acid (**2f**), colorless powder from ligroin with mp 122°, yield 0.65 g (5%); ir (potassium bromide): 3070 (aromatic CH stretch), 1770 (C=O stretch), 1620, 1610, 1580, 1560 (phenyl, pyridine C=C, C=N stretch), 780, 750, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 7.35-8.0 (m, 4H, *H*-6, *H*-7, *H*-8 of the anellated phenyl ring, *H*-5 of the pyridine ring), 8.2-8.4 (m, 2H, *H*-6 of the pyridine, *H*-5 of the anellated phenyl ring), 8.6 (m, 1H, *H*-4 of the pyridine ring); ms: (90 eV) m/z = 258 (46%, M^+), 76 (100%, $C_6H_4^+$).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$ (258.7): C, 60.4; H, 2.7; N, 10.8. Found: C, 60.3; H, 2.9; N, 10.5.

2-(3-Thienylmethyl)-4*H*-3,1-benzoxazin-4-one (**3h**).

Prepared by reaction of 6.9 g (50 mmoles) of **1** with 7.1 g (50 mmoles) of 3-thienylacetic acid (**2g**) for 3 hours in analogy to the procedure described for **3a**, pale yellow needles from ligroin with mp 77°, yield 0.7 g (6%); ir (potassium bromide): 3090 (aromatic CH stretch), 1750 (C=O stretch), 1640 (C=N stretch), 1600, 1530 (phenyl C=C stretch), 770, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.85 (s, 2H, CH_2), 7.0-7.2

(dd, 2H, *H*-4 and *H*-5 of the thienyl ring, ^3J = 5 Hz), 7.3-7.42 (m, 3H, *H*-2 of the thienyl ring, *H*-6 and *H*-8 of the anellated phenyl ring), 7.6 (pt, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 8.15 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 243 (56%, M^+), 146 (100%, M-C_5H_5S).

Anal. Calcd. for $C_{13}H_9NO_2S$ (243.3): C, 64.2; H, 3.7; N, 5.8. Found: C, 64.3; H, 3.9; N, 5.7.

2-[(3,4-Diethoxyphenyl)methyl]-4*H*-3,1-benzoxazin-4-one (**3i**).

Prepared in analogy to **3a** by reaction of 6.9 g (50 mmoles) of **1** with 11.2 g (50 mmoles) of 3,4-diethoxyphenylacetic acid (**2h**). The crude product was recrystallized repeatedly from ligroin to furnish a colorless powder with mp 98°, yield 0.97 g (9%); ir (potassium bromide): 2980, 2940, 2880 (aromatic CH stretch), 1760 (C=O stretch), 1600, 1590, 1510 (phenyl C=C, C=N stretch), 760 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.3-1.5 (m, 6H, CH_2CH_3), 3.7 (s, 2H, CH_2), 3.95-4.15 (m, 4H, CH_2CH_3), 6.8-7.2 (m, 4H, *H* of the substituted phenyl ring, *H*-6 of the anellated phenyl ring), 7.6 (pt, 1H, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 8.15 (d, 1H, *H*-8 of the anellated phenyl ring, ^3J = 8 Hz), 8.7 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 325 (29%, M^+), 123 (100%).

Anal. Calcd. for $C_{19}H_{19}NO_4 \cdot 0.5H_2O$ (334.2): C, 68.3; H, 6.0; N, 4.2. Found: C, 68.1; H, 6.0; N, 3.9.

2-[2-(4-Fluorophenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3j**).

Prepared and purified as described for **3a** from 6.9 g (50 mmoles) of **1** and 8.3 g (50 mmoles) of 4-fluorocinnamic acid (**2i**), pale yellow needles with mp 176°, yield 3.7 g (28%); ir (potassium bromide): 3060, 3040 (aromatic CH stretch), 1765 (C=O stretch), 1640 (aliphatic C=C stretch), 1595, 1570, 1510 (phenyl C=C, C=N stretch), 770, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.7 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 7.0-7.2 (m, 2H, *H*-3 and *H*-5 of the substituted phenyl ring), 7.6-7.8 (m, 4H, *H*-2 and *H*-6 of the substituted phenyl ring, *H*-2 of the ethenyl group, *H*-6 of the anellated phenyl ring), 7.7-7.9 (m, 2H, *H*-7 and *H*-8 of the anellated phenyl ring), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 267 (100%, M^+).

Anal. Calcd. for $C_{16}H_{10}FNO_2$ (267.3): C, 71.9; H, 3.8; N, 5.2. Found: C, 71.8; H, 3.6; N, 5.2.

2-[2-(4-Methoxyphenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3k**) [22].

Prepared in analogy to **3a** from 5.2 g (39.7 mmoles) of 4-methoxycinnamic acid (**2j**) and 5.4 g (39.7 mmoles) of **1**. After appropriate purification, yellow needles were obtained with mp 160°, yield 0.8 g (7%); ir (potassium bromide): 2920 (aliphatic stretch), 1750 (C=O stretch), 1630 (aliphatic C=C stretch), 1590, 1570, 1510 (phenyl C=C, C=N stretch), 770, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.8 (s, 3H, OCH_3), 6.62 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 6.92 (d, 2H, *H*-3 and *H*-5 of the substituted phenyl ring, ^3J = 8 Hz), 7.4-7.62 (m, 4H, *H*-2 and *H*-6 of the substituted phenyl ring, *H*-6 and *H*-8 of the anellated phenyl ring), 7.7-7.9 (m, 2H, *H*-2 of the ethenyl group, *H*-7 of the substituted phenyl ring), 8.2 (d, 1H, *H*-5 of the substituted phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 279 (100%, M^+).

Anal. Calcd. for $C_{17}H_{13}NO_3$ (279.2): C, 73.1; H, 4.7; N, 5.0. Found: C, 73.2; H, 4.7; N, 5.3.

2-[2-(2-Thienyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3l**).

Prepared as described for **3a** from 6.9 g (50 mmoles) of **1** and 7.7 g (50 mmoles) of 3-(2-thienyl)acrylic acid (**2k**) with a reaction time of 4 hours at 100°, yellow needles from acetone with mp 148°, yield 1.02 g (8%); ir (potassium bromide): 3040 (aromatic CH stretch), 1750 (C=O stretch), 1625 (aliphatic CH stretch), 1595, 1570 (phenyl C=C, C=N stretch), 770, 705 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.57 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 7.08 (pt, 1H, *H*-6 of the phenyl ring, ^3J = 8 Hz), 7.3-7.62 (m, 4H, *H* of the thienyl ring and *H*-8 of the phenyl ring), 7.78 (pt, 1H, *H*-7 of the phenyl ring, ^3J = 8 Hz), 7.93 (d, 1H, *H*-2 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 8.2 (d, 1H, *H*-5 of the phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 255 (100%, M^+).

Anal. Calcd. for $C_{14}H_9NO_2S$ (255.2): C, 65.9; H, 3.5; N, 5.5. Found: C, 65.9; H, 3.5; N, 5.5.

2-[2-(3-Nitrophenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3m**) [23].

Prepared from 8.2 g (60 mmoles) of **1** and 11.6 g (60 mmoles) of 3-nitrocinnamic acid (**2l**) by heating in phosphoryl chloride under nitrogen for 6.5 hours at 75°. After evaporation of the solvent, the oily residue was repeatedly recrystallized from acetone to furnish yellow needles with mp 283°, yield 1.2 g (7%); ir (potassium bromide): 3080 (aromatic CH stretch), 1760 (C=O stretch), 1600, 1570, 1520 (phenyl C=C, C=N stretch), 760, 735 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.8 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 7.2-8.65 (m, 9H, aromatic *H*, *H*-2 of the ethenyl group); ms: (90 eV) m/z = 5%, M^+), 85 (100%).

Anal. Calcd. for $C_{16}H_{10}N_2O_4$ (294.2): C, 65.3; H, 3.4; N, 9.5. Found: C, 65.8; H, 3.6; N, 9.8.

2-[2-(4-Chlorophenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3n**) [13].

Prepared and purified as described for **3a** from 6.9 g (50 mmoles) of **1** and 9.1 g (50 mmoles) of 4-chlorocinnamic acid (**2m**), yellow platelets with mp 202°, yield 3.84 g (27%); ir (potassium bromide): 3080, 3040 (aromatic CH stretch), 1770 (C=O stretch), 1640 (aliphatic C=C stretch), 1600, 1570 (phenyl C=C, C=N stretch), 780, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.75 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 7.3-7.7 (m, 6H, *H* of the substituted phenyl ring, *H*-6 and *H*-8 of the anellated phenyl ring), 7.73-7.9 (m, 2H, *H*-2 of the ethenyl group, *H*-7 of the anellated phenyl ring), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 283 (100%, M^+).

Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (283.6): C, 67.8; H, 3.5; N, 4.9. Found: C, 67.4; H, 3.6; N, 4.5.

2-[2-(3-Chlorophenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**3o**).

Prepared in analogy to **3a** from 4.11 g (30 mmoles) of **1** and 5.5 g (30 mmoles) of 3-chlorocinnamic acid (**2n**). The crude product was purified by repeated recrystallization from acetone to furnish colorless needles with mp 155°; yield 0.3 g (4%); ir (potassium bromide): 3060, 3040 (aromatic CH stretch), 1750 (C=O stretch), 1635 (aliphatic C=C stretch), 1600, 1570 (phenyl C=C, C=N stretch), 770, 710, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.78 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 7.3-7.9 (m, 8H, *H* of the substituted phenyl ring, *H*-6, *H*-7, *H*-8 of the anellated phenyl ring, *H*-2 of the ethenyl group), 8.2 (d, 1H, *H*-5 of the anellated phenyl ring, ^3J = 8 Hz); ms: (90 eV) m/z = 283 (100%, M^+).

Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (283.6): C, 67.8; H, 3.5; N, 4.9. Found: C, 67.5; H, 3.9; N, 4.8.

2-(2,6-Difluorophenyl)-4*H*-3,1-benzoxazin-4-one (**3p**).

Prepared in analogy to **3a** from 6.9 g (50 mmoles) of **1** and 7.9 g (50 mmoles) of 2,6-difluorobenzoic acid (**2o**), pale yellow platelets from ligroin with mp 90°, yield 0.8 g (6%); ir (potassium bromide): 3080 (aromatic CH stretch), 1760 (C=O stretch), 1600, 1580, 1520 (phenyl C=C, C=N stretch), 770, 740 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 6.6-7.15 (m, 3H, *H* of the substituted phenyl ring), 7.35-7.81 (m, 3H, *H*-6, *H*-7 and *H*-8 of the anellated phenyl ring), 8.3-8.5 (m, 1H, *H*-5 of the anellated phenyl ring); ms: (90 eV) m/z = 259 (100%, M^+).

Anal. Calcd. for $C_{14}H_7F_2NO_2$ (259.2): C, 64.9; H, 2.7; N, 5.4. Found: C, 64.9; H, 3.0; N, 5.3.

2-[4-(Bromomethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (**4a**).

Prepared and purified in analogy to **3a** from 5.5 g (40 mmoles) of **1** and 8.6 g (40 mmoles) of 4-bromomethylbenzoic acid (**2p**), pale yellow platelets with mp 140°, yield 2.0 g (16%); ir (potassium bromide): 1750 (C=O stretch), 1600, 1570 (phenyl C=C, C=N stretch), 770, 690 cm^{-1} (aromatic CH wagging); ms: (90 eV) m/z = 316 (4%, M^+), 236 (100%, M-Br).

Anal. Calcd. for $C_{15}H_{10}BrNO_2$ (316.1): C, 57.0; H, 3.2; N, 4.4. Found: C, 57.3; H, 3.2; N, 4.4.

2-[4-(Dimethylphosphonatomethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (**4b**).

Compound **4a** (0.95 g, 3 mmoles) was heated to boiling with 0.4 g of potassium iodide in 20.0 g (162 mmoles) of trimethyl phosphite (**5a**) for 4 hours. Excess trimethyl phosphite was removed by distillation under vacuum and the oily residue was repeatedly recrystallized from ethanol/water, pale yellow platelets with mp 126°; yield 0.6 g (58%); ir (potassium bromide): 3010 (aromatic CH stretch), 2950, 2920, 2840 (aliphatic CH stretch), 1760 (C=O stretch), 1610, 1570 (phenyl C=C, C=N stretch), 1230 (P=O stretch), 770, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 3.25 (d, 2H, CH_2-P, ^2J (H,P) = 22 Hz), 3.69 (d, 6H, OCH_3, ^3J (H,P) = 11 Hz), 7.38-7.6 (m, 3H, *H*-6 of the anellated phenyl ring, *H*-3 and *H*-5 of the substituted phenyl ring), 7.67 (d, 1H, *H*-8 of the anellated phenyl ring, ^3J = 8 Hz), 7.82 (pt, split, 1H, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 8.2-8.28 (m, 3H, *H*-5 of the anellated phenyl ring, *H*-2 and *H*-6 of the substituted phenyl ring); ms: (90 eV) m/z = 345 (100%, M^+).

Anal. Calcd. for $C_{17}H_{16}NO_5P$ (345.1): C, 59.2; H, 4.6; N, 4.1. Found: C, 59.0; H, 4.8; N, 3.9.

2-[4-(Diethylphosphonatomethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (**4c**).

Prepared in analogy to **4b** from 20.0 g (120 mmoles) of triethyl phosphite (**5b**), 0.95 g (3 mmoles) of **4a**, and 0.8 g of potassium iodide and recrystallized from ethanol/water, pale yellow needles with mp 101°, yield 1.0 g (89%); ir (potassium bromide): 2990, 2920 (aliphatic CH stretch), 1760 (C=O stretch), 1610, 1570, 1510 (phenyl C=C, C=N stretch), 1250 (P=O stretch), 780, 750 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 1.3 (t, 6H, CH_2CH_3, ^3J = 7 Hz), 3.22 (d, 2H, CH_2-P, ^2J (H,P) = 22 Hz), 3.9-4.1 (m, 4H, CH_2CH$_3$), 7.4-7.6 (m, 3H, *H*-3 and *H*-5 of the substituted phenyl ring, *H*-6 of the anellated phenyl ring), 7.67 (d, 1H, *H*-8 of the anellated phenyl ring), 7.82 (pt, split, 1H, *H*-7 of the anellated phenyl ring, ^3J = 8 Hz), 8.2-8.3 (m, 3H, *H*-5 of the anellated phenyl ring, *H*-2 and *H*-6 of the substituted phenyl ring); ms: (90 eV) m/z = 373 (100%, M^+).

Anal. Calcd. for $C_{19}H_{20}NO_5P$ (373.2): C, 61.2; H, 5.4; N, 3.8. Found: C, 61.3; H, 5.3; N, 3.9.

2-[2-(4-Methylphenyl)ethenyl]-4*H*-3,1-benzoxazin-4-one (**4d**) [23].

Prepared, isolated, and purified in analogy to the procedure for **3a** from 8.2 g (60 mmoles) of **1** and 9.7 g (60 mmoles) of 4-methylcinnamic acid (**2q**), colorless needles with mp 190°, yield 8.46 g (54%); ir (potassium bromide): 3020 (aromatic CH stretch), 2920 (aliphatic CH stretch), 1760 (C=O stretch), 1640 (aliphatic C=C stretch), 1590, 1570 (phenyl C=C, C=N stretch), 770, 700 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 2.3 (s, 3H, CH_3), 6.6 (d, 1H, *H*-1 of the ethenyl group, $^3J_{1,2}$ (E) = 16 Hz), 6.9-8.2 (m, 9H, *H* aromatic , *H*-2 of the ethenyl group); ms: (90 eV) m/z = 263 (100%, M^+).

Anal. Calcd. for $C_{17}H_{13}NO_2$ (263.2): C, 77.6; H, 4.9; N, 5.3. Found: C, 77.5; H, 4.9; N, 4.9.

2-{2-[4-(Dibromomethyl)phenyl]ethenyl}-4*H*-3,1-benzoxazin-4-one (**4e**).

Compound **4d** (8.4 g, 31.8 mmoles) and 6.0 g (33.7 mmoles) of *N*-bromosuccinimide were suspended in anhydrous tetrachloromethane, a spatula tip of benzoyl peroxide was added, and the mixture was heated to boiling for 1.5 hours. The reaction mixture was then filtered, the filtrate concentrated, and the residue repeatedly recrystallized from ethanol, pale yellow powder with mp 117°, yield 3.13 g (22%); ir (potassium bromide): 3020 (aromatic CH stretch), 2980, 2920, 2850 (aliphatic CH stretch), 1760 (C=O stretch), 1640 (aliphatic C=C stretch), 1600, 1590, 1520 (phenyl C=C, C=N stretch), 770, 760, 690 cm^{-1} (aromatic CH wagging); ^1H nmr (deuteriochloroform): δ (ppm) = 4.5 (s, 1H, C*H*Br$_2$), 6.8-8.2 (m, 10H,, *H* aromatic and *H* of the ethenyl group); ms: (90 eV) m/z = 422 (6%, M^+), 115 (100%, $C_9H_7^+$).

Anal. Calcd. for $C_{17}H_{11}Br_2NO_2$ (422.2): C, 48.5; H, 2.7; N, 3.3. Found: C, 48.6; H, 2.4; N, 3.0.

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