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ORIGINAL PAPER

Antineoplastic activity of fused nitrogen-phosphorus heterocycles and derived phosphonates

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Abstract A variety of derivatives incorporating substituted heterocycle-phosphor motifs is described. Substituted N,P-heterocycles and derived phosphonates were produced efficiently in a tandem operation without intermediate isolation. The synthesis methodology is based on the reaction of dialkyl phosphites with Schiff base Kabachnik–Fields intermediates, which are generated in situ from 2-amino-4,6-di-*tert*-butylphenol and substituted benzaldehydes in dry THF/$FeCl_3$ (10 %) solution, to yield fused oxazole-2-phosphonates in moderate yield (≈55 %). The latter products could be also obtained in excellent yield (≥76 %) by directly applying the same P(III) reagents to the parent Schiff bases. On the other hand, oxazaphosphinine-2-amines were isolated in high yields (≈77 %) when the Schiff bases were allowed to react with hexaalkyltriamidophosphites at rt. More P-heterocycles and the derived phosphonates were also obtained when the same reagents were applied to another imino derivative derived from the aminophenol, 2-hydroxybenzaldehyde oxime. The synthesized scaffolds were biologically evaluated and found to possess potent anticancer activities. On the basis of bioassay data, the produced N,P-heterocycles exhibit remarkable antitumor activity against 17 tested human tumor cell lines, representing breast and prostate cancer and melanoma. Several phosphonates were found to possess specific anti-breast cancer activity (especially MDA-MB-435 cell lines) while others possess specific effects against melanoma (MI4 and SK-MEL-2 cancer cell lines). These findings form a foundation for further investigation in our continuing efforts to develop selective anticancer agents.

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Keywords Oxazole-phosphor motifs · Oxazaphosphininones · Multicomponent reaction · Kabachnik–Fields reaction · Anticancer bioassay · QSAR

Introduction

Cancer is among the most critical health issues and considered the second leading cause of death worldwide, just after the circulatory diseases. Despite the availability of improved drugs, including targeted cancer therapies, according to the World Health Organization (WHO) the worldwide cancer burden is expected to increase by as much as 50 % by the year 2020 unless further preventive measures are put into practice [1–3]. Over the last two decades, a continuous trend is observed toward the chemistry of P-heterocycles and derived phosphonates, largely, because these compounds, especially those that contain high nitrogen contents tend to have higher antitumor activity [4–8].

The Kabachnik-reaction has been previously reported as a facile method for the preparation of new aminophosphonates and N,P-heterocycles [9–11]. Consecutively, several of these compounds were synthesized in our previous publications via the Kabachnik–Fields reaction starting with amine derivatives, substituted benzaldehydes, and nucleophilic P(III)-reagents. We have found that most of these rings possess remarkable inhibitory effect on carcinoma cell lines as well as they have anti-inflammatory properties [12–16].

In sequel, we are herein investigating the Kabachnik–Fields reaction further with an attempt to look for new antineoplastic motifs. A series of new N,P-heterocycles and their phosphonate derivatives were synthesized by the

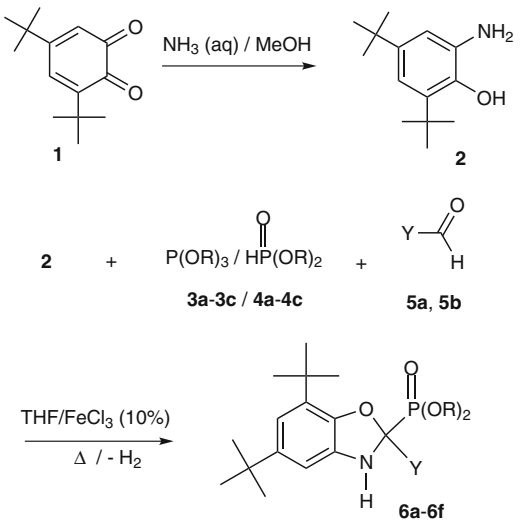
Kabachnik–Fields reaction of 2-amino-4,6-di-*tert*-butylphenol (**2**) with the appropriate aromatic aldehydes **5a** or **5b**, followed by addition of trialkyl phosphites (TAPs) **3a**–**3c**, dialkyl phosphites (DAPs) **4a**–**4c**, or hexaalkyltriamidophosphites **9**. The investigation also highlighted the influence of replacing the Schiff base moiety with the methylhydroxylamine motif (C=NOH) at the *ortho* position with respect to the phenolic group in the behavior toward the same phosphorus reagents. The quantitative structure-anticancer activity relationship (QSR) is also described in this paper.

Results and discussion

The required 2-amino-4,6-di-*tert*-butylphenol (**2**) is not commercially available, and was therefore synthesized by aminolysis of the parent 3,5-di-*tert*-butyl-1,2-benzoquinone (**1**) according to the reported method [17, 18] (Scheme 1). The substrate **2** could be used in situ without further purification for the next step.

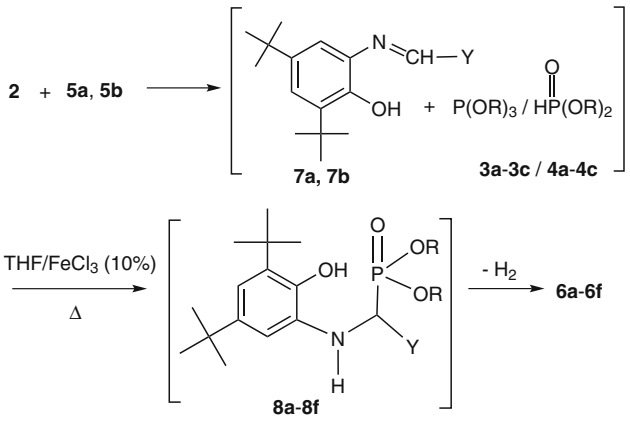
The Kabachnik–Fields reaction was carried out by mixing the amine **2** with the aldehyde **5a** or **5b** and TAPs **3a**–**3c** in THF/$FeCl_3$ (10 %) solution at rt, followed by heating under reflux for ≈12 h to yield the α-aminophosphonates **6a**–**6f** (≈55 %, Scheme 1). The oxazole ring structure was determined to be **6** (Scheme 2) based on the following: compatible elementary analysis and molecular weight determinations (MS) were measured for all adducts.

Scheme 1



	Y	R		Y	R
6a	4-F-C_6H_4	Me	**6d**	4-Me_2N-C_6H_4	Me
6b	4-F-C_6H_4	Et	**6e**	4-Me_2N-C_6H_4	Et
6c	4-F-C_6H_4	*i*-Pr	**6f**	4-Me_2N-C_6H_4	*i*-Pr

Scheme 2

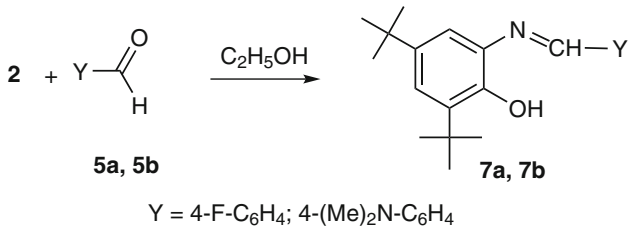


The IR spectra of **6a**–**6f** revealed the presence of NH around $\bar{\nu} \approx 3,340\ cm^{-1}$ and the lack of stretching vibrations at ≈3,450 cm^{-1} due to phenolic OH frequency (for compounds **2** and **7**: OH ≈3,455 cm^{-1}). The phenolic proton was not also displayed in the ^1H NMR ($CDCl_3$) spectra of **6a**–**6f**. Among other signals, the sp^3–C– of the oxazole ring appeared as a doublet ($^1J_{P-C} = 138.5$ Hz) at $\delta = 88.6$ ppm in the ^{13}C NMR ($CDCl_3$) spectrum of **6a**. A plausible explanation for the mechanism of the reaction is proposed in Scheme 2. According to the Kabachnik–Fields reaction [9–11], the first step may involve the condensation between the aldehyde and the amine in the presence of $FeCl_3$ and the formation of the intermediate Schiff bases **7a** and **7b**, followed by the addition of the phosphorus reagents **3a**–**3c** or **4a**–**4c** to produce **6a**–**6f** via the intermediates **8a**–**8f** in a tandem extrusion of H_2. We considered that the thermal condition, coupled with the presence of an excess of $FeCl_3$ used for the coupling reaction, had promoted the oxidation process. Furthermore, the tendency of the intramolecular cyclization process was previously discussed for the transformation of 3,5-di-*tert*-butyl-2-hydroxyphenylamino derivatives to the corresponding benzoxazoles [17]. Nevertheless, the formation of dialkyl, and not trialkyl adducts is acceptable since the presence of acidic medium ($FeCl_3$) causes the hydrolysis of TAPs to DAP counterparts.

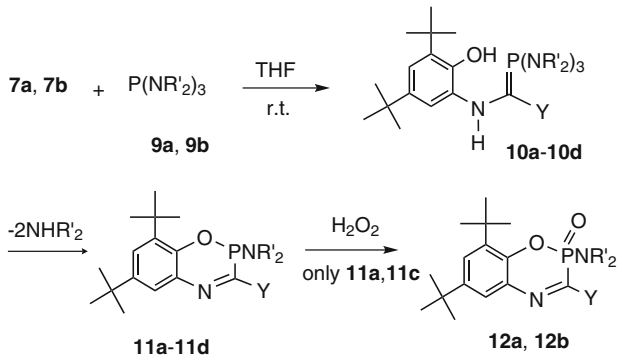
In favor of this mechanism, phosphonates **6a**–**6f** were independently synthesized in higher yield (≥76 %) by treating 2,4-di-*tert*-butyl-6-(4-fluorobenzylideneamino) phenol (**7a**) or 2,4-di-*tert*-butyl-6-[4-(dimethylamino)benzylideneamino]phenol (**7b**) with TAPs/DAPs in THF/$FeCl_3$ (10 %) solution. The required Schiff bases **7a** and **7b** were initially prepared from the condensation of the aldehydes **5** with the amine **2** in ethanol solution [17, 18] (Scheme 3).

Conversely, when the Schiff bases **7a** and **7b** were allowed to react with an excess of hexaalkyltriamidophosphites **9a** or

Scheme 3



Scheme 4



11a,**12a**, Y = 4-F-C_6H_4; R' = Me; **11b**, Y = 4-F-C_6H_4; R' = Et; **11c**, **12b**, Y = 4-$(Me)_2$N-C_6H_4; R' = Me; **11d,** Y = 4-$(Me)_2$N-C_6H_4; R' = Et

9b in dry THF, the reactions went smoothly at rt (8 h) and afforded the oxazaphosphinines **11a–11d** in high yield (≈77 %). The synthesis route in Scheme 4 [19] shows that **11** was formed through the initial formation of the phosphinimines **10**, followed by intramolecular cyclization reaction to give the oxazaphosphinines **11** with concomitant elimination of two moles of dialkylamine. The structures of **11a–11d** were confirmed by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS spectroscopic data, and elemental analysis. Compounds **11a–11d** were quite stable at normal conditions, nevertheless, for the pharmacological studies, **11a** and **11c**, as representative examples, were oxidized to the oxazaphosphininone form **12a**, **12b** by boiling in THF containing hydrogen peroxide. Compounds **12a**, **12b** showed ^{31}P NMR ($CHCl_3$) chemical shifts around $\delta = 11.8$ and 13.6 ppm, confirming the presence of the C–P–N linkage as an oxazaphosphininone moiety [20, 21]. This finding eliminates the formation of a phosphonate for which a signal at $\delta > 17$ ppm would be expected.

The investigation was next extended to obtain additional substituted N,P-heterocycles and the corresponding phosphonate derivatives by applying the same P(III) reagents to the oxime **14**. The substrate **14** was obtained by treating the parent 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**13**) with hydroxylamine hydrochloride [22]. Unfortunately, no reaction was observed between **14** and trialkyl phosphites, even after heating the reaction mixture in toluene solution under reflux for 48 h. On the other hand, the reaction between dialkyl phosphites **4a–4c** and **14** proceeded only when a catalytic amount of TEA or benzoyl peroxide was added to the reactants in absence of solvent (best yield was obtained with benzoyl peroxide), and yielded the respective isoxazol-3-ylphosphonates **16a–16c** (≈68 % yield) as it is outlined in Scheme 5. Obviously, the phosphonates **16** resulted from the loss of a molecule of H_2O from the (hydroxyamino)methylphosphonate intermediates **15** initially formed.

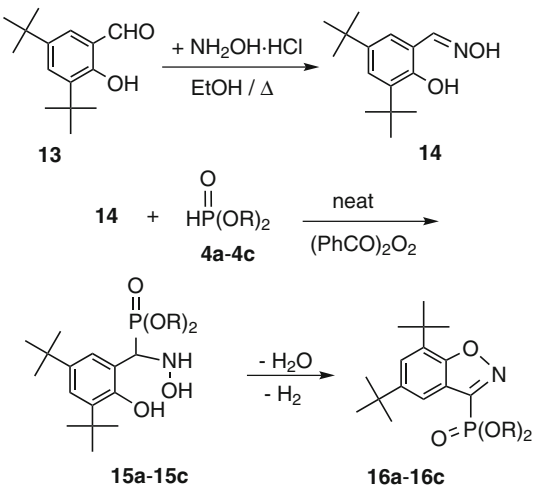
Finally, when the oxime **14** was stirred with an excess of amidophosphites **9a** or **9b** in THF (or toluene) at rt for 12 h, oxaphospholes **18a** and **18b** were isolated in high yields (≈77 %). When **18a** and **18b** were treated with H_2O_2 in THF solution, oxaphosphol-2-oxides **19a** and **19b** (≈77 %, $\delta_P = 12.7$, 14.2 ppm) were formed as it was predicted in Scheme 6.

Satisfactory elementary analysis and molecular weight determinations (MS) confirmed structures **18** and **19**, ^{31}P NMR signals of **18a** and **18b** were found at $\delta = 123.6$ and 120.5 ppm. The ^{1}H NMR spectrum ($CDCl_3$) of **18a** showed among others the NMe_2 protons as a doublet ($^{3}J_{P-H} = 10.4$ Hz) at $\delta = 3.23$ ppm. The ^{13}C NMR ($CDCl_3$) spectrum of **18a** displayed the P–C=N signal at $\delta = 143.6$ ppm (d, $^{1}J_{P-C} = 166.3$ Hz).

Antitumor activity screening

Antitumor activity for the synthesized nitrogen-phosphorus heterocycles and derived phosphonates **6a–6e**, **12a**, **12b**,

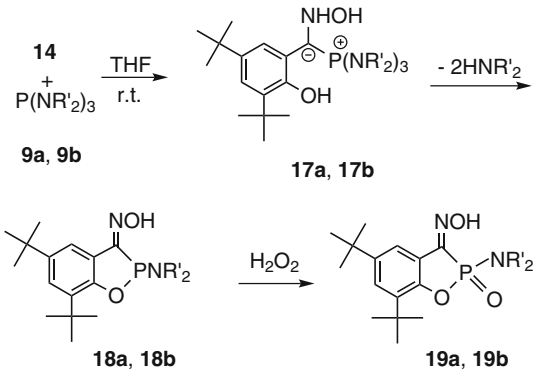
Scheme 5



16a, R = Me; **16b**, R = Et; **16c**, R = *i*-Pr

16a, **16b**, **19a**, and **19b** at a dose of 10 μM utilizing seventeen different human tumor cell lines representing breast and prostate cancer and melanoma was carried out according to the previously reported methods [23, 24]. Substrates **7a** and **14** were also biologically tested in a trial to reflect the effect of introducing phosphor moiety. The obtained results represent percentage growth of the tumor cell lines treated with compounds under investigation relative to control cell.

Scheme 6



The pharmacological results displayed in Table 1 show that other than the substrates **7a** and **14**, all tested compounds reflect remarkable antitumor activity against breast (especially MDA-MB-23/ATCC cell lines) and prostate cancer, whereas a moderate effect was observed on melanoma. On the other hand, only the fused phosphor-heterocycles **12a**, **12b**, **19a**, and **19b** showed sensitivity against melanoma. However, we considered that cell line growth inhibition with >50 % at a concentration of 10 μM usually seems to be a noticeable activity. Structural activity relationship (SAR) correlation for the reported observations reveals that the presence of the fused phosphorus ring usually associated with an enhancement in the antitumor properties as indicated in our observations in Table 1.

Conclusion

Summarizing, previous [4–8] and present investigations have shown that multicomponent reactions in a one-pot synthesis are of significant value from both the synthetic, chemical, and biological points of view. The convenience and novelty of this work is reflected in its several advantages, such as mild reaction conditions, short reaction time, and easy workup procedure without the need to chromatographic purification. The present study has also

Table 1 Concentrations resulting in growth inhibition of 50 % (GI_{50}/mg dm^{-3}) of in vitro human tumor cell lines

Panel/cell line	Compounds											
	7a/14	**6a**	**6b**	**6c**	**6d**	**6e**	**12a**	**12b**	**16a**	**16b**	**19a**	**19b**
Breast cancer												
McF7	>48	9.48	10.85	17.58	11.42	8.40	5.27	5.27	10.25	11.85	8.84	9.45
NCl/ADR-RES	>48	18.31	17.56	26.50	16.21	20.1	6.76	6.08	19.16	17.56	8.97	9.88
MDA-MB-231/ATCC	>48	9.73	10.43	20.68	14.35	14.98	8.65	9.23	13.12	13.48	11.42	13.22
HS578T	>48	18.72	20.42	24.80	22.64	20.42	12.10	10.42	20.74	19.34	16.92	15.43
MDA-MB-435	>48	7.52	6.05	19.60	13.4	14.05	13.44	13.07	16.33	16.97	10.05	10.56
BT-549	>48	12.76	12.44	23.3	11.97	11.97	15.85	15.25	12.44	12.44	16.32	17.13
T-47D	>48	11.88	12.18	30.95	13.08	12.14	15.06	12.11	12.38	12.18	14.12	14.76
Prostate cancer												
PC-3	>48	20.46	18.73	29.6	10.82	19.4	6.86	7.82	18.03	18.37	14.2	16.21
DU-145	>48	15.3	>52	14.5	15.3	8.75	10.98	10.24	16.47	14.34	7.57	8.73
Melanoma												
LOXIMVI	>50	30.15	33.41	33.42	34.51	34.11	9.38	8.30	24.52	24.52	13.24	15.16
MALME-3M	>50	14.33	14.74	28.61	14.73	16.43	10.36	8.66	31.31	31.31	11.75	12.55
MI4	>50	17.25	15.72	40.23	5.64	7.66	12.57	15.72	27.52	27.52	12.15	12.95
SK-MEL-2	>50	28.56	27.03	30.35	10.33	10.44	15.78	13.43	26.47	26.47	14.23	14.92
SK-MEL-28	>50	16.35	14.38	30.36	14.35	15.75	16.96	14.09	30.03	30.32	26.61	24.21
SK-MEL-5	>50	18.54	11.44	14.22	11.44	13.64	17.76	14.16	22.34	37.4	12.42	12.06
UACC-257	>50	8.64	13.44	19.23	8.64	8.21	10.16	10.46	23.25	21.22	10.54	11.88
UACC-62	>50	20.17	20.51	33.26	22.21	27.61	12.16	11.62	23.66	24.77	9.52	9.52

demonstrated that although the initial step is the nucleophilic attack by the P(III) reagents at the azomethine-C portion in the two C–N multiple bond substrates, the anils **7** and the oxime **14**, the consequences of the initial step varied markedly according to the type of both the functional group and the type of the phosphorus reagent. In parallel, it has also been noticed that some of these motifs (e.g., compounds **6a** and **6b**) were found to possess specific anti-breast cancer activity (especially to MDA-MB-435 cell lines) and others (e.g., compounds **6d** and **6e**) possess specific effects against melanoma (MI4 and SK-MEL-2 cell lines). Importantly, the introduction of an oxazole-phosphor motif framework produced very potent anticancer compounds. Finally, on the basis of bioassay results, the produced N,P-heterocycles **12a** and **12b** exhibited remarkable antitumor activity against the seventeen tested human tumor cell lines representing breast and prostate cancer and melanoma. They could be considered as lead molecules to be modified in order to improve their anticancer activity. Furthermore, these findings form the foundation for further investigation in our continuing efforts to develop selective anticancer agents.

Experimental

Melting points were determined with an open capillary tube on an Electrothermal (variable heater) melting point apparatus and are corrected. IR spectra were recorded on a Perkin Elmer 297 grating IR spectrophotometer using KBr pellets. NMR spectra were measured with a JEOL E.C.A-500 MHz (^{13}C: 125 MHz, ^{1}H: 500 MHz, ^{31}P: 200 MHz) spectrometer. ^{31}P NMR spectra were recorded with H_3PO_4 (85 %) as an external reference. ^{1}H and ^{13}C NMR spectra were measured using $SiMe_4$ as an internal reference in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are given in ppm. Mass spectrometry was performed on a JEOL JMS-AX 500 spectrometer. The appropriate precautions in handling moisture-sensitive compounds were considered. Solvents were dried using standard techniques. Thin-layer chromatography (TLC) used Merck 0.2 mm silica gel 60 F254 aluminum plates. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using Elemental C, H, N analyzer Vario EL III Germany. Their values agreed favorably with the calculated ones.

*General procedure for the one-pot preparation of phosphonates **6a–6f***

A stirred mixture of 0.8 g of aldehyde **5a**, **5b** (6 mmol), 1.3 g of amine **2** (6 mmol), and trialkyl phosphite (trimethyl (**3a**), triethyl (**3b**), or triisopropyl phosphite (**3c**), 6.2 mmol) in 10 cm^3 of dry THF/$FeCl_3$ (10 %) was heated under reflux for 10–15 h. After completion of the reaction (the evolved H_2 gas was observed but not tested), 10 cm^3 AcOEt was added to the mixture. The organic phase was separated, washed with 20 cm^3 distilled H_2O, and dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure, and the residue therein was crystallized from the proper solvent to give the corresponding phosphonates **6a–6f**.

The products **6a–6f** were obtained in analogy, almost in the same yield, when DAPs [dimethyl (**4a**), diethyl (**4b**), or diisopropyl phosphite (**4c**)] replaced the TAP counterpart in the above reactions whereas experimental conditions, stoichiometric amounts, and work up were inclusively used.

Dimethyl 5,7-di-tert-butyl-2-(4-fluorophenyl)-2,3-dihydrobenzo[d]oxazol-2-ylphosphonate
(**6a**, $C_{23}H_{31}FNO_4P$)
Colorless crystals; m.p.: 119 °C (cyclohexane); yield: 1.4 g (53 %); IR (KBr): $\bar{\nu}$ = 3,350$_w$ (NH), 1,240 (P=O), 1,164 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.35, 1.40 [2 s, 2 × 9H, 2(Me_3C)], 3.70 (d, $^{3}J_{P-H}$ = 11.6 Hz, 6H, $(MeO)_2$P), 6.23 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 7.40, 7.70 (2 m, 4H, H–Ar), 8.78 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 163.5, 149.0, 148.7, 134.2, 132.2, 128.5, 120.8, 117.3, 116.7, 112.0 (C–Ar), 88.6 (d, $^{1}J_{P-C}$ = 138.5 Hz, C–P), 54.6 (d, $^{2}J_{P-C}$ = 14.8 Hz, $(MeO)_2$P), 37.7, 30.5 (2*C*Me_3), 31.1, 29.6 (2*Me*$_3$C) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 27.6 ppm; MS (EI, 70 eV): *m/z* (%) = 434 (35) [M$^+$−1], 414 (23) [M$^+$−20, (H + F)], 305 (100) [M$^+$−129, (H + F + P(O)$(OMe)_2$)], 191 (84), 109 (66) [P(O)$(OMe)_2$)], 77 (80).

Diethyl 5,7-di-tert-butyl-2-(4-fluorophenyl)-2,3-dihydrobenzo[d]oxazol-2-ylphosphonate
(**6b**, $C_{25}H_{35}FNO_4P$)
Colorless crystals; m.p.: 114 °C (pentane); yield: 1.5 g (54 %); IR (KBr): $\bar{\nu}$ = 3,345$_w$ (NH), 1,245 (P=O), 1,125 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.29 (dt, J_{H-H} = 6.6 Hz, $^{4}J_{P-H}$ = 4.8 Hz, 6H, $(MeCO)_2$P), 1.37, 1.44 [2 s, 2 × 9H, 2(Me_3C)], 4.22 (dq, J_{H-H} = 6.6, $^{3}J_{P-H}$ = 5.7 Hz, 4H, $(H_2CO)_2$P), 6.35 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.96 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 7.36, 7.82 (2 m, 4H, H–Ar), 8.91 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 163.9, 149.2, 148.6, 134.0, 132.3, 128.2, 119.4, 117.5, 116.4, 112.2 (C–Ar), 90.2 (d, $^{1}J_{P-C}$ = 136 Hz, C–P), 63.2 (d, $^{2}J_{P-C}$ = 14.8 Hz, $(CH_2O)_2$P), 38.7, 30.5 (2*C*Me_3), 31.2, 29.4 (2*Me*$_3$C), 16.2 (d, $^{3}J_{P-C}$ = 7.8 Hz, *Me*COP) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 27.9 ppm; MS (EI, 70 eV): *m/z* (%) = 462 (23) [M$^+$−1], 442 (53) [M$^+$−20, (H + F)], 305 (100)

[M^+-157, (H + F + P(O)$(OEt)_2$)], 191 (90), 138 (62) [P(O)$(OEt)_2$)], 77 (78).

Diisopropyl 5,7-di-tert-butyl-2-(4-fluorophenyl)-2,3-dihydrobenzo[d]oxazol-2-ylphosphonate (**6c**, $C_{27}H_{39}FNO_4P$)
Colorless crystals; m.p.: 123 °C (cyclohexane); yield: 1.7 g (58 %); IR (KBr): $\bar{\nu} = 3{,}336_w$ (NH), 1,242 (P=O), 1,064 (P–O–C) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.25$ (dd, $J_{H-H} = 6.5$ Hz, $^4J_{P-H} = 5.1$ Hz, 12H, $(Me_2CO)_2P$), 1.35, 1.40 [2 s, 2 × 9H, 2(Me_3C)], 4.28 (dsept, $J_{H-H} = 6.5$, $^3J_{P-H} = 5.8$ Hz, 2H, $(HCO)_2P$), 6.26 (d, $J_{H-H} = 4.2$ Hz, 1H, H(4)-Ar), 6.86 (d, $J_{H-H} = 4.2$ Hz, 1H, H(6)-Ar), 7.34, 7.76 (2 m, 4H, H–Ar), 8.88 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): $\delta = 164.0$, 150.2, 148.3, 133.8, 132.0, 128.0, 119.1, 117.7, 116.3, 112.7 (C–Ar), 103.5 (d, $^1J_{P-C} = 135.5$ Hz, C–P), 69.4 (d, $^2J_{P-C} = 9.5$ Hz, $(CHO)_2P$), 39.7, 30.5 (2*C*Me_3), 31.1, 29.6 (2*Me*$_3$C), 23.7 (d, $^3J_{P-C} = 7.9$ Hz, *Me*$_2$CO) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): $\delta = 31.2$ ppm; MS (EI, 70 eV): *m/z* (%) = 490 (28) [M^+-1], 470 (35) [M^+-20, (H + F)], 305 (100) [M^+-185, (H + F + P(O)$(OC_3H_7)_2$)], 191 (92), 165 (55) [P(O)$(OC_3H_7)_2$)], 77 (85).

Dimethyl 5,7-di-tert-butyl-2-[4-(dimethylamino)phenyl]-2,3-dihydrobenzo[d]oxazol-2-ylphosphonate
(**6d**, $C_{25}H_{37}N_2O_4P$)
Straw yellow needles; m.p.: 133 °C (CH_2Cl_2); yield: 1.5 g (55 %); IR (KBr): $\bar{\nu} = 3{,}334_w$ (NH), 1,248 (P=O), 1,155 (P–O–C) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.35$, 1.47 [2 s, 2 × 9H, 2(Me_3C)], 2.93 (s, 6H, $(Me)_2N$), 3.78 (d, $^3J_{P-H} = 12.3$ Hz, 6H, $(MeO)_2P$), 6.28 (d, $J_{H-H} = 4.2$ Hz, 1H, H(4)-Ar), 6.95 (d, $J_{H-H} = 4.2$ Hz, 1H, H(6)-Ar), 7.28, 7.48 (2 m, 4H, H–Ar), 9.07 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): $\delta = 150.2$, 149.0, 148.7, 134.0, 132.6, 127.2, 118.2, 117.9, 113.7, 112.1 (C–Ar), 95.6 (d, $^1J_{P-C} = 129.5$ Hz, C–P), 54.6 (d, $^2J_{P-C} = 14.8$ Hz, $(MeO)_2P$), 40.4 (Me_2N), 37.5, 30.5 (2*C*Me_3), 32.4, 29.5 (2*Me*$_3$C) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): $\delta = 24.6$ ppm; MS (EI, 70 eV): *m/z* (%) = 459 (18) [M^+-1], 414 (67) [M^+-45, (H + NMe_2)], 305 (100) [M^+-154, (H + NMe_2 + P(O)$(OMe)_2$)], 191 (87), 109 (72) [P(O)$(OMe)_2$], 77 (85).

Diethyl 5,7-di-tert-butyl-2-[4-(dimethylamino)phenyl]-2,3-dihydrobenzo[d]oxazol-2-ylphosphonate
(**6e**, $C_{27}H_{41}N_2O_4P$)
Straw yellow needles; m.p.: 127 °C (CH_2Cl_2); yield: 1.6 g (56 %); IR (KBr): $\bar{\nu} = 3{,}340_w$ (NH), 1,235 (P=O), 1,110 (P–O–C) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.29$ (dt, $J_{H-H} = 6.6$ Hz, $^4J_{P-H} = 4.8$ Hz, 6H, $(MeCO)_2P$), 1.31, 1.47 [2 s, 2 × 9H, 2(Me_3C)], 2.86 (s, 6H, $(Me)_2N$), 4.17 (dq, $J_{H-H} = 6.6$, $^3J_{P-H} = 6.2$ Hz, 4H, $(H_2CO)_2P$), 6.22 (d, $J_{H-H} = 4.2$ Hz, 1H, H(4)-Ar), 6.78 (d, $J_{H-H} = 4.2$ Hz, 1H, H(6)-Ar), 7.28, 7.69 (2 m, 4H, H–Ar), 8.83 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): $\delta = 151.2$, 149.6, 148.2, 133.7, 132.6, 127.0, 117.5, 117.2, 113.0, 112.4 (C–Ar), 102.1 (d, $^1J_{P-C} = 140$ Hz, C–P), 63.2 (d, $^2J_{P-C} = 14.8$ Hz, $(CH_2O)_2P$), 40.4 (Me_2N), 39.7, 30.5 (2*C*Me_3), 32.5, 29.2 (2*Me*$_3$C), 16.8 (d, $^3J_{P-C} = 6.8$ Hz, *Me*COP) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): $\delta = 23.8$ ppm; MS (EI, 70 eV): *m/z* (%) = 487 (17) [M^+-1], 442 (22) [M^+-45, (H + NMe_2)], 305 (100) [M^+-182, (H + NMe_2 + P(O)$(OEt)_2$)], 191 (74), 137 (48) [P(O)$(OEt)_2$], 77 (83).

Diisopropyl 5,7-di-tert-butyl-2-[4-(dimethylamino)phenyl]-2,3-dihydrobenzo[d]oxazol-2-yl-phosphonate
(**6f**, $C_{29}H_{45}N_2O_4P$)
Straw yellow crystals; m.p.: 140 °C (MeCN); yield: 1.6 g (52 %); IR (KBr): $\bar{\nu} = 3{,}356_w$ (NH), 1,236 (P=O), 1,144 (P–O–C) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.22$ (dd, $J_{H-H} = 6.8$ Hz, $^4J_{P-H} = 5.8$ Hz, 12H, $(Me_2CHO)_2P$), 1.33, 1.51 (2 s, 2 × 9H, 2(Me_3C)), 3.09 (s, 6H, Me_2N), 4.35 (dsept, $J_{H-H} = 6.8$, $^3J_{P-H} = 4.6$ Hz, 2H, $(HCO)_2P$), 6.25 (d, $J_{H-H} = 4.2$ Hz, 1H, H(4)-Ar), 6.95 (d, $J_{H-H} = 4.2$ Hz, 1H, H(6)-Ar), 7.27, 7.69 (2 m, 4H, H–Ar), 8.94 (br s, 1H, HN) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): $\delta = 150.2$, 149.4, 148.0, 134.0, 132.5, 127.8, 117.5, 116.4, 114.0, 112.5 (C–Ar), 103.5 (d, $^1J_{P-C} = 136.5$ Hz, C–P), 69.5 (d, $^2J_{P-C} = 8.5$ Hz, $(CHO)_2P$), 40.4 (Me_2N), 38.7, 29.5 (2*C*Me_3), 32.2, 29.0 (2*Me*$_3$C), 23.5 (d, $^3J_{P-C} = 7.9$ Hz, *Me*$_2$CO) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): $\delta = 25.8$ ppm; MS (EI, 70 eV): *m/z* (%) = 515 (15) [M^+-1], 470 (47) [M^+-45, (H + NMe_2)], 305 (100) [M^+-210, (H + $N(Me)_2$ + P(O)$(OC_3H_7)_2$)], 191 (72), 165 (47) [P(O)$(OC_3H_7)_2$], 77 (69).

*Preparation of the Schiff bases **7a** and **7b***

According to Refs. [17, 18], a mixture of 8.0 g of 2-amino-4,6-di-*tert*-butylphenol (**2**, 36.2 mmol) and the aldehyde **5a** or **5b** (36.3 mmol) in 50 cm^3 ethanol was refluxed for 3 h. The product mixture was further concentrated to its half, followed by filtration. The collected material was crystallized from ethanol to give 2,4-di-*tert*-butyl-6-(4-fluorobenzylideneamino)phenol (**7a**, 10 g, 84 %) or 2,4-di-*tert*-butyl-6-[4-(dimethylamino)benzylideneamino]phenol (**7b**, 11.2 g, 87 %).

*Synthesis of **6a–6f** by reaction of **7a**, **7b** with dialkyl phosphites **4a–4c***

A mixture of 0.8 g of the Schiff bases **7a**, **7b** (2.2 mmol) and dimethyl (**4a**), diethyl (**4b**), or diisopropyl phosphite (**4c**) (2.5 mmol) in 15 cm^3 THF containing 10 % $FeCl_3$ was heated under reflux for 10–15 h (TLC). After the usual

working up, as it is described in the general procedure, and crystallization from the proper solvent, phosphonates **6a–6f** were isolated: **6a**: 727 mg (76 %); **6b**: 795 mg (78 %); **6c**: 864 mg (80 %); **6d**: 779 mg (77 %); **6e**: 827 mg (77 %); **6f**: 863 mg (76 %). Compounds **6a–6f** were characterized by m.p., mixed m.p., and comparable IR spectra with the material previously obtained.

*Synthesis of **11a** and **11b** by reaction of the Schiff bases **7a**, **7b** with hexaalkyltriamidophosphites **9a** and **9b***

The amidophosphite **9a** (R' = Me) or **9b** (R' = Et) (2.3 mmol) in 4 cm^3 dry THF was added dropwise to 0.8 g **7a**, **7b** (2.2 mmol) in 15 cm^3 THF and the reaction mixture was stirred at rt for 8 h (TLC). The solvent was evaporated under vacuum, the residue was collected, washed with light petroleum, and crystallized from the proper solvent to give compounds **11a–11d**.

6,8-Di-tert-butyl-3-(4-fluorophenyl)-N,N-dimethyl-2H-benzo[e][1,4,2]oxazaphosphinin-2-amine
(**11a**, $C_{23}H_{30}FN_2OP$)
Yellow crystals; m.p.: 147 °C (*n*-hexane); yield: 563 mg (78 %); IR (KBr): $\bar{\nu}$ = 1,320, 863 (P–NMe_2) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): δ = 1.30, 1.36 [2 s, 2 × 9H, 2(Me_3C)], 2.89 (d, $^3J_{P–H}$ = 10.8 Hz, 6H, Me_2N–P), 6.25 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(4)-Ar), 6.97 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(6)-Ar), 7.33, 7.64 (2 m, 4H, H–Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 163.0, 148.8, 144.1, 142.5, 140.0, 132.4, 127.9, 120.9, 118.9, 116.2 (C–Ar), 154.1 (d, $^1J_{P–C}$ = 166.3 Hz, C–P), 38.0 (d, $^2J_{P–C}$ = 25.2 Hz, Me_2N–P), 37.6, 30.5 (2CMe_3), 31.3, 29.9 (2Me_3C) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 121.2 ppm; MS (EI, 70 eV): *m/z* (%) = 400 (21) [M^+], 381 (28) [M^+−19, F], 306 (100) [M^+−94, (F + $PNMe_2$)], 191 (52), 77 (83).

6,8-Di-tert-butyl-N,N-diethyl-3-(4-fluorophenyl)-2H-benzo[e][1,4,2]oxazaphosphinin-2-amine
(**11b**, $C_{25}H_{34}FN_2OP$)
Yellow crystals; m.p.: 137 °C (CH_2Cl_2); yield: 678 mg (72 %); IR (KBr): $\bar{\nu}$ = 1,328, 848 (P–NEt_2) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): δ = 0.98 (dt, $J_{H–H}$ = 6.8, $^4J_{P–H}$ = 4.6 Hz, 6H, Me_2CN–P), 1.35, 1.42 [2 s, 2 × 9H, 2(Me_3C)], 3.97 (dq, $J_{H–H}$ = 6.8, $J_{P–H}$ = 5.7 Hz, 2H, H_2CN–P), 6.24 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(4)-Ar), 6.88 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(6)-Ar), 7.38, 7.88 (2 m, 4H, H–Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 163.5, 149.2, 142.5, 141.9, 140.3, 132.8, 127.1, 121.4, 118.5, 116.0 (C–Ar), 155.7 (d, $^1J_{P–C}$ = 160.6 Hz, C–P), 41.4 (d, $^2J_{P–C}$ = 25.7 Hz, CH_2–N–P), 38.7, 30.6 (2CMe_3), 32.2, 29.2 (2Me_3C), 15.2 (d, $^3J_{P–C}$ = 8.8 Hz, *Me*CN–P) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 123.1 ppm; MS (EI, 70 eV): *m/z* (%) = 428 (13) [M^+], 409 (28) [M^+−19, F], 306 (100) [M^+−122, (F + $PNEt_2$)], 191 (52), 77 (83).

6,8-Di-tert-butyl-3-[4-(dimethylamino)phenyl]-N,N-dimethyl-2H-benzo[e][1,4,2]oxazaphosphinin-2-amine
(**11c**, $C_{25}H_{36}N_3OP$)
Yellow crystals; m.p.: 159 °C ($CHCl_3$); yield: 748 mg (80 %); IR (KBr): $\bar{\nu}$ = 1,334, 856 (P–NMe_2) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): δ = 1.42, 1.48 (2 s, 2 × 9H, 2(Me_3C)), 2.96 (s, 6H, Me_2N-Ar), 3.38 (d, $^3J_{P–H}$ = 11.4 Hz, 6H, Me_2N–P), 6.33 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(4)-Ar), 6.99 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(6)-Ar), 7.31, 7.53 (2 m, 4H, H–Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 151.1, 149.5, 143.0, 142.5, 140.2, 129.6, 127.0, 120.3, 118.5, 113.2 (C–Ar), 154.1 (d, $^1J_{P–C}$ = 143.3 Hz, C–P), 39.9 (s, 6H, Me_2N), 37.5 (d, $^2J_{P–C}$ = 22.2 Hz, Me_2N–P), 39.6, 30.9 (2CMe_3), 30.5, 28.9 (2Me_3C) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 123.6 ppm; MS (EI, 70 eV): *m/z* (%) = 425 (13) [M^+], 381 (22) [M^+−44, NMe_2], 306 (100) [M^+−119, (NMe_2 + $PNMe_2$)], 191 (77), 77 (92).

6,8-Di-tert-butyl-3-[4-(dimethylamino)phenyl]-N,N-diethyl-2H-benzo[e][1,4,2]oxazaphosphinin-2-amine
(**11d**, $C_{27}H_{40}N_3OP$)
Straw yellow crystals; m.p.: 145 °C (MeCN); yield: 697 mg (75 %); IR (KBr): $\bar{\nu}$ = 1,344, 836 (P–NEt_2) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): δ = 0.89 (dt, $J_{H–H}$ = 6.2, $^4J_{P–H}$ = 3.5 Hz, 6H, MeCN–P), 1.30, 1.36 [2 s, 2 × 9H, 2(Me_3C)], 2.96 (s, 6H, Me_2N-Ar), 3.21 (dq, $J_{H–H}$ = 6.2, $^3J_{P–H}$ = 5.8 Hz, 4H, H_2CN–P), 6.23 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(6)-Ar), 7.00, 7.49 (2 m, 4H, H–Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 153.0, 149.5, 141.8, 141.1, 140.5, 129.0, 126.4, 120.3, 117.5, 112.5 (C–Ar), 155.7 (d, $^1J_{P–C}$ = 163.7 Hz, C–P), 41.4 (d, $^2J_{P–C}$ = 25.7 Hz, CH_2–N–P), 39.9 (s, Me_2N–P), 37.6, 30.9 (2CMe_3), 31.5, 30.3 (2Me_3C), 15.8 (d, $^3J_{P–C}$ = 8.8 Hz, *Me*CN–P) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 118.4 ppm; MS (EI, 70 eV): *m/z* (%) = 453 (20) [M^+], 409 (17) [M^+−44, NMe_2], 306 (100) [M^+−147, (NMe_2 + $PNEt_2$)], 191 (62), 77 (95).

*Synthesis of **12a** and **12b** by oxidation of **11a** and **11c***

When the compounds **11a** and **11c** were treated with H_2O_2 in THF solution at rt, the oxazaphosphininones **12a** and **12b** were formed after 1 h.

6,8-Di-tert-butyl-3-(4-fluorophenyl)-N,N-dimethyl-2H-benzo[e][1,4,2]oxazaphosphininone-2-amine
(**12a**, $C_{23}H_{30}FN_2O_2P$)
Straw yellow crystals; m.p.: 167 °C (EtOH); yield: 713 mg (78 %); IR (KBr): $\bar{\nu}$ = 1,262 (P=O), 1,338, 874 (P–NMe_2) cm^{-1}; ^1H NMR (500.7 MHz, $CDCl_3$): δ = 1.30, 1.36 [2 s, 2 × 9H, 2(Me_3C)], 3.11 (d, $^3J_{P–H}$ = 10.4 Hz, 6H, Me_2N–P), 6.35 (d, $J_{H–H}$ = 4.2 Hz, 1H, H(4)-Ar), 6.83 (d,

J_{H-H} = 4.2 Hz, 1H, H(6)-Ar) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 11.8 ppm; MS (EI, 70 eV): *m/z* (%) = 416 (24) [M^+], 397 (33) [M^+-19, F], 306 (100) [M^+-110, (F + P(O)NMe_2)], 191 (57), 77 (80).

6,8-Di-tert-butyl-3-[4-(dimethylamino)phenyl]-N,N-dimethyl-2H-benzo[e][1,4,2]oxazaphosphininone-2-amine (**12b**, $C_{25}H_{36}N_3O_2P$)

Straw yellow crystals; m.p.: 177 °C (EtOH); yield: 776 mg (80 %); IR (KBr): $\bar{\nu}$ = 1,255 (P=O), 1,325, 867 (P–NMe_2) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.29, 1.39 [2 s, 2 × 9H, 2(Me_3C)], 2.93 (s, 6H, $(Me)_2$N), 3.25 (d, $^3J_{P-H}$ = 10.4 Hz, 6H, Me_2N–P), 6.22 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 6.94 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 7.00, 7.49 (m, 4H, H–Ar) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 13.6 ppm; MS (EI, 70 eV): *m/z* (%) = 441 (11) [M^+], 397 (48) [M^+-44, NMe_2], 306 (100) [M^+-135, (NMe_2 + P(O)NMe_2)], 191 (62), 77 (82).

*Synthesis of the phosphonate derivatives **16a–16c** by reaction of the oxime **14** with dialkyl phosphites **4a–4c***

To a mixture of 0.8 g of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde oxime (**14**, 3.2 mmol) and dimethyl (**4a**), diethyl (**4b**), or diisopropyl phosphite (**4c**) (3.3 mmol), a catalytic amount of benzoylperoxide was added. The reaction mixture was further refluxed for 12–15 h (evolution of H_2 gas was observed but not tested). After the usual working up, as it is described in the general procedure, and crystallization from the proper solvent the phosphonates **16a–16c** were isolated.

Dimethyl 5,7-di-tert-butylbenzo[d]isoxazol-3-ylphosphonate (**16a**, $C_{17}H_{26}NO_4P$)

Colorless crystals; m.p.: 141 °C (CH_2Cl_2); yield: 737 mg (68 %); IR (KBr): $\bar{\nu}$ = 1,262 (P=O), 1,180 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.34, 1.57 [2 s, 2 × 9H, 2(Me_3C)], 3.88 (d, $^3J_{P-H}$ = 12.6 Hz, 6H, $(MeO)_2$P), 6.33 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.97 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 153.5, 143.4, 135.2, 127.8, 123.2, 119.6 (C–Ar), 134.2 (d, $^1J_{P-C}$ = 172 Hz, C–P), 52.8 (d, $^2J_{P-C}$ = 14.8 Hz, $(MeO)_2$P), 36.8, 34.5 (2$C$$Me_3$), 31.4, 29.6 (2 Me_3C) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 26.2 ppm; MS (EI, 70 eV): *m/z* (%) = 339 (42) [M^+], 230 (100) [M^+-109, $(P(O)(OMe)_2)$], 191 (73), 109 (65), 77 (80).

Diethyl 5,7-di-tert-butylbenzo[d]isoxazol-3-ylphosphonate (**16b**, $C_{19}H_{30}NO_4P$)

Colorless crystals; m.p.: 127 °C (cyclohexane); yield: 763 mg (65 %); IR (KBr): $\bar{\nu}$ = 1,275 (P=O), 1,155 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.31 (dt, J_{H-H} = 6.8 Hz, $^4J_{P-H}$ = 5.8 Hz, 6H, $(MeCO)_2$P), 1.35, 1.53 [2 s, 2 × 9H, 2(Me_3C)], 4.24 (dq, J_{H-H} = 6.8, $^3J_{P-H}$ = 5.8 Hz, 4H, $(H_2CO)_2$P), 6.26 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.87 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 153.0, 143.7, 135.8, 128.2, 122.7, 118.9 (C–Ar), 135.9 (d, $^1J_{P-C}$ = 168 Hz, C–P), 62.2 [d, $^2J_{P-C}$ = 14.8 Hz, $(CH_2O)_2$P)], 36.2, 34.5 (2$C$$Me_3$), 30.8, 29.4 (2$Me_3$C), 15.8 (d, $^3J_{P-C}$ = 6.8 Hz, (MeCO)$_2$P) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 25.7 ppm; MS (EI, 70 eV): *m/z* (%) = 367 (45) [M^+], 230 (100) [M^+-137, $(P(O)(OEt)_2)$], 191 (70), 138 (64), 77 (84).

Diisopropyl 5,7-di-tert-butylbenzo[d]isoxazol-3-ylphosphonate (**16c**, $C_{21}H_{34}NO_4P$)

Colorless crystals, m.p.: 155 °C ($CHCl_3$); yield: 884 mg (70 %); IR (KBr): $\bar{\nu}$ = 1,265 (P=O), 1,165 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.21 (dd, J_{H-H} = 6.6 Hz, $^4J_{P-H}$ = 3.8 Hz, 2 × 6H, (Me_2CHO)$_2$P), 1.35, 1.53 [2 s, 2 × 9H, 2(Me_3C)], 4.43 (dsept, J_{H-H} = 6.6, $^3J_{P-H}$ = 7.2 Hz, 2H, (HC(Me)$_2$O)$_2$P), 6.31 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 6.97 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 154.5, 142.4, 134.8, 126.8, 121.2, 117.8 (C–Ar), 137.5 (d, $^1J_{P-C}$ = 192 Hz, C–P), 70.8 (d, $^2J_{P-C}$ = 8.5 Hz, $(CHO)_2$P), 37.2, 35.0 (2$C$$Me_3$), 32.4, 28.6 (2$Me_3$C), 23.4 (d, $^3J_{P-C}$ = 7.9 Hz, Me_2CO) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 26.5 ppm; MS (EI, 70 eV): *m/z* (%) = 395 (48) [M^+], 230 (100) [M^+-165, $(P(O)(OC_3H_7)_2)$], 191 (66), 165 (58), 77 (87).

*Synthesis of **18a** and **18b** by reaction of the oxime **14** with hexaalkyltriamidophosphites **9a** and **9b***

The aminophosphine **9a** (R'=Me) or **9b** (R'=Et) (3.3 mmol) in 4 cm^3 dry THF was added dropwise to 0.8 g **14** (3.2 mmol) in 15 cm^3 of the same solvent, and the reaction mixture was stirred at rt for 10 h (TLC). The solvent was evaporated under reduced pressure; the residue was collected, washed with light petroleum, and crystallized from the proper solvent to give compounds **18a** and **18b**.

5,7-Di-tert-butyl-2-(dimethylamino)benzo[d][1,2]oxaphosphol-3(2H)-oxime (**18a**, $C_{17}H_{27}N_2O_2P$)

Yellow crystals; m.p.: 214 °C (EtOH); yield: 773 mg (75 %); IR (KBr): $\bar{\nu}$ = 3,335 (NOH), 1,320, 863 (P–NMe_2) cm^{-1}; ^{1}H NMR (500.7 MHz, DMSO-d_6): δ = 1.25, 1.37 [2 s, 2 × 9H, 2(Me_3C)], 3.23 (d, $^3J_{P-H}$ = 10.4 Hz, 6H, Me_2N–P), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 10.55 (br s, 1H, HON) ppm; ^{13}C NMR (125.4 MHz, DMSO-d_6): δ = 150.9, 140.4, 137.6, 128.9, 126.2, 122.5 (C–Ar), 143.6 (d,

$^{1}J_{P-C}$ = 166.3 Hz, C–P), 37.5 (d, $^{2}J_{P-C}$ = 22.2 Hz, Me_2N–P), 34.9, 34.4 (2CMe_3), 31.4, 30.6 (2Me_3C) ppm; ^{31}P NMR (200.7 MHz, DMSO-d_6): δ = 123.6 ppm; MS (EI, 70 eV): *m/z* (%) = 322 (14) [M^+], 321 (18) [M^+-1], 291 (48) [M^+-31, NOH], 216 (100) [M^+-106, (NOH + $PNMe_2$)], 77 (83).

5,7-Di-tert-butyl-2-(diethylamino)benzo[d][1,2]oxaphosphol-3(2H)-oxime (**18b**, $C_{19}H_{31}N_2O_2P$)
Yellow crystals; m.p.: 188 °C (EtOH); yield: 873 mg (78 %); IR (KBr): $\bar{\nu}$ = 3,345 (NOH), 1,317, 874 (P–NEt_2) cm^{-1}; ^{1}H NMR (500.7 MHz, DMSO-d_6): δ = 0.99 (dt, J_{H-H} = 6.4 Hz, $^{4}J_{P-H}$ = 4.2 Hz, 6H, Me_2CN–P), 1.25, 1.37 [2 s, 2 × 9H, 2(Me_3C)], 3.62 (q, $^{3}J_{P-H}$ = 6.4 Hz, 4H, H_2CN–P), 6.41 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 10.82 (br s, 1H, HON) ppm; ^{13}C NMR (125.4 MHz, DMSO-d_6): δ = 152.8, 143.4, 137.2, 128.5, 125.2, 122.3 (C–Ar), 146.3 (d, $^{1}J_{P-C}$ = 178 Hz, C–P), 41.4 (d, $^{2}J_{P-C}$ = 19.7 Hz, $(CH_2)_2$N–P), 35.2, 32.4 (2CMe_3), 30.9, 28.6 (2Me_3C), 15.6 (d, $^{3}J_{P-C}$ = 8.8 Hz, Me_2N–P) ppm; ^{31}P NMR (200.7 MHz, DMSO-d_6): δ = 120.5 ppm; MS (EI, 70 eV): *m/z* (%) = 350 (18) [M^+], 349 (28) [M^+-1], 319 (54) [M^+-31, NOH], 216 (100) [M^+-134, (NOH + $PNEt_2$)], 77 (80).

*Synthesis of **19a** and **19b** by oxidation of **18a** and **18b***

When the compounds **18a**, **18b** were treated with H_2O_2 in THF solution at rt, the amidates **19a**, **19b** were formed after 1 h.

5,7-Di-tert-butyl-2-(dimethylamino)benzo[d][1,2]oxaphosphone-3(2H)-oxime (**19a**, $C_{17}H_{27}N_2O_3P$)
Yellow crystals; m.p.: 223 °C (EtOH); yield: 811 mg (75 %); IR (KBr): $\bar{\nu}$ = 3,337 (NOH), 1,256 (P=O), 1,328, 855 (P–NMe_2) cm^{-1}; ^{1}H NMR (500.7 MHz, DMSO-d_6): δ = 1.25, 1.37 [2 s, 2 × 9H, 2(Me_3C)], 3.11 (d, $^{3}J_{P-H}$ = 10.4 Hz, 6H, Me_2N–P), 6.41 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.99 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 10.40 (br s, 1H, HON) ppm; ^{31}P NMR (200.7 MHz, DMSO-d_6): δ = 12.7 ppm; MS (EI, 70 eV): *m/z* (%) = 338 (21) [M^+], 337 (44) [M^+-1], 307 (23) [M^+-31, NOH], 77 (86).

5,7-Di-tert-butyl-2-(diethylamino)benzo[d][1,2]oxaphosphone-3(2H)-oxime (**19b**, $C_{19}H_{31}N_2O_2P$)
Yellow crystals; m.p.: 198 °C (EtOH); yield: 874 mg (78 %); IR (KBr): $\bar{\nu}$ = 3,340 (NOH), 1,252 (P=O), 1,330, 872 (P–NEt_2) cm^{-1}; ^{1}H NMR (500.7 MHz, DMSO-d_6): δ = 1.11 (dt, J_{H-H} = 6.4 Hz, $^{4}J_{P-H}$ = 4.2 Hz, 6H, Me_2CN–P), 1.25, 1.37 [2 s, 2 × 9H, 2(Me_3C)], 3.19 (q, $^{3}J_{P-H}$ = 6.8 Hz, 4H, H_2C–N–P), 6.41 (d, J_{H-H} = 4.2 Hz, 1H, H(4)-Ar), 6.93 (d, J_{H-H} = 4.2 Hz, 1H, H(6)-Ar), 10.40 (br s, 1H, NOH) ppm; ^{31}P NMR (200.7 MHz, DMSO-d_6): δ = 14.2 ppm; MS (EI, 70 eV): *m/z* (%) = 366 (18) [M^+], 365 (34) [M^+-1], 335 (40) [M^+-31, NOH], 77 (84).

Antitumor activity screening

Antitumor potency of the new phosphorus compounds **6a**-**6e**, **12a**, **12b**, **16a**, **16b**, **19a**, and **19b** in addition to the substrates **7a** and **14** was tested at a dose of 10 μM utilizing 17 different human tumor cell lines, representing breast and prostate cancer and melanoma using adriamycin as a reference standard according to the reported methods [23, 24]. The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5 % fetal bovine serum and 2 mm^3 glutamine.

Percentage growth inhibition (*GI*) is calculated as [(*Ti*−*Tz*)/(*C*−*Tz*)] × 100 for concentration for which *Ti* ≥ *Tz* and [(*Ti*−*Tz*)/*Tz*)] × 100 for concentration for which *Ti* < *Tz*. Growth inhibition of 50 % (GI_{50}) is calculated from [(*Ti*−*Tz*)/(*C*−*Tz*)] × 100 = 50, which is the tested compound concentration resulting in a 50 % reduction in the net protein increase (as measured in SRB staining) in control cells during the compound incubation. Table 1 displays the observed percentage growth of each cell line treated with a certain tested compound relative to control cell line experiments.

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