Synthesis and characterization of novel bis–(α–aminophosphonates) with terminal chromone moieties

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Abstract
The 1,2,4,3,5-triazadiphosphinanyl derivative **5** and bis–(α–aminophosphonate) derivatives **6** and **8a,b** bearing chromone moieties were synthesized by addition of diethyl phosphite to new condensation products that formed by condensation of 4-oxo-4*H*-chromene-3-carboxaldehyde (**1**) with phosphonic dihydrazide, 1,3-diaminopropane and 1,4-diaminobutane.

Keywords: Synthesis, bis–(α–aminophosphonates), chromone

Introduction

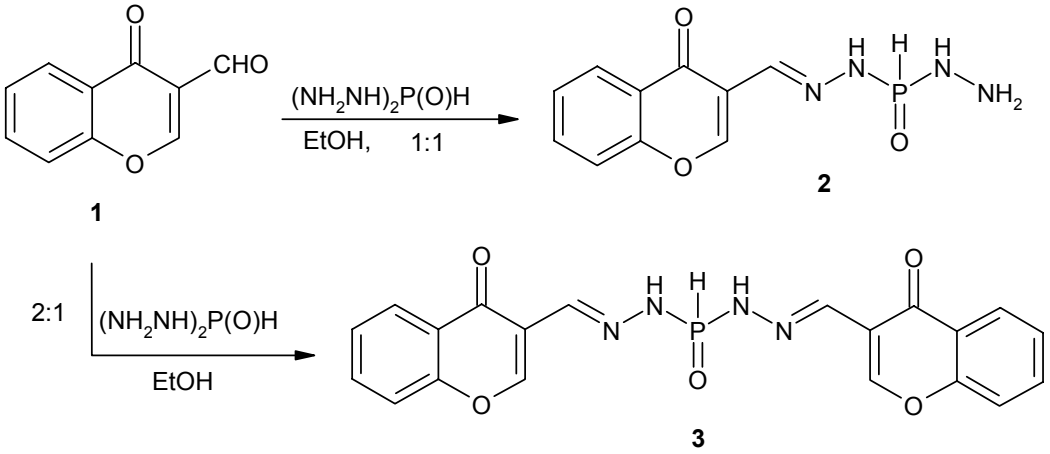
α–Aminophosphonates and α–aminophosphonic acids as analogues α–amino acids have received great interest due to their useful biological activities as antifungal agents,[1,2] herbicides,[3,4] and plant growth regulators.[2,5] 4-Oxo-4*H*-chromene derivatives display antimicrobial,[6,7] antifungal,[8,9] antiparasitic and immunosuppressant properties[10] and are important agents for dying fibres especially hair.[11] Incorporation of a chromone functionality into the α-aminophosphonate moiety may enhance the biological properties. However only few such compounds are known.[12,13]

In this article, we report the synthesis and characterization of some novel α-aminophosphonate derivatives bearing chromone moieties prepared by addition of diethyl phosphite to new condensation products between 4-oxo-4*H*-chromene-3-carboxaldehyde (**1**) and phosphonic dihydrazide, 1,3-diaminopropane and 1,4-diaminobutane.

Results and Discussion

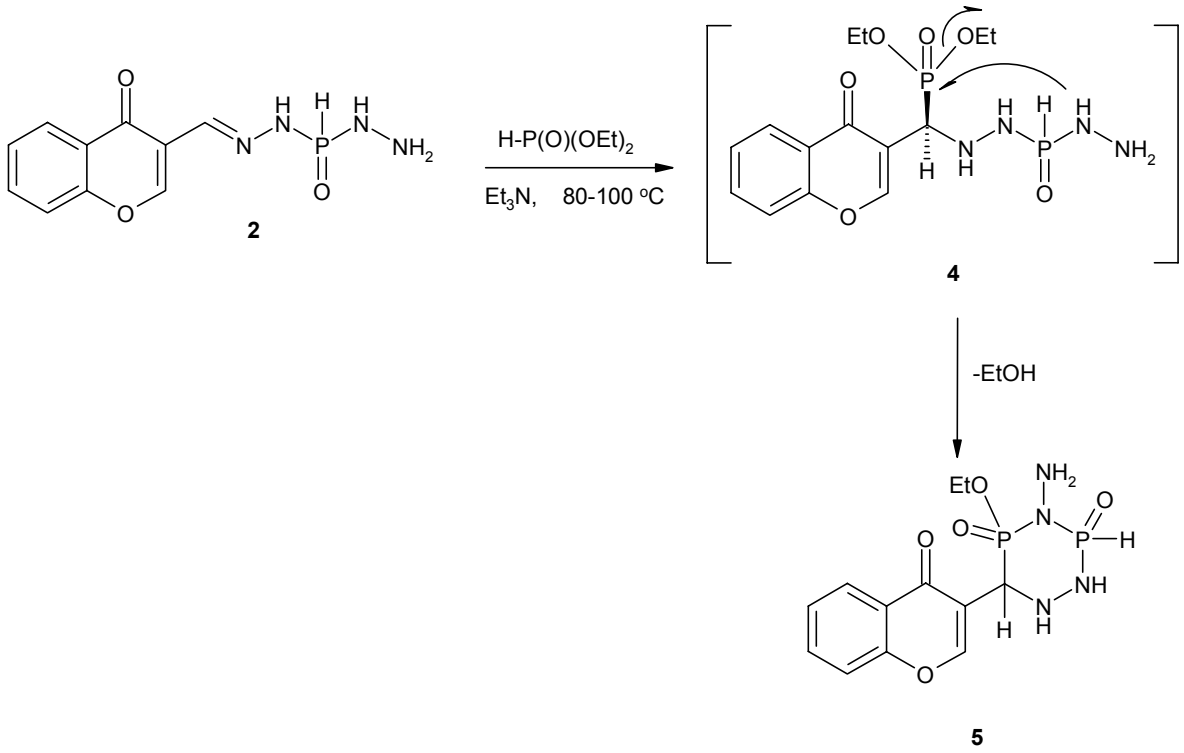
Condensation of 4-oxo-*4H*-chromene-3-carboxaldehyde (**1**) with phosphonic dihydrazide took place when heated in the ratio 1:1 and 2:1 in boiling ethanol (Scheme 1) to give new hydrazones such as *N`*-[(4-oxo-*4H*-chromen-3-yl)methylene]phosphonic dihydrazide (**2**) and N^1,N^5-bis[(4-

oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide (**3**), respectively, in good yields. The hydrazones were characterized by elemental analysis, IR and ^{1}H NMR spectrum (See Experimental Section).



Scheme 1

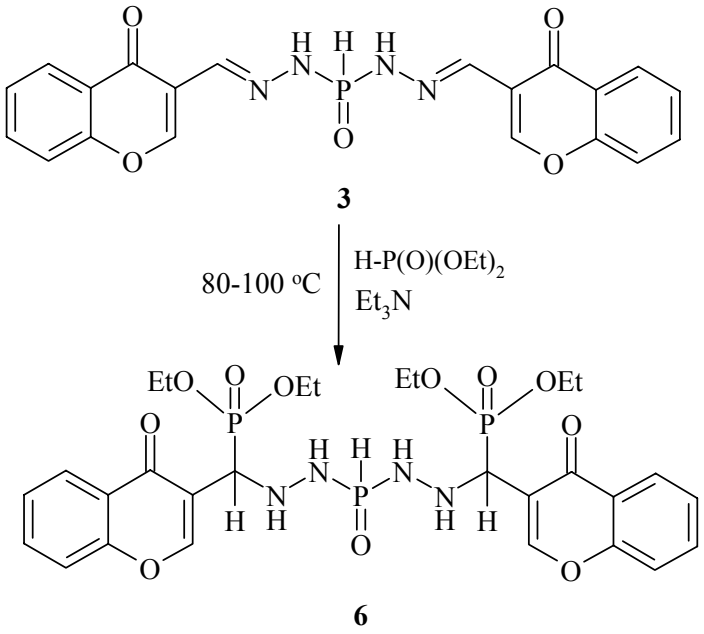
Addition of diethyl phosphite to the azomethine bond of the hydrazone **2** required heating at 80-100 ^{o}C and triethylamine as a catalyst and gave 3-(4-amino-5-ethoxy-3,5-dioxido-1,2,4,3,5-triazadiphosphinan-6-yl)-4*H*-chromen-4-one (**5**). Most likely, the addition leads to intermediate **4** (not isolated), which undergoes intramolecular cyclization *via* elimination of ethanol affording compound **5** (Scheme 2). The structure of compound **5** was established on the basis of elemental analysis and spectral data (IR, ^{1}H-, ^{13}C- and ^{31}P-NMR). The absorption bands at 1221, 1237 and 3084–3145 cm^{-1} observed in the IR spectrum were assigned to stretching frequencies of P=O, NH_2 and NH groups. The ^{1}H NMR spectrum showed the presence of one ethoxy group and a doublet at δ 3.95 ppm splitted by a H–P coupling of 24.5 Hz. The ^{13}C NMR spectrum showed signals for a CH_3CH_2O and CHP groups. The ^{31}P NMR spectrum displayed signals at δ 5.28 ppm (d, J=658 Hz) and 8.15 ppm (dt, J=9.11 and 696 Hz) corresponding to a O=P–H and a O=P–OEt group, respectively.[14]



2 **4** **5**

Scheme 2

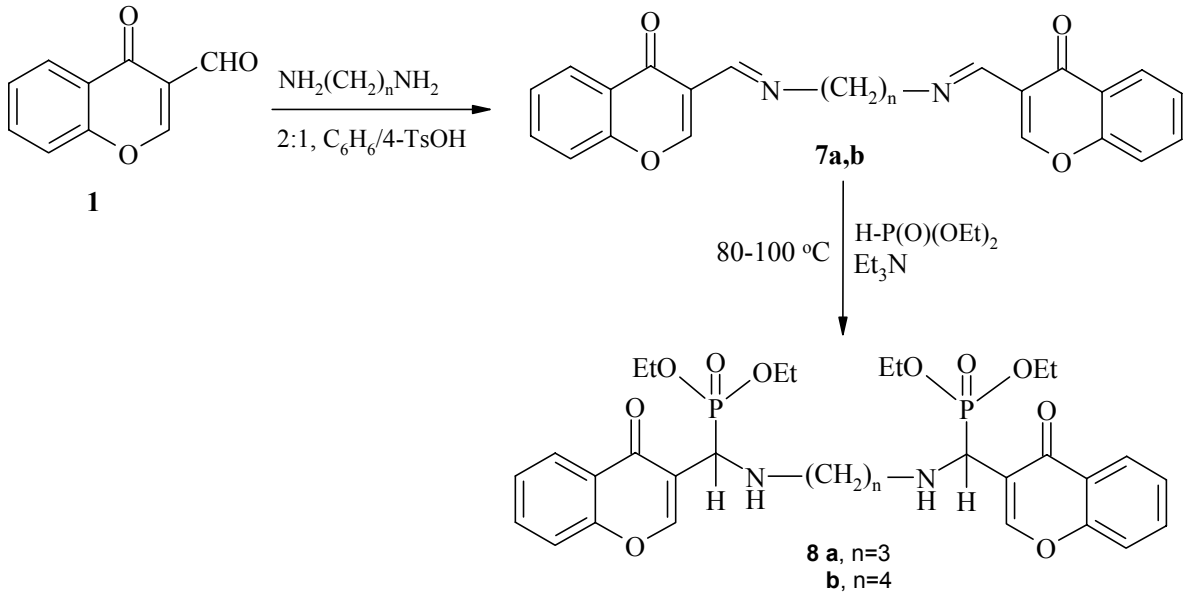
Fusing of the bis-hydrazone **3** with diethyl phosphite at 80-100 °C in the presence of catalytic amounts of triethylamine produced *N*^{1},*N*^{5}-bis{*N*-methyl(diethoxyphosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)}phosphonic dihydrazide (**6**) as the sole product (Scheme 3). The structure was established by elemental analysis and the IR spectrum which showed absorption bands of NH and P=O groups at 3150 and 1214 cm^{-1}. The ^{1}H NMR spectrum of **6** revealed the presence of two ethoxy and CH–P groups. Accordingly, the ^{13}C NMR showed two signals at 45.46 and 51.32 ppm for CH–P of CH–P(O)(OEt)$_2$ groups. Moreover, the ^{31}P NMR showed triplet signal at δ 5.11 (t, J= 8.74 Hz) and singlet signal 21.75 ppm from the O=P–H and P(O)(OEt)$_2$ groups, respectively. Only one isomer was observed.



Scheme 3

Alternatively, 3-{[(4-oxo-4*H*-chromen-3-yl)methylene]amino}propyl)imino]methyl}-4*H*-chromen-4-one (**7a**) and 3-{[(4-{[(4-oxo-4*H*-chromen-3-yl)methylene]amino}butyl)imino] methyl}-4*H*-chromen-4-one (**7b**) were prepared in moderate yield by condensation of aldehyde **1** with1,3-diaminopropane or 1,4-diaminobutane in dry benzene containing catalytic amounts of 4-toluenesulfonic acid (Scheme 4). The structures of the new bis–imines **7a,b** were established using elemental analysis, IR, and ^{1}H NMR spectra (See Experimental Section).

The addition of diethyl phosphite to compounds **7a,b** was carried out in dry benzene containing few drops of triethylamine as catalyst to yield the corresponding bis-(α-aminophosphonates) derivatives **8a,b**, respectively (Scheme 4). The IR spectra of **8a,b** displayed absorptions at 1219–1218 (P=O) and 3116–3100 cm^{-1} (NH). The ^{1}H NMR spectra of compound **8a,b** showed the presence of ethoxy groups. The ^{13}C NMR showed signals from the CHP group as doublets. The ^{31}P NMR spectra of compounds **8a,b** had singlet signals at δ 23.64 and 24.19 ppm, respectively, consistent with the presence of a phosphonate group.[15]



Scheme 4

The addition of diethyl phosphite to bis-imines **3** and **7a,b** should lead to a mixture of the *meso* and *racemic* diasteromers.[16,17] Each of the compounds **6** and **8a,b** gave one spot by thin layer chromatography (TLC) and exhibited only one set of signals in the ^{1}H, ^{13}C and ^{31}P NMR spectra suggesting that only one diasteromer is formed.

Experimental Section

General Procedures. Melting points of the products were determined on a Kofler microscope and are uncorrected. The IR spectra were recorded on a Bruker IFS 1113 spectrophotometer in $CDCl_3$ solvent or KBr disks. ^{1}H NMR spectra (solvent DMSO-d_6 or $CDCl_3$) were recorded on a Bruker DRX (250 or 600 MHz) spectrometer using TMS as an internal standard. ^{13}C and ^{31}P NMR spectra were registered on a Varian Inova 500 MHz spectrometer using TMS as an internal standard and 85% H_3PO_4 as external reference, respectively. Thin layer chromatography (TLC) was performed on Kieselgel 60 F254 plastics sheets (Merck Sigma Chemical Co. Germany) applying the samples as solutions in $CHCl_3$ and eluting with benzene-methanol (10:1). 4-Oxo-4*H*-chromene-3-carboxaldehyde (**1**)[18] and phosphonic dihydrazide[19] were prepared by the published methods.

***N*'-[(4-Oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide** (**2**). Phosphonic dihydrazide (1.10 g, 0.01 mol) was dissolved in water (3 ml) and added to a solution of 4-oxo-4*H*-chromene-3-carboxaldehyde (**1**) (1.74 g, 0.01 mol) in ethanol (30 mL). The mixture was heated under reflux for 30 min. The yellow precipitate was filtered off and crystallized from 70

% aqueous ethanol. Yield 84 %, mp 108–110 °C. IR, υ_{max} (KBr): 3152 (NH_2); 3121 (NH); 2966; 2873; 2751 (P–H); 1628 ($C=O_{pyrone}$); 1590 (C=N); 1484; 1443; 1236 (P=O). ^{1}H NMR; δ_H (DMSO; 600 MHz): 2.07 (2H, s, NH_2); 2.51 (1H, s, NH); 6.75 (1H, dd, ^{1}J= 657.14 and ^{2}J= 7.8 Hz, P–H); 6.95 (1H, t, J= 7.2 Hz, H–7); 6.99 (1H, d, J= 8.4 Hz, H–8), 7.47 (1H, t, J= 6 Hz, H–6); 7.70 (1H, d, J= 7.2 Hz, H–5), 8.04 (1H, s, CH=N); 8.19 (1H, s, H–2); 11.24 (1H, br, NH). Anal. Calcd for $C_{10}H_{11}N_4O_3P$, requires C, 45.12; H, 4.17; N, 21.05. Found: C, 44.89; H, 3.91; N, 20.92 %.

***N*^{1},*N*^{5}-Bis[(4-oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide (3).** Phosphonic dihydrazide (1.10 g, 0.01 mol) was dissolved in water (3 mL) and added to a solution of 4-oxo-4H-chromene-3-carboxaldehyde (**1**) (3.48 g, 0.02 mol) in ethanol (30 mL). The mixture was heated under reflux for 1 h. The yellow precipitate was filtered off and crystallized from dimethylformamide. Yield 91 %, mp 230–232 °C; IR, υ_{max} (KBr): 3087 (NH); 1666 ($C=O_{pyrone}$); 1611 (C=C), 1569 (C=N); 12291 (P=O); 1050 (P–O–C). ^{1}H NMR; δ_H (DMSO; 250 MHz): 7.11 (1H, br, P–H), 7.15–7.19 (2H, m, H–7 and H–7`), 7.34–7.48 (4H, m, H–8, H–8`, H–6 and H–6`), 7.52 (2H, d, H–5 and H–5`), 8.09 (2H, s, CH=N), 8.12 (2H, s, H–2`), 11.24 (2H, s, NH). Anal. Calcd for $C_{20}H_{15}N_4O_5P$, requires C, 56.88; H, 3.58; N, 13.27. Found: C, 56.42; H, 3.41; N, 12.93 %.

3-(4-Amino-5-ethoxy-3,5-dioxido-1,2,4,3,5-triazadiphosphinan-6-yl)-4*H*-chromen-4-one (5). A mixture of *N`*-[(4-oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide (**2**) (0.005 mol, 1.33 g), diethyl phosphite (0.007 mol, 0.966 g) and two drops of triethylamine was heated at 80–100 °C for 10 h. The excess of diethyl phosphite was removed in vacuum and the oily residue was extracted with ethyl acetate. Removal of the ethyl acetate, filtration and recrystallization from ethyl acetate gave yellow crystals. Yield 72 %, mp 70–72 °C; R_f=0.89; IR, υ_{max} ($CDCl_3$, film): 3145 (br, NH_2); 3084 (NH); 2983; 2872; 2715 (P–H); 1624 ($C=O_{pyrone}$); 1485; 1445; 1237 (P=O); 1221 (P=O); 1050 (P–O–C). ^{1}H NMR; δ_H ($CDCl_3$; 250 MHz): 1.31 (3H, t, J= 7 Hz, $OCH_2\underline{CH_3}$); 2.10 (2H, s, NH_2), 3.95 (1H, d, J= 24.5 Hz, CHP); 4.10 (2H, q, J= 7.75 Hz, $O\underline{CH_2}CH_3$); 6.78 (1H, d, J= 696.11 Hz, P–H), 6.87 (1H, t, J= 7.25 Hz, H–7); 6.95 (1H, d, J= 8.25 Hz, H–8); 7.42 (1H, t, J= 7.75 Hz, H–6); 7.80 (1H, D, J= 7.5 Hz, H–5), 8.09 (1H, s, H–2); 10.21 (1H, br, NH); 10.97 (1H, br, NH). ^{13}C NMR; δ_C ($CDCl_3$; 62.90 MHz): 16.07 (CH_3, J= 5.66 Hz); 45.65 (CHP); 61.82 (CH_2O, J= 5.67 Hz); 118.03 (C–8), 118.8 (C–3), 119.93 (C–4a); 120.79 (C–5); 131.11 (C–6); 136.61 (C–7); 138.00 (C–2); 162.19 (C–8a); 192.47 ($C=O_{pyrone}$). ^{31}P NMR; δ_P ($CDCl_3$; 101.25 MHZ): 5.28 (d, J= 658.19 Hz, O=P–H); 8.15 (dt, J= 9.11 and 695.64, O=P–OEt). Anal. Calcd for $C_{12}H_{16}N_4O_5P_2$, requires C, 40.23; H, 4.50; N, 15.64. Found: C, 40.07; H, 4.06; N, 15.39 %.

***N*^{1},*N*^{5}-bis{*N*-methyl(diethoxyphosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)}phosphonic dihydrazide (6).** A mixture of *N*^{1},*N*^{5}-bis[(4-oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide (**3**) (0.005 mol, 2.11 g), diethyl phosphite (0.014 mol, 1.932 g) and two drops of triethylamine was heated at 80–100 °C for 10 h. The excess of diethyl phosphite was removed under vacuum and the oily residue was treated with ethyl acetate to give red thick oil. Yield 78 %; R_f =0.63; IR, υ_{max} ($CDCl_3$, film): 3150 (br, NH); 2988; 2911; 2700 (P–H); 1653 (br,

C=O_{pyrone}); 1610 (C=C), 1487; 1457; 1214 (br, P=O); 1013 (P–O–C). ^{1}H NMR; δ_H (DMSO; 600 MHz): 1.03 (3H, t, J= 7.2 Hz, $OCH_2\underline{CH_3}$); 1.17 (3H, t, J= 7.2 Hz, $OCH_2\underline{CH_3}$); 3.01 (1H, br, NH–C); 3.15 (1H, br, C–NH); 3.42 (1H, q, J= 7.2 Hz, $O\underline{CH_2}CH_3$); 3.87 (2H, q, J=7.2 Hz, $O\underline{CH_2}CH_3$); 3.98–3.99 (2H, m, CHP); 6.10 (1H, d, P–H), 7.14–7.33 (8H, m, H–7,H–7`, H–8, H–8`, H–6, H–6`, H–5 and H–5`); 8.40 (1H, br, H–2); 11.68 (2H, br, NHP=O). ^{13}C NMR; δ_C (DMSO; 150.91 MHz): 16.48 (CH_3, J= 6 Hz); 16.73 (CH_3, J= 6 Hz); 45.46, 51.32 (2 CHP); 60.60 (CH_2O, J= 6 Hz); 62.50 (OCH_2, J= 6 Hz); 117 (C–8, C–8`), 118 (C–3, C–3`), 119 (C–4a, C–4a`); 122 (C–5, C–5`); 128.74 (C–6, C–6`); 135.83 (C–7, C–7`); 142.0 (C–2, C–2`); 155 (C–8a, C–8a`); 193 (2 C=O_{pyrone}). ^{31}P NMR; δ_P ($CDCl_3$; 242.92 MHZ): 5.11 (t, J= 8.74 Hz, O=P–H); 21.75 (s, O=P–OEt). Anal. Calcd for $C_{28}H_{37}N_4O_{11}P_3$ requires C, 48.14; H, 5.34; N, 8.02. Found: C, 47.95; H, 5.19; N, 7.96 %.

3-{[(4-Oxo-4*H*-chromen-3-yl)methylene]amino}propyl)imino]methyl}-4*H*-chromen-4-one (7a) and 3-{[(4-{[(4-oxo-4*H*-chromen-3-yl)methylene]amino}butyl)imino]methyl}-4*H*-chromen-4-one (7b). 1,3-Diaminopropane (0.74 g, 0.01 mol) and/or 1,4-diaminobutane (0.88 g, 0.01 mol) was added to a solution of 4-oxo-4*H*-chromene-3-carboxaldehyde (**1**) (3.48 g, 0.02 mol) in dry benzene (50 mL) containing 4-toluenesulfonic acid (0.1 g). The mixture was heated under reflux for 4 h. Cooling to room temperature, filtration and crystallized from benzene/petroleum ether gave yellow **7a,b**, respectively.

Compound 7a. Yield 75 %, mp 99–100 ^{o}C. IR, υ_{max} (KBr): 3067 (C–H_{arom}), 2952, 2869 (C–H_{aliph}); 1652 (C=O_{pyrone}); 1605 (C=C); 1588 (C=N); 1481; 1465. ^{1}H NMR; δ_H (DMSO; 600 MHz): 2.08–2.28 (2H, m, C–CH_2–C); 3.48-3.51 (4H, m, CH_2–N); 6.89–7.98 (10H, m, H–7, H–7`, H–8, H–8`, H–6, H–6`, H–5, H–5` and CH=N), 8.05–8.11 (2H, m, H–2). Anal. Calcd for $C_{23}H_{18}N_2O_4$, requires C, 71.49; H, 4.70; N, 7.25. Found: C, 71.13; H, 4.52; N, 7.25 %.

Compound 7b. Yield 76 %, mp 95–97 ^{o}C. IR, υ_{max} (KBr): 3067 (C–H_{arom}), 2937, 2866 (C–H_{aliph}); 1653 (C=O_{pyrone}); 1606 (C=C); 1591 (C=N); 1465. ^{1}H NMR; δ_H (DMSO; 600 MHz): 2.07–2.27 (4H, m, C–CH_2CH_2–C); 3.47–3.58 (4H, m, NCH_2); 6.86–7.97 (10H, m, H–7,H–7`, H–8, H–8`, H–6, H–6`, H–5, H–5`and CH=N), 8.00–8.15 (2H, m, H–2). Anal. Calcd for $C_{24}H_{20}N_2O_4$, requires C, 71.74; H, 4.87; N, 7.12. Found: C, 71.66; H, 4.85; N, 6.89 %.

***N*^{1},*N*^{3}-Bis{*N*-methyl(diethoxyphosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)}diaminopropane (8a) and *N*^{1},*N*^{4}-bis{*N*-methyl(diethoxyphosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)}diamino-butane (8b).** A mixture of 3-{[(4-oxo-4*H*-chromen-3-yl)methylene]amino}propyl) imino]methyl}-4*H*-chromen-4-one (**7a**) (0.005 mol, 1.93 g) and/or 3-{[(4-{[(4-oxo-4*H*-chromen-3-yl)methylene] amino}butyl)imino]methyl}-4*H*-chromen-4-one (**7b**) (0.005 mol, 2.00 g) and diethyl phosphite (0.014 mol, 1.932 g) in dry benzene (40 mL) containing two drops of triethylamine was heated under reflux for 10 h. The solvent was removed under vaccum and the oily residue was triturated with petroleum ether. Removal of the solvent gave bis–(α–aminophosphonates) derivatives **8a,b**, respectively as orange crystals.

Compound 8a. Yield 71 %, mp 66–68 ^{o}C; R_f=0.61; IR, υ_{max} ($CDCl_3$, film): 3116 (NH); 2925; 2854; 1640 (C=O_{pyrone}); 1419; 1219 (P=O); 1051 (P–O–C). ^{1}H NMR; δ_H ($CDCl_3$; 250 MHz): 1.12 (3H, t, J= 7.25 Hz, $OCH_2\underline{CH_3}$); 1.27 (3H, t, J= 7.5 Hz, $OCH_2\underline{CH_3}$); 1.86–2.03 (2H, m,

C–CH_2–C); 3.01 (2H, q, NH–C); 3.31 (4H, br, CH_2–N); 3.66–3.71 (1H, m, J= 7.2 and 14 Hz, CHP); 3.84–3.90 (1H, m, J= 7.25 and 14.75 Hz, CHP); 4.11 (2H, q, J= 7 Hz, O$\underline{CH_2}CH_3$); 4.17 (2H, q, J=7 Hz, O$\underline{CH_2}CH_3$); 6.88–7.97 (8H, m, H–7,H–7`, H–8, H–8`, H–6, H–6`, H–5 and H–5` H–7, H–7`, H–8, H–8`, H–6, H–6`, H–5 and H–5`), 8.07–8.26 (2H, m, H–2 and H–2`). $^{13}$C NMR; $\delta_C$ ($CDCl_3$; 150.91 MHz): 16.32 ($CH_3$, J= 6 Hz); 29.34 (C–$CH_3$–C, J= 49.5 Hz); 31.90 ($NCH_2$, J= 115 Hz), 45.47 (2 CHP); 61.82 ($CH_2O$, J= 6 Hz); 118.33 (C–8, C–8`), 118.92 (C–3, C–3`), 120.18 (C–4a, C–4a`); 125.75 (C–5, C–5`); 128.82 (C–6, C–6`); 131.30 (C–7, C–7`); 135.72 (C–2, C–2`); 162.0 (C–8a, C–8a`); 192.0 (2 $C=O_{pyrone}$). ^{31}P NMR; δ_P ($CDCl_3$; 101.25 MHZ): δ 23.64 ppm. Anal. Calcd for $C_{31}H_{40}N_2O_{10}P_2$ requires C, 56.19; H, 6.08; N, 4.23. Found: C, 56.19; H, 5.85; N, 4.03 %.

Compound 8b. Yield 69 %, mp 69–70 ^oC; R_f=0.60; IR, υ_{max} ($CDCl_3$, film): 3100 (NH); 2980; 2868; 1646 ($C=O_{pyrone}$); 1466; 1218 (P=O); 1050 (P–O–C).^{1}H NMR; δ_H ($CDCl_3$; 250 MHz): 1.19 (3H, t, J= 7.25 Hz, $OCH_2\underline{CH_3}$); 1.24 (3H, t, J= 7.25 Hz, $OCH_2\underline{CH_3}$); 2.01–2.27 (4H, m, C–CH_2CH_2–C)**;** 2.96–3.05 (6H, m, NCH_2 and NH) 3.81–3.86 (2H, m, CHP); 4.07 (2H, q, J= 7.25 Hz, O$\underline{CH_2}CH_3$); 4.13 (2H, q, J=7.25 Hz, O$\underline{CH_2}CH_3$); 6.88–7.69 (8H, m, H–7,H–7`, H–8, H–8`, H–6, H–6`, H–5 and H–5`), 8.16–8.20 (2H, m, H–2 and H–2`). $^{13}$C NMR; $\delta_C$ ($CDCl_3$: 62.90 MHz): 16.39 ($CH_3$, J= 6 Hz); 28.90, 30.33 (C–$CH_2CH_2$–C); 30.94 ($NCH_2$), 45.58 (2 CHP); 63.34 ($CH_2O$); 118.28 (C–8, C–8`), 119.0 (C–3, C–3`), 125.82 (C–4a, C–4a`); 126.0 (C–5, C–5`); 128.79 (C–6, C–6`); 130.91 (C–7, C–7`); 136.0 (C–2, C–2`); 156.0 (C–8a, C–8a`); 185.20 (2 $C=O_{pyrone}$). ^{31}P NMR; δ_P ($CDCl_3$; 101.25 MHZ): δ 24.19 ppm. Anal. Calcd for $C_{32}H_{42}N_2O_{10}P_2$ requires C, 56.80; H, 6.26; N, 4.14. Found: C, 56.59; H, 5.99; N, 3.98 %.

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