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ORIGINAL PAPER

Multicomponent reactions in a one-pot synthesis of α-aminophosphonates and α-aminophosphonic diamides with anti-inflammatory properties

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Abstract Schiff-base Kabachnik–Fields intermediates generated in situ from substituted pyrazole-4-carbaldehyde and 2-aminothiophene derivatives were trapped by dialkyl phosphites to produce the corresponding α-aminophosphonates in moderate yields. The latter products could be also obtained in excellent yields (≥75%) by directly applying the phosphorus reagents to the Schiff bases. Next, dialkyl phosphites were applied to one of the parent aldehydes to give the expected α-hydroxyphosphonate derivatives. Applying hexaalkyl triamidophosphites to the Schiff base in ethanol afforded methylphosphonic diamide derivatives, whereas ring attack on the pyrazole ring occurred when the same amidophosphites were applied to the parent aldehyde to give the corresponding alkylidenephosphorane ylides in an open structure form in good yields. Some of the new compounds exhibited considerable anti-inflammatory properties.

Keywords α-Aminophosphonates · α-Hydroxyphosphonates · Schiff base · Kabachnik–Fields reactions · Anti-inflammatory

Introduction

The chemistry of substituted heterocyclic phosphor esters has attracted a lot of attention due to their unique structural features and diverse applications in biological systems [1]. α-Aminophosphonates in particular constitute an important class of compounds that attract medicinal chemists because of their wide uses in drug development; for example, α-aminophosphonates can serve as both hyperglycemic and hypoglycemic agents in different concentrations [2, 3], antitumor agents [4, 5], pharmacogenic agents [6], and as inhibitors of serine hydrolases [7]. As part of our continued interest in the development of new synthesis routes to heterocycle-based mono- and bisphosphonates [8–14] we now report on multicomponent reactions (MCRs), with three or more reactants combined in a one-pot procedure to give a single product. Accordingly, efficient syntheses of (*E*)-2-[[3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-4-yl]-methyleneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile-based phosphor derivatives from 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile, 2-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-2-carbaldehyde, and the phosphorus reagents trialkyl phosphites (TAPs), dialkyl phosphites (DAPs) or hexaalkyl triamidophosphites could smoothly be achieved as previously reported [15–18] using 10% $FeCl_3$ in tetrahydrofuran (THF) solution to facilitate the Mannich-type reaction of the aldehyde, the amine, and the phosphorus reagent. Selected products were tested, and the toxicity of the most promising new anti-inflammatory active compounds was further evaluated.

Results and discussion

The reactions were carried out by mixing the amine **3** with the aldehyde **1** in THF solution containing 10% $FeCl_3$. TAPs **2a**–**2c** were then added at r.t., followed by heating under reflux for ~6 h to give the α-aminophosphonates **4a**–**4c**.

The structures of compounds **4a**–**4c** were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. The ^1H and

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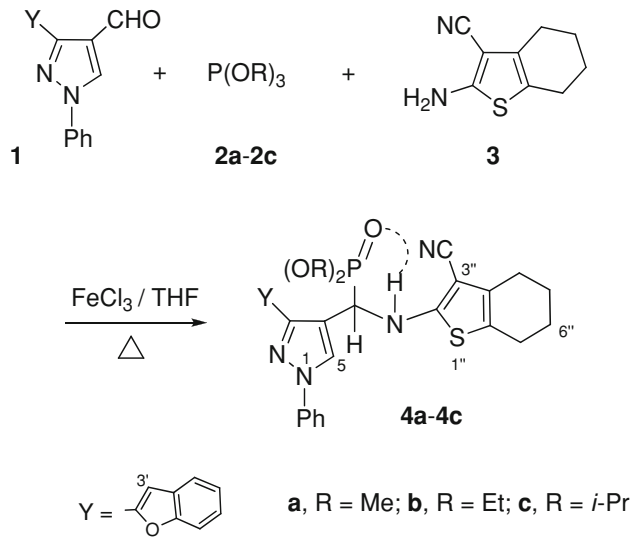
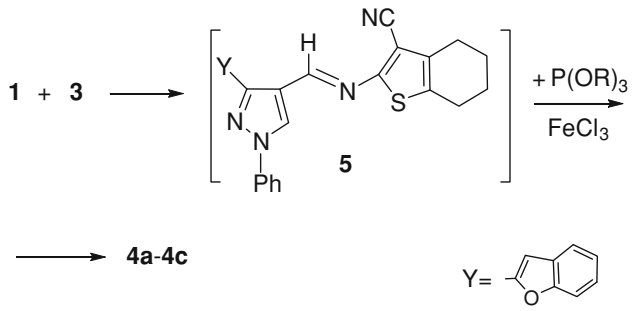
^{13}C nuclear magnetic resonance (NMR) spectroscopic data as well as infrared (IR) spectra were also in agreement with the proposed structures. The configuration of **4** was assigned as (*E*) based on the ^{1}H NMR spectrum of **4a**, which exhibited a doublet of doublets centered at $\delta = 5.52$ ppm ($J_{H–H} = 8.8$, $^{2}J_{P–H} = 17.5$ Hz) ascribed to the proton at the exocyclic asymmetric (chiral) carbon and confirming the presence of CH and NH in an (*E*) arrangement. Thus, nuclear Overhauser effect (NOE) experiments showed the lack of NOE effect between H-5 [or C(3″)CN, $\delta_c = 94.3$ ppm] and NH in **4a**. This can be explained by preferred formation of an intramolecular hydrogen bond between the NH proton and the phosphonate oxygen atom. Therefore H-5 is too far from NH to give an observable NOE. The NOE experiments also showed that the NH proton is localized at the nitrogen of NH group and there is no tautomerism observed in the solution (Scheme 1).

A plausible explanation for the mechanism of the reaction is proposed in Scheme 2. According to the Kabachnik–Fields reaction [19, 20], the first step may involve condensation between the aldehyde and the amine in the presence of $FeCl_3$ and formation of the intermediate Schiff base **5**, followed by addition of the phosphorus reagent **2** to produce **4a–4c**. The formation of dialkyl and not trialkyl adducts is acceptable since, in the presence of acidic medium ($FeCl_3$), TAPs are hydrolyzed to their DAP counterparts.

In favor of this mechanism, compounds **4a–4c** were independently synthesized in higher yield (~75%) and characterized (Scheme 3). Thus, **4a–4c** could be obtained by treating (*E*)-2-[[3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-4-yl]methyleneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**5**) in THF/$FeCl_3$ (10%) solution with DAPs **6a–6c**. The required new Schiff base **5** was initially



Scheme 1

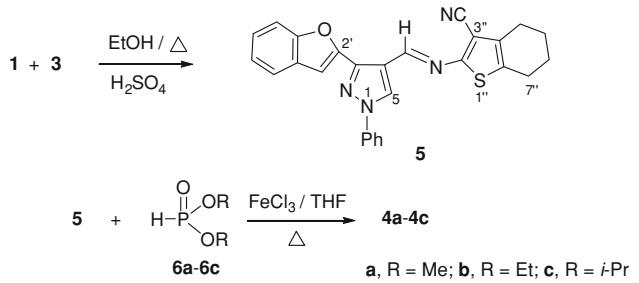


Scheme 2

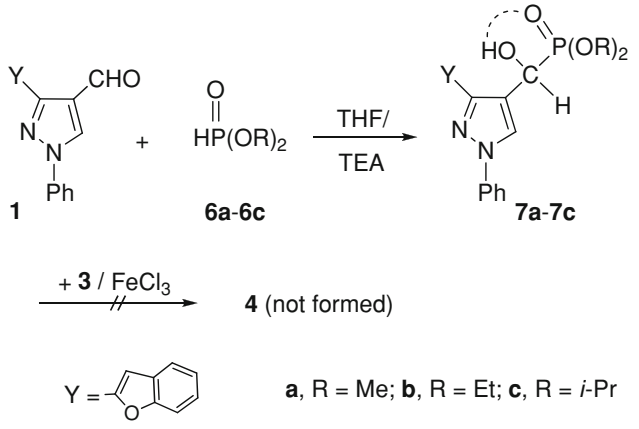
prepared, for the first time, from condensation of aldehyde **1** with amine **3** in the presence of a catalytic amount of conc. H_2SO_4.

On the other hand, when we allowed α-hydroxyphosphonates **7a–7c**, initially obtained via the Pudovik reaction of aldehyde **1** with dialkyl phosphites **6a–6c** in the presence of triethylamine (TEA), to condense with amine **3**, this did not lead to the products **4a–4c**, but the phosphonates **7a–7c** were isolated and identified (Scheme 4).

The investigation was next extended to obtain more substituted heterocyclic phosphor derivatives via applying hexaalkyl triamidophosphites to the anil **5** and the aldehyde **1**. When the anil **5** was treated with tris(dialkylamino)phosphines **8a** or **8b** (2 molar amounts) in boiling



Scheme 3

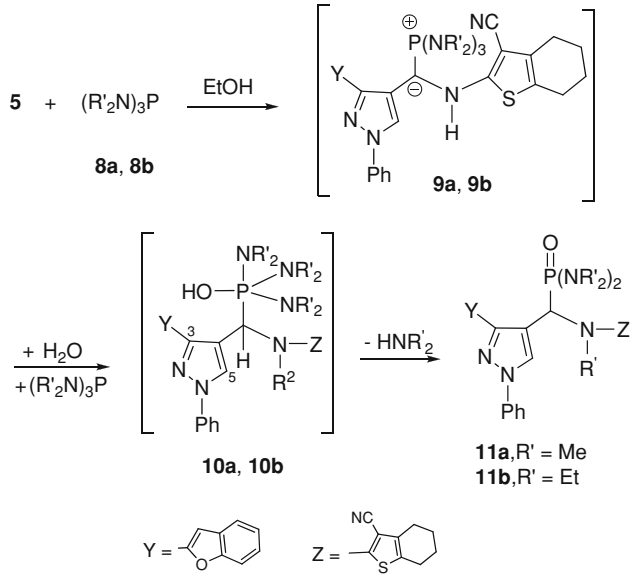


Scheme 4

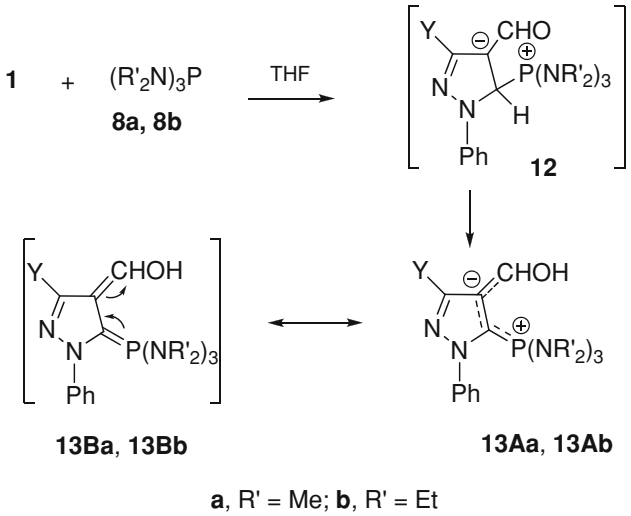
THF (or toluene), the substrates remained practically unchanged, even after 2 days. Changing the reaction medium using a polar solvent (e.g., EtOH), methyl-*N*,*N*,*N*,*N*-tetraalkylphosphinic diamide derivatives **11a** and **11b** were isolated in ~60% yield. Satisfactory elementary analyses and molecular weight determinations (mass spectrometry, MS) confirmed structure **11**. ^{31}P NMR signals of **11a** and **11b** were found at $\delta \approx 33$ ppm. The ^{1}H NMR spectrum ($CDCl_3$) of **11a** showed, among others, the NMe protons at $\delta = 3.23$ ppm and two doublets ($^{3}J_{P-H} = 10.4$ Hz) centered at $\delta = 2.42, 2.73$ ppm assigned to 12H of the two magnetically inequivalent dimethylamino groups connected to phosphorus. The ^{13}C NMR ($CDCl_3$) spectrum of **11a** displayed the N–CH–P signal at $\delta = 50.6$ ppm (d, $^{1}J_{P-C} = 178.8$ Hz).

Obviously, compounds **11a** and **11b** were formed through an initial addition of the aminophosphine **8** to **5** giving rise to the phosphonium dipolar ion intermediate **9**. Stabilization of **9** was attained by its reaction with fortuitous water to give the intermediates **10**, followed by *N*-alkylation and an extrusion of dialkyl amine moiety leading to **11a** and **11b** (Scheme 5). Considering the *N*-alkylation of compound **11** in Scheme 5 by hexaalkyl triamidophosphites, an analogous process has been observed on similar occasions [21, 22].

Conversely, the reactions of **8a** and **8b** with the aldehyde **1** proceeded smoothly in THF after warming (at 40 °C) for ~3 h. The resulting crystalline 1:1 adducts were formulated as trisaminophosphonium dipolar ion structure **13A** for the following reasons: (1) the ^{31}P NMR spectrum of these adducts has one signal around $\delta \approx 26$ ppm, which indicates an open dipolar ion structure



Scheme 5



Scheme 6

with quadruply connected phosphorus [23]; (2) the ^{1}H NMR spectrum of **13Aa** showed a doublet centered at 2.54 ppm ($^{3}J_{P-H} = 10.8$ Hz) due to 18H of the three magnetically equivalent dimethylamino groups. Nucleophilic attack of the phosphines **8** at C-5 of the α,β-unsaturated system in the aldehyde **1** afforded the *C*-phosphonium betaine **12**, which followed by further hydrogen migration to give the more stable ylide ↔ enol structure **13A** ↔ **13B** (Scheme 6). Analogous ring attack accompanied by proton shifts has been observed in the reactions of triphenylphosphine and hexaalkyl triamidophosphites with *p*-quinones [23, 24] and with maleic anhydride [25].

Anti-inflammatory activity screening

The in vivo anti-inflammatory activity of the selected synthesized substituted heterocyclic phosphor derivatives **4a**–**4c**, **7a**–**7c**, **11a**, and **11b** was determined. The substrates **1** and **5** were also tested to reflect the effect of introducing the phosphor moiety. Following the standard procedure [26], mice were surgically implanted with acute carrageenin-induced paw edema (CPE). The anti-inflammatory property of the examined compounds at 50 mg/kg body weight was measured at successive time intervals (1, 2, and 4 h after carrageenin injection) and compared with that of indomethacin (**A**) at the same dose as a reference standard. However, when the rats were reused, carrageenin injection was given into the right hind paw. The results are shown in Table 1.

The recorded data in Table 1 show that, other than the substrates **1** and **5**, six of eight of the tested new compounds had good anti-inflammatory properties when compared with the standard **A**, without toxic side-effects. The phosphonic diamides **11a** and **11b** possess maximum

Table 1 Anti-inflammatory activity of new products **4a–4c**, **7a–7c**, **11a**, **11b**, **1**, and **5** in acute carrageenin-induced paw edema in rats

Cmpd	Mean swelling[a] volume/cm^3 (percentage inhibition of edema)			Potency[d] (%)
	1 h	2 h	4 h	
Control	0.586 ± 0.192[c] (00.0)	0.622 ± 0.067[c] (00.0)	0.726 ± 0.058[c] (00.0)	–
A[b]	0.284 ± 0.016[c] (51.5)	0.368 ± 0.021[c] (40.8)	0.402 ± 0.024[c] (44.6)	100
4a	0.278 ± 0.020[c] (52.5)	0.362 ± 0.026[c] (41.8)	0.454 ± 0.018[c] (37.5)	84.1
4b	0.316 ± 0.022[c] (46.0)	0.372 ± 0.064[c] (40.1)	0.467 ± 0.036[c] (35.7)	80.0
4c	0.375 ± 0.041[c] (36.0)	0.512 ± 0.073[c] (17.6)	0.675 ± 0.028[c] (7)	15.7
7a	0.342 ± 0.033[c] (41.6)	0.388 ± 0.042[c] (37.6)	0.432 ± 0.044[c] (40.5)	90.8
7c	0.356 ± 0.036[c] (39.2)	0.378 ± 0.072[c] (39.2)	0.440 ± 0.011[c] (39.4)	88.3
7c	0.463 ± 0.035[c] (20.9)	0.570 ± 0.092[c] (8.3)	0.624 ± 0.046[c] (14.0)	31.4
11a	0.232 ± 0.021[c] (60.4)	0.305 ± 0.072[c] (50.9)	0.372 ± 0.056[c] (48.8)	109.4
11b	0.245 ± 0.028[c] (58.1)	0.311 ± 0.047[c] (50.0)	0.354 ± 0.066[c] (51.2)	114.8
1	0.555 ± 0.036[c] (5.2)	0.585 ± 0.032[c] (5.9)	0.678 ± 0.079[c] (6.6)	14.8
5	0.565 ± 0.052[c] (3.5)	0.612 ± 0.077[c] (1.6)	0.688 ± 0.053[c] (5.2)	11.6

[a] Data are means of two independent determinations at least, and the deviation in absorbance values was less than 10%

[b] **A** = indomethacin (used as a reference standard); each value represents the mean ± of two independent experiments with six animals in each group

[c] *SEM* standard error of the mean: statistical significance of results was established using Student's test relative to the standard at $P < 0.05$

[d] Potency was expressed as percentage edema inhibition of the tested compounds relative to percentage edema inhibition of **A** at 4 h effect

inhibitory effect at all detected time intervals when compared with the standard group. Nevertheless, the isopropyl phosphonate derivatives **4c** and **7c** showed poor effects as anti-inflammatory agents. Other compounds, i.e., **4a**, **4b**, **7a**, and **7b**, displayed good to moderate effects on inhibitory properties at all intervals.

In acute toxicity experiments, the in vivo promising compounds had a 50% lethal dose >0.3 mmol/kg body weight. Thus, toxicological studies of **11a** and **11b** were performed using the LD_{50} standard method in mice at 500, 750, and 1,000 mg/kg (body weight), i.e., 10–20-fold the used anti-inflammatory effective dose. However, no toxic symptoms or mortality were observed 24 h after administration, corroborating the safe behavior of the used doses.

Conclusions

We report a one-pot synthesis of α-aminophosphonates via Kabachnik–Fields reaction, starting from substituted amines and aldehyde derivatives in the presence of phosphorus reagents (trialkyl phosphites or dialkyl phosphites). The reactions proceeded smoothly using 10% $FeCl_3$ in THF solution to facilitate the Mannich-type reaction. The present procedure is performed under neutral conditions, and the starting material can be used without any activation or modification. Finally, the produced α-aminophosphonates, α-hydroxyphosphonates, and phosphine diamides have potential synthetic and pharmaceutical interest.

Experimental

Melting points were measured on an Electrothermal melting point apparatus. IR spectra were recorded on a PerkinElmer 317 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. ^{1}H and ^{13}C NMR spectra were measured using $SiMe_4$ as an internal reference, whereas ^{31}P NMR spectra were recorded relative to external H_3PO_4 (85%). Mass spectrometry was performed on a JEOL JMS-AX 500 spectrometer. The appropriate precautions in handling moisture-sensitive compounds were considered. Solvents were dried by standard techniques. Thin-layer chromatography (TLC) used Merck 0.2 mm silica gel 60 F254 anal aluminum plates. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt; their values agreed favorably with the calculated ones. All international principles and local regulations concerning care and use of laboratory animals were considered during the pharmacological screening.

*General procedure for the one-pot preparation of **4a–4c***

A stirred mixture of 0.8 g 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**, 2.7 mmol), 0.49 g 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**3**, 2.7 mmol), and trimethyl (**2a**), triethyl (**2b**) or

triisopropyl phosphite (**2c**) (3.2 mmol) in 10 cm^3 tetrahydrofuran (THF) containing 10% $FeCl_3$ (or 2 cm^3 glacial AcOH; best results with $FeCl_3$) was heated under reflux for 4–6 h. After completion of the reaction (TLC), 10 cm^3 AcOEt was added to the mixture. The organic phase was separated, washed with 20 cm^3 distilled water, and dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum, and the residue was crystallized from the proper solvent to give compounds **4a**–**4c**.

Products **4a**–**4c** were equally obtained, in almost the same yields, when dimethyl (**6a**), diethyl (**6b**) or diisopropyl phosphite (**6c**) replaced the trialkyl phosphite counterpart in the above reactions, whereas experimental conditions, stoichiometric amounts, and work-up were exclusively used.

Dimethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl]-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl-amino)methylphosphonate (**4a**, $C_{29}H_{27}N_4O_4PS$)

Pale-yellow crystals; yield 548 mg (58%); m.p.: 198–200 °C (EtOH); IR (KBr): $\bar{\nu}$ = 3,340 (NH), 2,195 (CN), 1,221 (P = O), 1,045 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.81, 2.88 (2 m, 8H, hexene), 3.65, 3.82 (2d, $^3J_{P–H}$ = 13.4 Hz, 2 × 3H, $(MeO)_2P$), 5.52 (dd, $J_{H–H}$ = 8.8, $^2J_{P–H}$ = 17.5 Hz, 1H, HC–P), 6.43 (br, 1H, NH), 7.23 (d, $J_{P–H}$ = 8.4 Hz, 1H, C-5-H), 7.34–7.77, 8.24 (m, 10H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 128.3 (d, $^3J_{P–C}$ = 9.6 Hz, C-3), 124.8 (d, $^3J_{P–C}$ = 8.6 Hz, C-5), 123.4 (d, $^2J_{P–C}$ = 14.2 Hz, C-4), 168.2 (d, $^3J_{P–C}$ = 11.6 Hz, C-2″), 152.8, 141.6, 130.3, 129.2, 127.4, 126.5, 119.0, 111.6 (C–Ar, C–Ph), 117.5 (CN), 94.3 (C-3″), 54.6 (d, $^2J_{P–C}$ = 7.8 Hz, $(MeO)_2P$), 53.4 (d, $^1J_{P–C}$ = 166.3 Hz, HC–P), 26.3, 26.1, 23.5, 21.7 (4″-, 5″-, 6″-, 7″-C-hexene) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 23.3 ppm; MS (EI, 70 eV): *m/z* (%) = 559 (11) [M^+ + 1], 558 (14) [M^+], 449 (55) [M^+–$P(O)(OCH_3)_2$], 421 (8) [M^+-(2H + CN + $P(O)(OCH_3)_2$)], 382 (100) [M^+-$C_9H_8N_2S$].

Diethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl]-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl-amino)methylphosphonate (**4b**, $C_{31}H_{31}N_4O_4PS$)

Pale-yellow crystals; yield 637 mg (64%); m.p.: 224–226 °C (AcOEt); IR (KBr): $\bar{\nu}$ = 3,339 (NH), 2,202 (CN), 1,223 (P = O), 1,029 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.12, 1.32 (2dt, $J_{H–H}$ = 6.6, $^4J_{P–H}$ = 4.5 Hz, 2 × 3H, $(MeCO)_2P$), 1.71, 2.44 (2 m, 8H, hexene), 4.23, 4.26 (2dq, $^3J_{P-H}$ = 10.8 Hz, 2 × 2H $(CH_2O)_2P$), 5.43 (dd, $J_{H–H}$ = 8.8, $^2J_{P–H}$ = 18.4 Hz, 1H, HC–P), 6.36 (br, 1H, NH), 7.23 (d, $J_{P–H}$ = 8.4 Hz, 1H, C-5-H), 7.27–7.78, 8.26 (m, 10H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 129.8 (d, $^3J_{P–C}$ = 10.6 Hz, C-3), 125.8 (d, $^3J_{P–C}$ = 8.6 Hz, C-5), 123.6 (d, $^2J_{P–C}$ = 14.2 Hz, C-4), 168.8 (d, $^3J_{P–C}$ = 10.8 Hz, C-2″), 152.8, 141.3, 130.7, 129.1, 129.4, 128.5, 127.5, 126.4, 119.6, 111.8 (C–Ar, C–Ph), 118.8 (CN), 93.4 (C-3″), 62.4 (d, $^2J_{P–C}$ = 8.7 Hz, $(CH_2O)_2P$), 56.4 (d, $^1J_{P–C}$ = 169.4 Hz, HC-P), 26.3, 26.1, 23.7, 21.5 (4″-, 5″-, 6″-, 7″-C-hexene), 16.6 (d, $^3J_{P–C}$ = 7.7 Hz, $(MeCO)_2P$) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 25.6 ppm; MS (EI, 70 eV): *m/z* (%) = 587 (28) [M^+ + 1], 586 (33) [M^+], 449 (62) [M^+-$P(O)(OC_2H_5)_2$], 421 (27) [M^+-(2H + CN + P(O) $(OC_2H_5)_2$)], 409 (100) [M^+-$C_9H_8N_2S$], 177 (34) [$C_9H_8N_2S$].

Diisopropyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl](3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl-amino)methylphosphonate (**4c**, $C_{33}H_{35}N_4O_4PS$)

Yellow crystals; yield 646 mg (62%); m.p.: 228–230 °C (AcOEt); IR (KBr): $\bar{\nu}$ = 3,383 (NH), 2,196 (CN), 1,235 (P=O), 1,011 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.11, 1.33 (2dd, $J_{H–H}$ = 6.6, $^4J_{P–H}$ = 5.8 Hz, 2 × 6H, $(Me_2CO)_2P$), 1.72, 2.43 (2 m, 8H, hexene), 4.62, 4.81 (2sept, $^3J_{P–H}$ = 12.4 Hz, 2 × 1H, $(CHO)_2P$), 5.32 (dd, $J_{H–H}$ = 8.8, $^2J_{P–H}$ = 18 Hz, 1H, HC-P), 5.63 (br, 1H, NH), 7.22 (d, $J_{P–H}$ = 8.4 Hz, 1H, C-5-H), 7.37–7.77, 8.24 (m, 10H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 129.6 (d, $^3J_{P–C}$ = 10.6 Hz, C-3), 124.8 (d, $^3J_{P–C}$ = 8.6 Hz, C-5), 123.4 (d, $^2J_{P–C}$ = 14.2 Hz, C-4), 168.4 (d, $^3J_{P–C}$ = 10.8 Hz, C-2″), 152.9, 141.7, 130.2, 129.5, 129.7, 128.3, 127.5, 126.6, 126.3, 119.1, 111.9 (C–Ar, C–Ph), 116.5 (CN), 94.0 (d, $^4J_{P–C}$ = 3.7 Hz, C-3″), 76.1 (d, $^2J_{P–C}$ = 9.8 Hz $(CHO)_2P$), 57.6 (d, $^1J_{P–C}$ = 164.4 Hz, HC–P), 26.4, 26.2, 23.5, 21.2 (4″-, 5″-, 6″-, 7″-C-hexene), 24.0 (d, $^3J_{P–C}$ = 8.2 Hz, $(Me_2CO)_2P$) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 27.3 ppm; MS (EI, 70 eV): *m/z* (%) = 616 (9) [M^+ + 2], 614 (15) [M^+], 529 (5), 449 (100) [M^+-$P(O)(OC_3H_7)_2$], 419 (96) [M^+-(2H + CN +P(O) $(OC_3H_7)_2$)], 438 (20) [M^+-$C_9H_8N_2S$], 177 (96) [$C_9H_8N_2S$].

(E)-2-[[3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl]methyleneamino]-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carbonitrile (**5**, $C_{27}H_{20}N_4OS$)

To a mixture of 5 g 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**, 17.4 mmol) and 3.1 g 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**3**, 17.4 mmol) in 50 cm^3 ethanol/dimethylformamide (DMF) (8:2 v/v) solution was added 0.5 cm^3 sulfuric acid. The reaction mixture was refluxed for 3 h. The product mixture was concentrated to its half, followed by filtration. The collected material was crystallized from ethanol to give the Schiff base **5** as yellow crystals. Yield 6.7 g (86%); m.p.: 182–184 °C (EtOH); IR (KBr): $\bar{\nu}$ = 2,210 (CN), 1,612 (C=N) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.74, 2.46 (2 m, 8H, hexene), 6.32 (s, 1H, HC, exocyclic), 7.27–7.97 (m, 11H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 162.2 (HC=N, exocyclic), 159.7, 152.8, 140.1, 137.7, 130.4, 128.7, 126.3, 125.2,

124.9, 119.1, 111.9 (C–Ar, C–Ph), 114.7 (CN), 104.0 (C-3), 28.4, 28.0, 23.4, 21.2 (4″-, 5″-, 6″-, 7″-C-hexene) ppm; MS (EI, 70 eV): *m/z* (%) = 449 (13) [M^++1], 448 (35) [M^+], 442 (25) [M^+-CN], 272 (15) [M^+-$C_9H_8N_2S$], 177 (26) [$C_9H_8N_2S$], 77 (100) [C_6H_5].

*Synthesis of **4a–4c** by reaction of **5** with dialkyl phosphites **6a–6c***

A mixture of 0.8 g anil **5** (1.8 mmol) and 2.5 mmol dimethyl (**6a**), diethyl (**6b**) or diisopropyl phosphite (**6c**) in 15 cm^3 THF containing 10% $FeCl_3$ (or 2 cm^3 glacial acetic acid) was heated under reflux for 2-4 h (TLC). The product mixture was extracted with 50 cm^3 AcOEt, washed with 20 cm^3 distilled water, and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum, and the residue was then crystallized from the proper solvent to give the corresponding phosphonate **4a–4c** in higher yields: **4a**: 690 mg (73%); **4b**: 747 mg (75%); **4c**: 730 mg (70%). Compounds **4a–4c** were characterized by m.p., mixed m.p., and comparable IR spectra with the material previously obtained.

*Pyrolysis of **4b***

Compound **4b** (0.3 g) was heated in a cold finger sublimator at 170–180 °C (bath temperature) under reduced pressure (13 mbar) for 30 min. The material that sublimed was collected (66 mg, ~72%), recrystallized from cyclohexane, and proved to be the Schiff base **5** (m.p., mixed m.p.). Diethyl phosphite was also detected in the receiver by the development of a violet color on addition of 3,5-dinitrobenzoic acid and in the presence of alkali [27].

*Synthesis of compounds **7a–7c** by reaction of 3-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**1**) with dialkyl phosphites **6a–6c***

A mixture of 0.8 g aldehyde **1** (2.7 mmol) and 3.5 mmol dimethyl (**6a**), diethyl (**6b**) or diisopropyl phosphite (**6c**) in THF was heated under reflux in the presence of a catalytic amount (0.05 cm^3) of triethylamine for 4–6 h (TLC). Excess of the volatile materials was removed under vacuum, and the residue was washed several times with light petroleum and crystallized from the proper solvent to give the corresponding phosphonates **7a–7c**.

Dimethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl] hydroxymethylphosphonate (**7a**, $C_{20}H_{19}N_2O_5P$)
Colorless crystals; yield 881 mg (82%); m.p.: 172–174 °C (MeCN); IR (KBr): $\bar{\nu}$ = 3,434 (OH), 1,257 (P=O), 1,080 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 3.46 (d, $^3J_{P–H}$ = 12.5 Hz, 6H, $(MeO)_2P$), 5.53 (dd, $J_{H–H}$ = 4.4, $^2J_{P–H}$ = 14.7 Hz, 1H, HC-P), 7.42 (s, 1H, C-5-H), 7.43–7.67, 8.41 (m, 10H, Ar–H), 12.4 (br, 1H, OH) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 129.6 (d, $^3J_{P-C}$ = 10.6 Hz, C-3), 124.8 (d, $^2J_{P–C}$ = 8.6 Hz, C-5), 123.4 (d, $^2J_{P–C}$ = 14.2 Hz, C-4), 152.4, 142.3, 141.6, 135.2, 129.8, 126.5, 125.4, 125.2, 119.0, 111.6, 109.3 (C–Ar, C–Ph), 57.4 (d, $^1J_{P-C}$ = 147.3 Hz, HC-P), 52.8 (d, $^2J_{P-C}$ = 7.8 Hz, $(MeO)_2P$) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 29.3 ppm; MS (EI, 70 eV): *m/z* (%) = 398 (8) [M^+], 288 (12) [M^+-$HOP(OCH_3)_2$], 271 [M^+-(OH + $HOP(OCH_3)_2$)], 109 (58) [$P(O)(OCH_3)_2$], 77 (100) [C_6H_5].

Diethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl]-hydroxymethylphosphonate (**7b**, $C_{22}H_{23}N_2O_5P$)
Colorless crystals; yield 920 mg (80%); m.p.: 138–140 °C (CH_2Cl_2); IR (KBr): $\bar{\nu}$ = 3,450 (OH), 1,253 (P = O), 1,060 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.16 (dt, $J_{H–H}$ = 6.6, $^4J_{P–H}$ = 5.4 Hz, 6H, $(MeCO)_2P$), 3.98 (q, $^3J_{P–H}$ = 10.8 Hz, 4H, CH_2O), 5.57 (d, $^2J_{P–H}$ = 22.6 Hz, 1H, HC–P), 7.23 (s, 1H, C-5-H), 7.27–7.82, 8.32 (m, 10H, Ar–H), 12.36 (br, 1H, OH) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 128.4 (d, $^3J_{P–C}$ = 8.4 Hz, C-3), 124.6 (d, $^3J_{P–C}$ = 11.6 Hz, C-5), 123.2 (d, $^2J_{P–C}$ = 13.6 Hz, C-4), 153.0, 142.1, 141.6, 130.3, 127.4, 126.5, 125.2, 119.0, 111.4, 109.7 (C–Ar, C–Ph), 65.2 (d, $^3J_{P–C}$ = 8.8 Hz, $(CH_2O)P$), 60.4 (d, $^1J_{P–C}$ = 144.8 Hz, HC–P), 16.4 (d, $^3J_{P–C}$ = 7.7 Hz, $(MeCO)_2P$) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 27.8 ppm; MS (EI, 70 eV): *m/z* (%) = 426 (25) [M^+], 289 (100) [M^+-$P(O)(OC_2H_5)_2$], 272 (18) [M^+-(OH + $P(O)(OC_2H_5)_2$)], 77 (94) [C_6H_5].

Diisopropyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl]hydroxymethylphosphonate (**7c**, $C_{24}H_{27}N_2O_5P$)
Straw-yellow crystals; yield 919 mg (75%); m.p.: 165–167 °C (MeCN); IR (KBr): $\bar{\nu}$ = 3,435 (OH), 1,235 (P=O), 1011 (P–O–C) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.23 (dd, $J_{H–H}$ = 6.6, $^4J_{P–H}$ = 5.6 Hz, 2 × 6H, $(Me_2CO)_2P$), 4.26 (sept, $^3J_{P–H}$ = 12.4 Hz, 2 × 1H, $(CHO)_2P$), 5.54 (d, $^2J_{P–H}$ = 21.2 Hz, 1H, HC–P), 7.21 (d, $^4J_{P–H}$ = 4.4 Hz, 1H, C-5-H), 7.37–7.77, 8.24 (m, 10H, Ar–H), 12.50 (br, 1H, OH) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 128.4 (d, $^3J_{P–C}$ = 8.4 Hz, C-3), 124.6 (d, $^3J_{P–C}$ = 11.6 Hz, C-5), 123.2 (d, $^2J_{P–C}$ = 13.6 Hz, C-4), 153.0, 142.1, 141.6, 130.3, 129.8, 127.4, 126.5, 125.2, 119.0, 111.4, 109.7 (C–Ar, C–Ph), 69.4 (d, $^2J_{P–C}$ = 11.6 Hz, $(CHO)_2P$), 62.4 (d, $^1J_{P–C}$ = 166.4 Hz, HC–P), 24.3 (d, $^3J_{P–C}$ = 5.8 Hz, $(Me_2CO)_2P$) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 29.7 ppm; MS (EI, 70 eV): *m/z* (%) = 454 (15) [M^+], 289 (100) [M^+-$P(O)(OC_3H_7)_2$], 272 (22) [M^+-(OH + $P(O)(OC_3H_7)_2$)], 77 (95) [C_6H_5].

*Synthesis of **11a** and **11b** by reaction of the Schiff base **5** with hexaalkyltriamidophosphites **8a** and **8b***

No reaction occurred when equimolar amounts of **5** and phosphine **8a** or **8b** were heated under reflux in THF (or benzene) even after 3 days, after which compound **5** was recovered practically unchanged in 88% yield. A stirred solution of 0.8 g **5** (2.7 mmol) and 4.1 mmol phosphine **8a** or **8b** in 25 cm^3 ethyl alcohol was boiled under reflux for 2 days (TLC). The volatile materials were evaporated under vacuum; the residue was collected, washed with light petroleum, and crystallized from the proper solvent to give compounds **11a** and **11b**.

N,N,N′,N′-Tetramethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl][N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-N-methylamino]methylphosphonic diamide (**11a**, $C_{32}H_{35}N_6O_2PS$)

Colorless crystals; yield 677 mg (68%); m.p.: 210–212 °C (EtOH); IR (KBr): $\bar{\nu}$ = 2,005 (CN), 1,251 (P=O), 1,320, 860 (P–N(Me_2)$_2$) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.83, 2.76 (2 m, 8H, hexene), 2.42, 2.73 (2d, $^3J_{P–H}$ = 10.4 Hz, 12H, (Me_2N)$_2$–P), 3.23 (2d, 3H, $^4J_{P–H}$ = 5.4 Hz, 3H, MeN), 4.78 (d, $^2J_{P–H}$ = 20.8 Hz, 1H, HC–P), 7.02 (d, $^4J_{P–H}$ = 4.6 Hz, 1H, HC-5), 7.34–7.77, 8.24 (m, 10H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 146.3 (d, $^3J_{P–C}$ = 9.6 Hz, C-2″), 152.5, 141.7, 140.4, 130.8, 129.8, 127.5, 126.4, 125.3, 124.4 (C–Ar, C–Ph), 121.8 (d, $^2J_{P–C}$ = 14.4 Hz, C-4), 120.7 (d, $^3J_{P–C}$ = 8.6 Hz, C-5), 119.3 (d, $^3J_{P–C}$ = 8.2 Hz, C-3), 117.8 (CN), 98.4 (C-3″), 50.6 (d, $^1J_{P–C}$ = 178.8 Hz, CH–P), 41.4 (d, $^3J_{P–C}$ = 6.6 Hz, MeN), 38.3 (d, $^2J_{P-C}$ = 27.4 Hz, Me_2N)$_2$P), 26.5, 25.1, 23.4, 21.7 (4″-, 5″-, 6″-, 7″-C-hexene) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 33.3 ppm; MS (EI, 70 eV): *m/z* (%) = 599 (11) [M^+ + 1], 598 (14) [M^+], 583 [M^+-Me], 448 (48) [M^+-(Me + P(O)(NMe_2)$_2$)], 422 (12) [M^+-(Me + CN + P(O)N-(Me_2)$_2$)], 407 (100) [M^+-(Me + $C_9H_8N_2S$)].

N,N,N′,N′-Tetraethyl [3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl][N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-N-ethylamino]methylphosphonic diamide (**11b**, $C_{37}H_{45}N_6O_2PS$)

Colorless crystals; yield 859 mg (72%); m.p.: 186–188 °C ($CHCl_3$); IR (KBr): $\bar{\nu}$ = 2,012 (CN), 1,255 (P=O), 1,323, 864 (P-($N(Et_2)_2$) cm^{-1}; ^{1}H NMR (500.7 MHz, $CDCl_3$): δ = 1.07, 1.13 (2dt, $J_{H–H}$ = 6.4, $^4J_{P–H}$ = 4.8 Hz, 12H, *Me*CNP), 1.47 (t, $J_{H–H}$ = 6.8 Hz, *Me*C–N), 1.74, 2.66 (2 m, 8H, hexene), 3.77 (q, $J_{H–H}$ = 6.8 Hz, 2H, MeCH_2N), 4.42–4.51 (m, 8H, MeCH_2NP), 4.80 (d, $^2J_{P–H}$ = 21.3 Hz, 1H, HC–P), 7.18 (d, $^3J_{P–H}$ = 13.2 Hz, HC-5), 7.32–7.77, 8.24 (m, 10H, Ar–H) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 146.5 (d, $^3J_{P–C}$ = 9.6 Hz, C-2″), 152.3, 141.8, 140.1, 129.7, 129.2, 128.5, 126.3, 125.6, 124.2 (C–Ar, C–Ph), 122.6 (d, $^2J_{P–C}$ = 14.5 Hz, C-4), 119.3 (d, $^3J_{P–C}$ = 8.2 Hz, C-3), 118.7 (d, $^3J_{P–C}$ = 9.4 Hz, C-5), 118.3 (CN), 98.5 (C-3″), 53.7 (d, $^1J_{P–C}$ = 178.6 Hz, CH-P), 46.6 (d, $^3J_{P–C}$ = 6.6 Hz, H_2CN), 39.4 (d, $^2J_{P–C}$ = 28.4 Hz, (H_2CN)P), 26.5, 25.1, 23.4, 21.2 (4″-, 5″-, 6″-, 7″-C-hexene), 14.2 (*Me*CN), 14.9 (*Me*CP) ppm; ^{31}P NMR (200.7 MHz, $CDCl_3$): δ = 34.6 ppm; MS (EI, 70 eV): *m/z* (%) = 669 (9) [M^+ + 1], 668 (7) [M^+], 639 (24) [M^+-Et], 463 (100) [M^+-(C_2H_5 + $C_9H_8N_2S$)], 407 (56).

*Synthesis of **13a** and **13b** by reaction of **1** with **8a** and **8b***

The phosphine **8a** or **8b** (4.1 mmol) in 4 cm^3 dry THF was added dropwise to 0.8 g aldehyde **1** (2.7 mmol) in 15 cm^3 dry THF. The reaction mixture was stirred at r.t. for 3 h, and then the reaction was completed by warming to 40 °C. The volatile materials were evaporated under vacuum; the residue was collected, washed with light petroleum, and crystallized from the proper solvent to give compounds **13a** and **13b**.

[5-(Benzofuran-2-yl)-2,4-dihydro-4-(hydroxymethylene)-2-phenyl-3H-pyrazol-3-ylidene]-N,N,N′,N′,N″,N″-hexamethyltriaminophosphine (**13a**, $C_{24}H_{30}N_5O_2P$)

Pale-yellow crystals; yield 775 mg (64%); m.p.: 144–146 °C (cyclohexane); IR (KBr): $\bar{\nu}$ = 3,425 (OH), 1,310, 860 (P[($N(Me_2)$]$_3$) cm^{-1}; ^{1}H NMR (500.4 MHz, $CDCl_3$): δ = 2.54 (d, $^3J_{P–H}$ = 10.8 Hz, 18H, (Me_2N)$_3$–P)], 5.05 (d, $^4J_{P–H}$ = 4.2 Hz, 1H, HC–C-4), 7.37–7.77, 8.24 (m, 10H, Ar–H), 8.87 (s, 1H, OH, exchang. with D_2O) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 149.5 (d, $^3J_{P–C}$ = 9.6 Hz, C-3), 152.4, 151.4, 147.3, 127.8, 125.6, 125.2, 124.6, 115.9, 111.6, 107.4 (C–Ar, C–Ph), 96. 5 (d, $^1J_{P–C}$ = 144 Hz, C-5-P), 89.6 (d, $^3J_{P–C}$ = 14.4 Hz, CHOH), 82.5 (d, $^2J_{P–C}$ = 14.6 Hz, C-4), 36.3 (d, $^2J_{P–C}$ = 24.8 Hz, Me_2N-P) ppm; ^{31}P NMR (200.5 MHz, $CDCl_3$): δ = 26.4 ppm; MS (EI, 70 eV): *m/z* (%) = 451 (>5) [M^+], 450 (>5) [M^+ − 1], 271 (100) [M^+-(OH + P(NMe_2)$_3$)].

[5-(Benzofuran-2-yl)-2,4-dihydro-4-(hydroxymethylene)-2-phenyl-3H-pyrazol-3-ylidene]-N,N,N′,N′,N″,N″-hexaethyltriaminophosphine (**13b**, $C_{30}H_{42}N_5O_2P$)

Pale-yellow crystals; yield 920 mg (68%); m.p.: 124–126 °C (cyclohexane); IR (KBr): $\bar{\nu}$ = 3,428 (OH), 1,318, 855 (P[($N(Me_2)$]$_3$) cm^{-1}; ^{1}H NMR (500.4 MHz, $CDCl_3$): δ = 0.88 (dt, $J_{P–H}$ = 6.8, $^4J_{P–H}$ = 4.4 Hz, 18H, (Me_2CN)$_3$–P), 3.22 (q, $^3J_{P–H}$ = 10.4 Hz, 12H, H_2C–N–P), 5.24 (d, $^4J_{P–H}$ = 5.4 Hz, 1H, HC–C-4), 7.28–7.87, 8.22 (m, 10H, Ar–H), 9.27 (s, 1H, OH, exchang. with D_2O) ppm; ^{13}C NMR (125.4 MHz, $CDCl_3$): δ = 149.8 (d, $^3J_{P–C}$ = 9.6 Hz, C-3), 153.7, 151.5, 147.6, 127.0, 125.9, 125.4, 124.1, 116.2, 111.7, 108.1 (C–Ar, C–Ph), 97.2 (d, $^1J_{P–C}$ = 144.5 Hz, C-5-P), 89.6 (d, $^3J_{P–C}$ = 10.4 Hz, CHOH), 81.3 (d, $^2J_{P–C}$ =

14.6 Hz, C-4), 39.4 (d, $^{2}J_{P-C} = 24.8$ Hz, Me*C*H_2N–P), 17.6 (d, $^{3}J_{P-C} = 11.6$ Hz, *Me*CN-P) ppm; ^{31}P NMR (200.5 MHz, $CDCl_3$): $\delta = 26.2$ ppm; MS (EI, 70 eV): *m*/*z* (%) = 535 (>5) [M^+], 534 (>5) [$M^+ - 1$], 271 (100) [M^+-(OH + $P(NEt_2)_3$)].

Anti-inflammatory activity experiments in vivo: carrageenin-induced edema

All tested compounds were dispersed in sterilized saline at concentration of 0.11 mmol/kg, stabilized by 0.05% Tween-80 (vehicle solution), and administered intraperitoneally (i.p.). Fisher 344 male and female rats (pregnant excluded) weighing 180–220 g were used. The animals were divided into 12 groups of six animals each, and housed under standard conditions. Indomethacin **A** was administered at 0.11 mmol/kg b.w. as a standard drug.

Acute anti-inflammatory activity [26] (Table 1) was measured after 1, 2, and 4 h by reduction of rat paw carrageenin edema, induced by injection of 0.1 cm^3 carrageenin 2% (K100, commercially available) in sterilized saline, intradermally into the right foot pad. The examined compounds were administered simultaneously. Control animals received only vehicle. Paw volumes were measured volumetrically after 3.5 h with plethysmometer 7150 (UGO BASILE, Italy) and compared with the initial hind paw volume of each rat to determine the edema volume. Data were collected, checked, revised, and analyzed. Quantitative variables from normal distribution were expressed as means ± standard error (SE). Significant difference between groups was tested by using one-way analysis of variance (ANOVA) followed by least significant difference (LSD) test (p).

Anti-inflammatory activity was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group:

$$\%\,\text{Inhibition of edema} = [(V_c - V_t)/V_c] \times 100,$$

where V_c and V_t are the volumes of edema for the control and compound-treated animal groups, respectively, while potency of the tested compounds was calculated relative to the indomethacin-treated group according to the following equation:

$$\text{Potency} = \frac{\text{Group\% edema inhibition of tested compound}}{\text{Group\% edema inhibition of indomethacin}}.$$

Toxicity of the evaluated phosphorus heterocycles

The LD_{50} determination of the most promising synthesized anti-inflammatory active agents (**11a** and **11b**) was determined by the standard known LD_{50} method in mice. Albino mice weighing 20–25 g were divided into six groups of eight mice each. Tested compounds (**11a** and **11b**) dissolved in the same vehicle solution at 500, 750, and 1,000 mg/kg (body weight) were administered intraperitoneally. The control groups were given buffer solution only. Toxic symptoms, mortality rates, and post mortem findings in each group were recorded 24 h post administration. LD_{50} values of the tested compounds were calculated according to the following formula:

$$LD_{50} = D_m - \Sigma(z \times d)/n,$$

where D_m is the largest dose which killed all animals, z is the mean of dead animals between two successive groups, d is a constant factor between two successive doses, n is the number of animals in each group, and Σ is the sum of ($z \times d$).

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