

Microwave-assisted synthesis of α -aminophosphonate-chromone hybrids using Kabachnik-Fields Reaction

Kármén Emőke Szabó,^a Rama Akaili,^a Ádám Tajti,^b Nóra Popovics-Tóth,^b and Erika Bálint^{a*}

^aDepartment of Organic Chemistry and Technology, Budapest University of Technology and Economics,
Budafoki út 8., H-1111 Budapest, Hungary

^bBálint Analitika Ltd., Fehérvári út 144., H-1116 Budapest, Hungary

Email: balint.erika@vbk.bme.hu

Dedication to Prof. György Keglevich

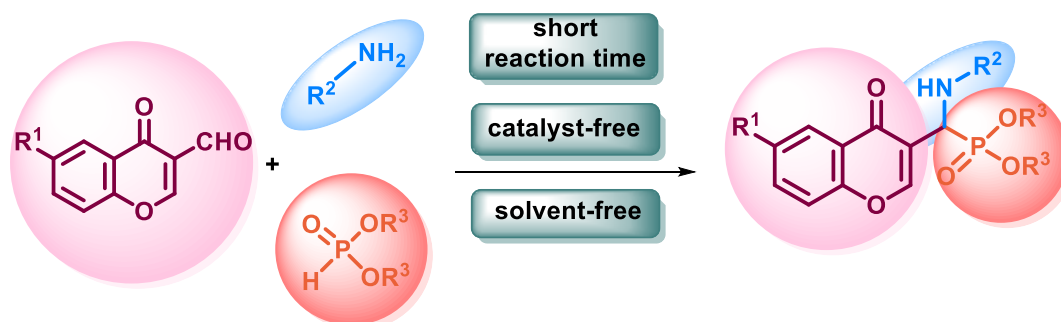
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Abstract

An efficient, practical, and green approach for the synthesis of α -aminophosphonates incorporating a chromone moiety by the one-pot Kabachnik-Fields reaction has been developed. The three-component reactions of 3-formylchromones, primary amines and dialkyl phosphites was carried out in short reaction times in the absence of any catalyst or solvent under microwave irradiation. The method developed did not require column chromatographic separation since the products could be recovered from the reaction mixture by simple filtration. The method developed could be applied to a range of primary amines and dialkyl phosphites, which confirmed the large scope and functional-group tolerance.



Keywords: α -Aminophosphonate, chromone, Kabachnik-Fields reaction, three-component reaction, microwave

Introduction

α -Aminophosphonates have a great importance among organophosphorus compounds as they have multiple applications.¹ Many members of this family of compounds are found in agriculture, organic and medicinal chemistry, as well as in the plastics industry.² The aminophosphonate backbone can be found in many drugs used for several indications, such as antibacterial, antiviral and antitumor agents, enzyme or osteoporosis inhibitors, as well as anti-metabolites.³⁻⁷

4*H*-Chromene is a bicyclic O-heterocycle containing two fused 6-membered rings, a benzene and a dihydropyran ring. 4*H*-Chromen-4-one or simply chromone contains a keto group at the 4th position of the pyran ring. 4*H*-Chromen-4-ones can be easily functionalized in the third position, e.g., 3-hydroxy or 3-sulfenylated chromone hybrid molecules can be synthesized.^{8,9}

Several derivatives can be found in nature and are widely used in the pharmaceutical industry.¹⁰⁻¹⁴ For example, 3-formylchromone, is an interesting starting material in multicomponent reactions since it has three different electron-deficient centres that can be reacted by nucleophiles which provide an opportunity to form a wide range of new chromone derivatives.¹⁵⁻¹⁸

A few chromone derivatives containing a phosphonate or a phosphine-oxide moiety also have significance (Figure 1). Some quinazoline-substituted chromonylphosphonate derivatives (**1**) were found to be active against human liver (HepG2) and human normal melanocyte (HFB4) cell lines.¹⁹ Furthermore, DPO-daidzein (**2**) can be included as a flame-retardant agent in polymers.²⁰

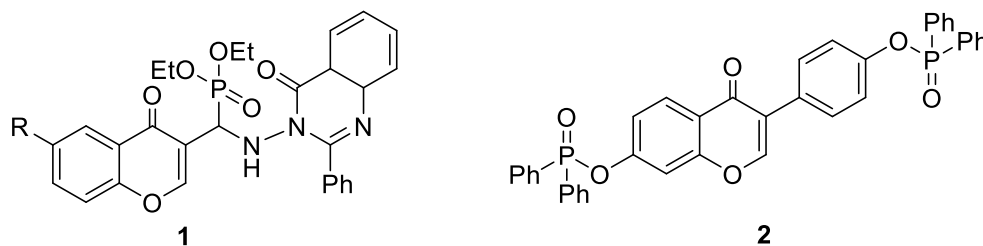


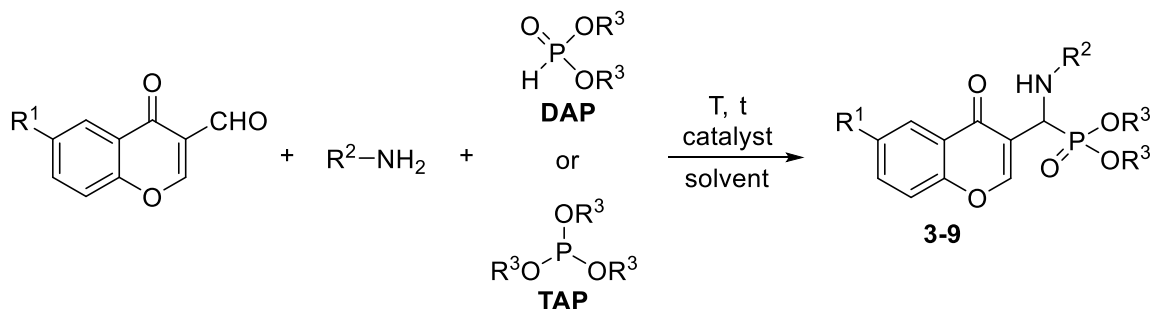
Figure 1. Biologically active chromone-aminophosphonate hybrids (**1**) and a flame-retardant agent (**2**).

Multicomponent syntheses, such as the Kabachnik-Fields reaction, in which an amine, an aldehyde or a ketone, and a dialkyl phosphite react with each other, are one of the most straightforward and efficient tools for the synthesis of α -aminophosphonates and their heterocyclic derivatives.²¹⁻²³ Applying multicomponent reactions, the target products are usually formed with high-atom efficiency in a “one-pot” manner starting from simple materials. The ability to use various reagents makes these reactions ideal for creating novel molecular libraries, and, in most cases, the principles of green chemistry also prevail to save time and energy.^{24,25}

Only a few examples have been described in the literature for the Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl- (**DAP**) or trialkyl phosphites (**TAP**) (Table 1).²⁶⁻³² In four cases, the (4-oxo-4*H*-chromen-3-yl)phosphonates (**3–6**) were synthesized in the presence of a catalyst.²⁶⁻²⁹ In the first two examples, the condensation was performed using rhodium-boron nitride or yttria-zirconia as a catalyst in acetonitrile for long reaction time (Table 1/Entries 1 and 2).^{26,27} In a solvent-free method, using triethylamine (TEA) as a base, the desired products (**5**) were obtained at 60-70 °C in yields of 70-100% (Table 1/Entry 3).²⁸ Porcine pancreatic lipase, as an enzyme catalyst, was also suitable for the three-component reaction of 3-formylchromone, primary amines and 1.2 equivalents of diethyl phosphite at 50 °C for 3 h (Table 1/Entry 4).²⁹ Catalyst-free examples can also be found in the literature.³⁰⁻³² Lang and co-workers performed the condensation

in toluene at 100 °C for 2-5 h, and the corresponding chromonyl-containing α -aminophosphonates (**7**) were obtained in variable yields (16-70%) (Table 1/Entry 5).³⁰ Diphenyl α -(benzyloxycarbonylamino)-chromonylphosphonate (**8**) was synthesized by the Kabachnik-Fields reaction of 3-formylchromones, benzyl carbamate and triphenyl phosphite at 80 °C for 1 h in acetic acid as a solvent (Table 1/Entry 6).³¹ To the best of our knowledge, only one catalyst- and solvent-free method was reported, where 3-formyl-6-methylchromone, 4-chloroaniline and 2 equivalents of diethyl phosphite were reacted at 70-80 °C for 6 hours, and the target chromonyl-containing aminophosphonate (**9**) was synthesized in a yield of 70% (Table 1/Entry 7).³²

Table 1. Synthesis of chromonyl-containing α -aminophosphonates by the Kabachnik-Fields reaction



Entry	R ¹	R ²	P-reagent R ³	Molar ratio	Catalyst	Solvent	T (°C)	t (h)	Yield (%) 3-5	ref.
1	H	-Ph	DAP	1:1:1	0.5 mol% rhodium- boron nitride	MeCN	82	6	90-96 (3)	25
		-2-MeC ₆ H ₄								
		-4-MeC ₆ H ₄								
		-2-MeOC ₆ H ₄								
		-4-MeOC ₆ H ₄								
		-4-ClC ₆ H ₄								
		-2-NO ₂ C ₆ H ₄								
-4-NO ₂ C ₆ H ₄										
-3,4-ClC ₆ H ₃										
2	H	-Bn	TAP	1:1:1	10 mol% yttria- zirconia	MeCN (10% H ₂ O)	60	6	99 (4)	26
		-Et								
3	Me	-Bn	DAP	1:1:1	TEA	-	60-70	6	70-100 (5)	27
		-4-ClC ₆ H ₄								
		-4-OHC ₆ H ₄								

Table 1. Continued

Entry	R ¹	R ²	P-reagent R ³	Molar ratio	Catalyst	Solvent	T (°C)	t (h)	Yield (%) 6-9	ref.
4	H	–(CH ₂) ₂ C ₆ H ₄	DAP –Et	1:1:1. 2	porcine pancreatic lipase (PPL)	–	50	3	98 (6)	28
		–4-CNC ₆ H ₄								
		–(CH ₂) ₂ 4- MeOC ₆ H ₄								
		–3-(MeF) ₃ C ₆ H ₄								
5	Me	–3-Cl,4-(MeF) ₃ C ₆ H ₃	DAP –Me –Et	1:1:1	–	toluene	100	2-5	16-70 (7)	29
		–3-Cl,4-FC ₆ H ₃								
		–(CH ₂) ₂ -4-Cl C ₆ H ₄								
		–CH ₂ -4-FC ₆ H ₄								
		–(CH ₂) ₂ -4-FC ₆ H ₄ - –Ph								
6	Me	–2-MeC ₆ H ₄	TAP –Ph	1.1:1: 1	–	acetic acid	80	1	93 (8)	30
		–4-MeC ₆ H ₄								
		–4-MeOC ₆ H ₄								
		–4-ClC ₆ H ₄								
7	Me	–2-NO ₂ C ₆ H ₄	DAP –Et	1:1:2	–	–	70-80	6	70 (9)	31
		–4-NO ₂ C ₆ H ₄								
		–CO ₂ CH ₂ C ₆ H ₅								

Based on the literature data, our aim in this paper was to develop an efficient microwave-assisted catalyst- and solvent-free method for the synthesis of novel α -aminophosphonates containing a chromone moiety by the Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites. Our aim was to optimize the process with respect to the heating mode, temperature and reaction time, and extend the process to various 3-formylchromones, primary amines and phosphorus reagents.

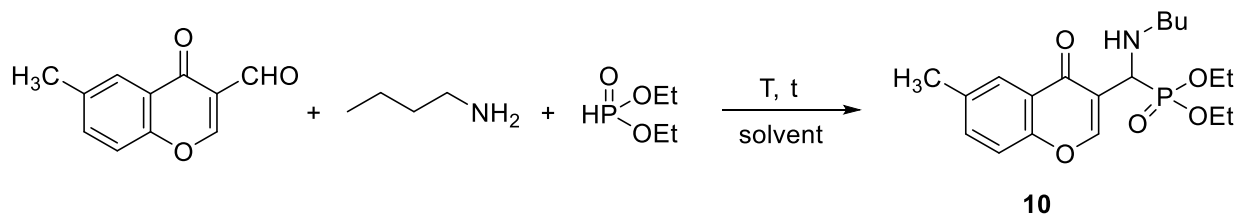
Results and Discussion

As the initial step of our work, the Kabachnik-Fields reaction of 3-formyl-6-methylchromonebutylamine and diethyl phosphite was studied (Table 2). The condensation was optimized with respect to the heating mode, temperature and reaction time.

At first, the three components were reacted with each other in acetonitrile without any catalyst, and at room temperature for 1 h, however, the conversion was very low (7%) (Table 2/Entry 1). Performing the condensation at 60 °C for 1 h in an oil bath, the ratio of the corresponding product (**10**) was increased to 24% (Table 2/Entry 2). Repeating this reaction under microwave (MW) irradiation, the diethyl-((butylamino)(6-

methyl-4-oxo-4*H*-chromen-3-yl)methyl)phosphonate (**10**) was formed in a conversion of 33% (Table 2/Entry 3). In the next round, the same experiment was carried out without any solvent, and the conversion was increased to 40% (Table 2/Entry 4). Performing the condensation at a higher temperature of 80 °C in the absence of any solvent, the conversion was doubled to 80%, indicating that the temperature increase had a large effect on the reaction (Table 2/Entry 5). Increasing the reaction time to 2 h, a 15% higher conversion to 95% was achieved (Table 2/Entry 6). Complete conversion was obtained at 100 °C for 1 h, and the diethyl ((butylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)phosphonate (**10**) was isolated in a yield of 86% (Table 2/Entry 7). Based on the reaction-optimization results, it can be concluded that the solvent-free MW-assisted reactions were more successful, and temperature had a greater effect on the transformation than reaction time.

Table 2. Three-component reaction of 3-formyl-6-methylchromone, butylamine and diethyl phosphite



Entry	Solvent	Heating mode	T (°C)	t (h)	Conversion (%) ^a	Yield (%) ^b
1	MeCN	–	25	1	7	–
2	MeCN	Δ	60	1	24	–
3	MeCN	MW	60	1	33	–
4	–	MW	60	1	40	–
5	–	MW	80	1	80	–
6	–	MW	80	2	95	–
7	–	MW	100	1	100	86

^aBased on HPLC (256 nm).

^bIsolated yield.

In the next series of experiments, the Kabachnik-Fields reaction of 3-formylchromones, various primary amines and dialkyl phosphites were carried out under the optimized conditions, i.e., without any catalyst and solvent at 100 °C for 1 h under MW irradiation (Table 3). After the model reaction investigated (3-formyl-6-methylchromone, butylamine and diethyl phosphite), the condensation reaction was extended to using diisopropyl or dibutyl phosphite as the P-reagent (Table 3/Entries 1 and 2). It was found that, in the reaction of 3-formyl-6-methylchromone, butylamine and dialkyl phosphites, among the phosphites, the diisopropyl phosphite was the less reactive (65% yield), likely due to the steric hindrance of the isopropyl group (Table 3/Entry 1). The condensation with diethyl and dibutyl phosphite was quite similar; the corresponding chromonyl-containing aminophosphonates (**10** and **12**) were obtained in yields of 86% and 80%, respectively (Table 2/Entry 7 and Table 3/Entry 2). After that, the amine component was changed and the reaction of 3-formyl-6-methylchromone and diethyl phosphite was performed with aliphatic amines, aminoalcohols, and aniline (Table 3/Entries 3-7). Using cyclohexyl- or benzylamine, the diethyl-((alkylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)phosphonates (**13** and **14**) were prepared in somewhat lower yields (65-69%) compared

to the reaction of butylamine (Table 3/Entries 3 and 4 vs. Table 2/Entry 7 and Table 3/Entry 2). Aminoalcohols, such as ethanol- or butanolamine, also proved to be efficient as the amine components since the required α -aminophosphonates **15** and **16** were obtained in high yields (78-81%) (Table 3/Entries 5 and 6). Among the amines, the aniline was the most reactive since the highest yield (89%) was obtained (Table 3/Entry 7). The bigger reactivity of aniline can be explained by its lower pKa value (4.6) compared to the pKa value of aliphatic amines or aminoalcohols (9-10).

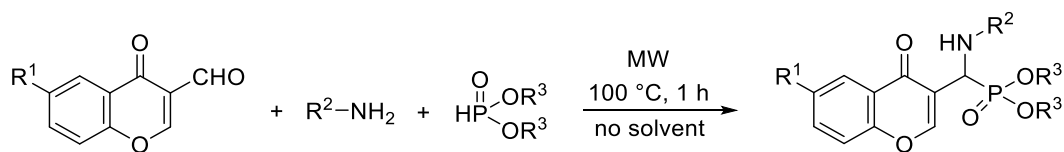
Next, the three-component reaction of 3-formyl-6-methylchromone and dibutyl phosphite was investigated with various aromatic amines (Table 3/Entries 8-12). Using aniline or a substituted aniline such as 4-methoxy- or 4-chloroaniline, it was found that, among them, aniline was the most reactive since 85% yield was achieved (Table 3/Entries 8-10). The electron-donating or electron-withdrawing group in the *para* position of aniline slightly reduced the reactivity in the condensation (74% and 70% yields were obtained, respectively). Naphthylamine **21** was also efficient as an amine component (85% yield, Entry 11), however, 4-pyridylamine **22** was less active since it is more basic than aniline (45% yield, Entry 12). It can, therefore, be concluded that more acidic amines favor the three-component reaction.

Following that, the aldehyde component was changed and the Kabachnik-Fields reaction of aniline and dibutyl phosphite was performed with 6-ethyl- and 6-fluoro-3-formylchromone, respectively (Table 3/Entries 13 and 14). The condensation of 3-formyl-6-ethylchromone gave a similar result with the reaction of 3-formyl-6-methylchromone (85% vs 83%; Table 3/Entries 8 and 13). Using 6-fluoro-3-formylchromone, however, the required aminophosphonate (**24**) was obtained in somewhat lower yield (77%) (Table 3/Entry 14).

Finally, the condensation of 6-ethyl- and 6-fluoro-3-formylchromone was carried out with aniline and ethyl-phenyl-*H*-phosphinate. The difference between the reactivity of the two formylchromones was similar with the previous experiments (Table 3/Entries 13-16). The corresponding products (**25** and **26**) were obtained as a mixture of two diastereomers due to the chiral center of the P-reagent.

Altogether, 16 new dialkyl-((amino)(4-oxo-4*H*-chromen-3-yl)methyl)phosphonates were prepared and characterized by ^{31}P , ^{13}C and ^1H NMR spectroscopy as well as by HRMS measurements.

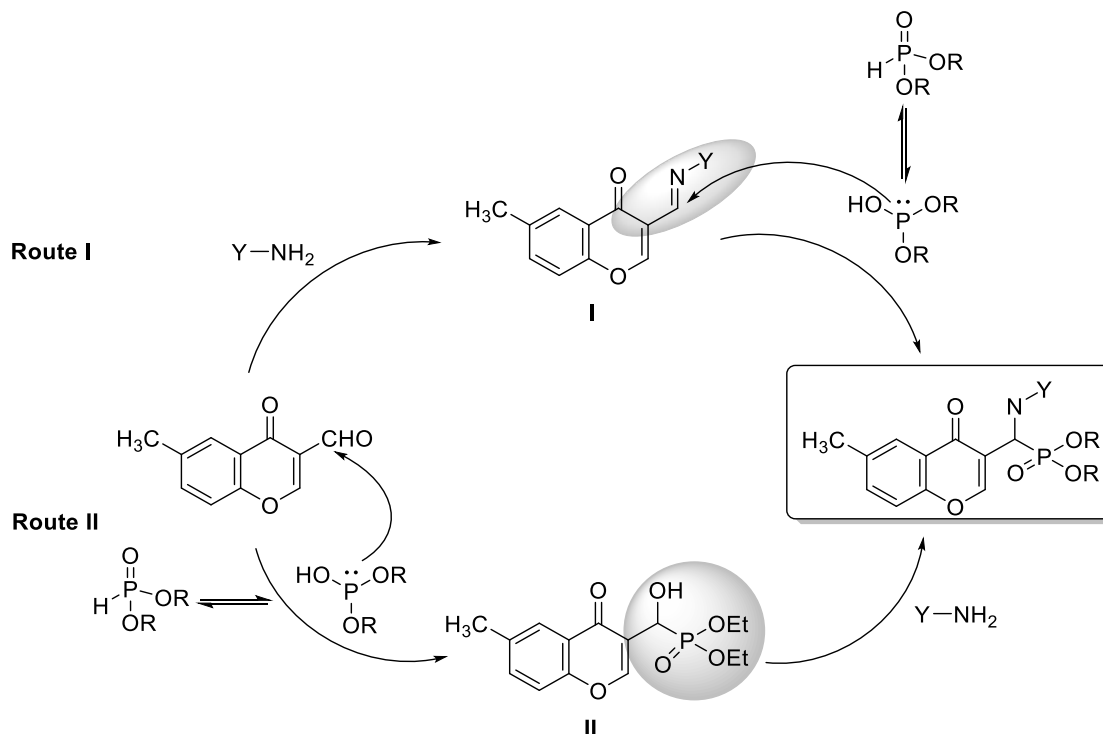
The formation of dialkyl-((amino)(4-oxo-4*H*-chromen-3-yl)methyl)phosphonates by the Kabachnik-Fields reaction can be explained by the proposed mechanisms shown in Scheme 1. The reaction can take place by two possible pathways: an imine intermediate (**I**) (Route I) or an α -hydroxyphosphonate intermediate (**II**) (Route II). In the first case, the 3-formylchromone can react with the amine forming an imine (**I**), which can react further with the dialkyl phosphite in a nucleophilic addition. The other route assumes the formation of an α -hydroxyphosphonate (**II**) by the addition of the dialkyl phosphite to the carbonyl group of the oxo component. The hydroxyphosphonate (**II**) then undergoes substitution by the amine to furnish the chromonyl-containing α -aminophosphonate.

Table 3. Microwave-assisted Kabachnik-Fields reaction of 3-formyl-6-methylchromones, primary amines and dialkyl phosphites

Entry	R ¹	R ²	R ³	Yield (%) ^b 11-26
1	Me	ⁿ Bu	ⁱ Pr	65% (11)
2	Me	ⁿ Bu	ⁿ Bu	80% (12)
3	Me	^c Hex	Et	65% (13)
4	Me	Bn	Et	69% (14)
5	Me	HO(CH ₂) ₂	Et	81% (15)
6	Me	HO(CH ₂) ₄	Et	78% (16)
7	Me	Ph	Et	89% (17)
8	Me	Ph	ⁿ Bu	85% (18)
9	Me	4-MeOC ₆ H ₄	ⁿ Bu	74% (19)
10	Me	4-ClC ₆ H ₄	ⁿ Bu	70% (20)
11	Me	2-Naphtyl	ⁿ Bu	85% (21)
12	Me	4-Pyridyl	ⁿ Bu	45% (22)
13	Et	Ph	ⁿ Bu	83% (23)
14	F	Ph	ⁿ Bu	77% (24)
15	Et	Ph	Et, Ph	72% (25) ^c
16	F	Ph	Et, Ph	65% (26) ^d

^aBased on HPLC (256 nm)^bIsolated yield^cA mixture of two diastereomers in a ratio of 48:52^dA mixture of two diastereomers in a ratio of 38:62

A few experiments were carried out to study the mechanism of the Kabachnik-Fields reaction investigated. At first, 3-formyl-6-methylchromone was reacted with butylamine under the optimized condition (MW, 100 °C, 1 h); the corresponding imine was formed in a conversion of 74%. The imine was reacted further with diethyl phosphite under similar conditions; however, the reaction was not complete, and only 70% of the α -aminophosphonate (**10**) was obtained. In the next part, the 3-formyl-6-methylchromone was reacted with diethyl phosphite under the optimized conditions, at 100 °C for 1 h under MW irradiation. This reaction was complete, and the chromonyl-containing α -hydroxyphosphonate (**II**) was reacted further with butylamine resulting in the diethyl-((butylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)phosphonate (**10**) in a yield of 80%.



Scheme 1. Proposed mechanisms for the synthesis of dialkyl-((amino)(4-oxo-4H-chromen-3-yl)methyl)phosphonates.

It can be concluded that the Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites take place both Route I and Route II; however, *via* the α-hydroxyphosphonate intermediate (II) (Route II) is more favorable for complete reactions. Furthermore, it was found that the two-step reaction was somewhat slower and resulted in a lower yield than the one-pot three-component synthesis.

Conclusions

We have developed a new MW-assisted catalyst- and solvent-free method for the synthesis of dialkyl-((amino)(4-oxo-4H-chromen-3-yl)methyl)phosphonates by the Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites. This approach has the advantages of a simple operation and green-reaction conditions (no catalyst, no solvent, and short reaction times) Another advantage is that it does not require chromatographic separation since the products could be recovered by crystallization. Our method is cheaper, faster and more environmentally friendly compared with other examples in the literature. In all, 16 new dialkyl-((amino)(4-oxo-4H-chromen-3-yl)methyl)phosphonates were synthesized in good-to-high yields and fully characterized. The mechanism of the reaction was also investigated, and it was found that the condensation takes place through the α-hydroxyphosphonate intermediate.

Experimental Section

General. All starting materials were purchased from commercial sources and were used without further purification. The microwave-assisted reactions were carried out in a sealed tube in a 300 W CEM Discover focused microwave reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller using 20–30 W irradiation under isothermal conditions. The reactions under conventional heating were carried out in an oil bath.

High-performance liquid chromatography-mass spectrometry (HPLC-MS) measurements were performed with an Agilent 1200 liquid chromatography system coupled with a 6130 Quadrupole Mass Spectrometer equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). Analysis was performed at 40 °C on a Gemini C18 column (150 mm × 4.6 mm, 3 μm; Phenomenex, Torrance, CA, USA) with a mobile phase flow rate of 0.6 mL/min. Composition of eluent A was 0.1% (NH₄)(HCOO) in water; eluent B was 0.1% (NH₄)(HCOO) and 8% water in acetonitrile, 0–3 min 5% B, 3–13 min gradient, 13–20 min 100% B. The injection volume was 2 μL. The chromatographic profile was registered at 254 nm. The MSD operating parameters were as follows: positive ionization mode, scan spectra from *m/z* 120 to 1000, drying gas temperature 300 °C, nitrogen flow rate 12 L/min, nebulizer pressure 60 psi, capillary voltage 4000 V.

High resolution mass spectrometric (HRMS) measurements were performed using a Sciex 5600+ Q-TOF mass spectrometer in positive electrospray mode.

The ¹H, ¹³C and ³¹P NMR spectra were taken in CDCl₃ solution on a Bruker AV-300 spectrometer operating at 300, 75.5 and 121.5 MHz, respectively. The chemical shifts (δ) are reported in parts per million (ppm) and downfield relative to 85% H₃PO₄, as well as TMS. The coupling constants (*J*) are reported in Hz. A non-equivalence effect was observed in ¹H and ¹³C {¹H} NMR spectra. Corresponding pairs of resonances were marked with (I) and (II).

General procedure for the dialkyl-((amino)(4-oxo-4*H*-chromen-3-yl)methyl)phosphonates. The mixture of 1.0 mmol of 3-formylchromones (3-formyl-6-methylchromone: 0.12 g, 6-ethyl-3-formylchromone: 0.20 g, 6-fluorochromone-3-carboxaldehyde: 0.19 g), 1.0 mmol of amines (butylamine: 0.10 ml, cyclohexylamine: 0.11 ml, benzylamine: 0.11 ml, ethanolamine: 0.09 ml, butanolamine: 0.09 ml, aniline: 0.09 ml, *p*-anisidine: 0.12 ml, 4-chloroaniline: 0.09 ml, 2-naphthylamine: 0.15 ml, 4-aminopyridine: 0.09 ml), 1 mmol of phosphorus reagents (diethyl phosphite: 0.13 ml, dibutyl phosphite: 0.20 ml, diisopropyl phosphite: 0.17 ml, ethyl phenyl-*H*-phosphinate: 0.15 ml) was irradiated in a sealed tube at 100 °C for 1 h in a CEM Discover® MW reactor equipped with a pressure controller. The crude mixtures obtained after the reactions were dissolved in a small amount of acetonitrile and were cooled down to 5 °C. After 3–4 h, the precipitated product was filtered out. The following products were thus prepared:

Diethyl ((butylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)phosphonate (10). Yield: 86% (0.33 g), light yellow oil; ³¹P (CDCl₃) δ 24.0; ¹³C NMR (CDCl₃) δ 13.8 (CH₃(CH₂)₃N), 16.3 (d, ³*J*_{CP} = 5.7, CH₃CH₂O^I), 16.4 (d, ³*J*_{CP} = 6.2, CH₃CH₂O^{II}), 20.2 (CH₂(CH₂)₂N), 20.9 (ArCH₃), 32.0 (CH₂CH₂N), 47.9 (d, ³*J*_{CP} = 14.3, CH₂N), 49.6 (d, ¹*J*_{CP} = 156.5, CHP), 62.6 (d, ²*J*_{CP} = 7.1, CH₂O^I), 63.2 (d, ²*J*_{CP} = 6.6, CH₂O^{II}), 117.9 (C₈), 120.1 (d, ²*J*_{CP} = 2.1, C₃), 123.2 (C_{4a}), 125.2 (C₅), 134.8 (C₇), 135.2 (C₆), 154.4 (C_{8a}), 155.6 (d, ³*J*_{CP} = 6.0, C₂), 176.4 (d, ³*J*_{CP} = 5.0, C₄); ¹H NMR (CDCl₃) δ 0.87 (t, *J*_{HH} = 7.2, 3H, CH₃(CH₂)₃N), 1.23 (t, *J*_{HH} = 7.1, 3H, CH₃CH₂O^I), 1.34 (t, *J*_{HH} = 7.0, 5H, CH₃CH₂O^{II}, CH₂(CH₂)₂N), 1.43 (q, *J*_{HH} = 6.9, 2H, CH₂CH₂N), 1.89 (brs, 1H, NH), 2.46 (s, 3H, ArCH₃), 2.60 (t, *J*_{HH} = 7.4, 2H, CH₂N), 4.09 (q, *J*_{HH} = 7.2, 2H, CH₂O^I), 4.23 (tt, *J*_{HH} = 7.2, *J*_{HH} = 3.9, 2H, CH₂O^{II}), 4.58 (d, ²*J*_{HP} = 19.6, 1H, CHP), 7.37 (d, *J*_{HH} = 8.5, 1H, C₈H), 7.49 (dd, *J*_{HH} = 8.6, *J*_{HH} = 2.3, 1H, C₇H), 8.01 (d, *J*_{HH} = 2.2, 1H, C₂H), 8.20 (d, 1H, *J*_{HH} = 3.4, C₅H); [M+H]⁺_{found} = 383.1780, C₁₉H₂₉NO₅P requires 383.1783.

Diisopropyl ((butylamino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (11). Yield: 65% (0.27 g), light yellow oil; ^{31}P (CDCl_3) δ 22.1; ^{13}C NMR (CDCl_3) δ 14.1 ($\text{CH}_3(\text{CH}_2)_3\text{N}$), 20.4 (ArCH_3), 21.1 ($\text{CH}_2(\text{CH}_2)_2\text{N}$), 23.9 (d, $^3J_{\text{CP}} = 5.0$, $\text{CH}_3\text{CHO}^{\text{I}}$), 24.0 (d, $^3J_{\text{CP}} = 5.3$, $\text{CH}_3\text{CHO}^{\text{II}}$), 24.2 (d, $^3J_{\text{CP}} = 3.7$, $\text{CH}_3\text{CHO}^{\text{III}}$), 24.4 (d, $^3J_{\text{CP}} = 3.1$, $\text{CH}_3\text{CHO}^{\text{IV}}$), 32.3 ($\text{CH}_2\text{CH}_2\text{N}$), 48.1 (d, $^3J_{\text{CP}} = 14.6$, CH_2N), 50.1 (d, $^1J_{\text{CP}} = 159.0$, CHP), 71.3 (d, $^2J_{\text{CP}} = 7.4$, CHO^{I}), 71.9 (d, $^2J_{\text{CP}} = 7.0$, CHO^{II}), 118.1 (C_8), 120.8 (C_{4a}), 123.5 (C_3), 125.3 (C_5), 135.0 (C_7), 135.4 (C_6), 154.6 (C_{8a}), 155.9 (d, $^3J_{\text{CP}} = 5.5$, C_2), 176.7 (d, $^3J_{\text{CP}} = 5.6$, C_4); ^1H NMR (CDCl_3) 0.83 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{N}$), 1.15 (d, $J_{\text{HH}} = 5.6$, 3H, $\text{CH}_3\text{CHO}^{\text{I}}$), 1.22 (t, $J_{\text{HH}} = 5.7$, 3H, $\text{CH}_3\text{CHO}^{\text{II}}$), 1.25–1.33 (m, 8H, $\text{CH}_3\text{CHO}^{\text{III}}$, $\text{CH}_3\text{CHO}^{\text{IV}}$, $\text{CH}_2(\text{CH}_2)_2\text{N}$), 1.39 (t, $J_{\text{HH}} = 7.4$, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 1.76 (brs, NH), 2.43 (s, 3H, ArCH_3), 2.56 (qd, $J_{\text{HH}} = 7.6$, $J_{\text{HH}} = 5.3$, $J_{\text{HH}} = 4.0$, 2H, CH_2N), 4.51 (dd, $^2J_{\text{HP}} = 19.8$, $J_{\text{HH}} = 3.6$, 1H, CHP), 4.63 (h, $J_{\text{HH}} = 5.9$, $J_{\text{HH}} = 5.3$, 1H, CHO^{I}), 4.78 (h, $J_{\text{HH}} = 6.1$, $J_{\text{HH}} = 5.6$, 1H, CHO^{II}), 7.33 (dd, $J_{\text{HH}} = 8.7$, $J_{\text{HH}} = 3.5$, 1H, C_7H), 7.45 (d, $J_{\text{HH}} = 8.5$, 1H, C_8H), 7.98 (s, 1H, C_2H), 8.20 (d, $J_{\text{HH}} = 3.6$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 410.2016$, $\text{C}_{21}\text{H}_{33}\text{NO}_5\text{P}$ requires 410.2018.

Dibutyl ((butylamino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (12). Yield: 80% (0.35 g), light yellow oil; ^{31}P (CDCl_3) δ 24.1; ^{13}C NMR (CDCl_3) δ 13.5 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 13.6 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 13.9 ($\text{CH}_3(\text{CH}_2)_3\text{N}$), 18.6 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$), 18.7 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$), 20.2 ($\text{CH}_2(\text{CH}_2)_2\text{N}$), 20.9 (ArCH_3), 32.0 ($\text{CH}_2\text{CH}_2\text{N}$), 32.4 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 32.6 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 47.9 (d, $^3J_{\text{CP}} = 14.2$, CH_2N), 49.6 (d, $^1J_{\text{CP}} = 156.8$, CHP), 66.3 (d, $^2J_{\text{CP}} = 7.4$, $\text{CH}_2\text{O}^{\text{I}}$), 66.9 (d, $^2J_{\text{CP}} = 7.0$, $\text{CH}_2\text{O}^{\text{II}}$), 117.9 (C_8), 120.3 (d, $^2J_{\text{CP}} = 1.9$, C_3), 123.2 (C_{4a}), 125.3 (C_5), 134.9 (C_7), 135.2 (C_6), 154.4 (C_{8a}), 155.6 (d, $^3J_{\text{CP}} = 5.9$, C_2), 176.4 (d, $^3J_{\text{CP}} = 5.0$, C_4); ^1H NMR (CDCl_3) 0.82 (t, $J_{\text{HH}} = 7.5$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 0.87 (t, $J_{\text{HH}} = 7.7$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{N}$), 0.92 (t, $J_{\text{HH}} = 7.7$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 1.28 (ddd, $J_{\text{HH}} = 15.1$, $J_{\text{HH}} = 7.1$, $J_{\text{HH}} = 2.7$, 6H, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$, $\text{CH}_2(\text{CH}_2)_2\text{N}$), 1.40 (dd, $J_{\text{HH}} = 10.7$, $J_{\text{HH}} = 4.6$, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 1.52 (dt, $J_{\text{HH}} = 8.4$, $J_{\text{HH}} = 6.6$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 1.65 (dt, $J_{\text{HH}} = 8.5$, $J_{\text{HH}} = 6.6$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 1.79 (brs, NH), 2.46 (s, 3H, ArCH_3), 2.60 (t, $J_{\text{HH}} = 7.4$, 2H, CH_2N), 3.99 (q, $J_{\text{HH}} = 6.7$, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.16 (p, $J_{\text{HH}} = 6.7$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 4.59 (d, $^2J_{\text{HP}} = 19.7$, 1H, CHP), 7.37 (d, $J_{\text{HH}} = 8.6$, 1H, C_8H), 7.49 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.3$, 1H, C_7H), 8.01 (d, $J_{\text{HH}} = 2.2$, 1H, C_2H), 8.20 (d, $J_{\text{HH}} = 3.4$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 438.2329$, $\text{C}_{23}\text{H}_{38}\text{NO}_5\text{P}$ requires 438.2331.

Diethyl ((cyclohexylamino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (13). Yield: 65% (0.26 g), light yellow oil; ^{31}P (CDCl_3) δ 24.5; ^{13}C NMR (CDCl_3) δ 16.3 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.5 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 21.0 (ArCH_3), 24.6 (C_4'), 24.9 (C_4''), 26.0 (C_3'), 32.5 (C_2'), 34.2 (C_2''), 46.4 (d, $^1J_{\text{CP}} = 156.8$, CHP), 54.6 (d, $^3J_{\text{CP}} = 13.7$, C_1'), 62.6 (d, $^2J_{\text{CP}} = 7.3$, $\text{CH}_2\text{O}^{\text{I}}$), 63.4 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_2\text{O}^{\text{II}}$), 118.0 (C_8), 121.0 (C_3), 123.3 (C_{4a}), 125.3 (C_5), 134.9 (C_7), 135.2 (C_6), 154.5 (C_{8a}), 155.8 (d, $^3J_{\text{CP}} = 6.0$, C_2), 176.4 (d, $^3J_{\text{CP}} = 4.8$, C_4); ^1H NMR (CDCl_3) 0.98–1.14 (m, 5H, $^{\text{c}}\text{HexH}$), 1.17 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.31 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 1.47–1.54 (m, 1H, $^{\text{c}}\text{HexH}$), 1.59–1.70 (m, 3H, $^{\text{c}}\text{HexH}$), 1.84 (brs, NH), 1.93 (d, $J_{\text{HH}} = 12.0$, 1H, $^{\text{c}}\text{HexH}$), 2.43 (s, 3H, ArCH_3), 4.02 (h, $J_{\text{HH}} = 10.2$, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.22 (ddtd, $J_{\text{HH}} = 17.1$, $J_{\text{HH}} = 10.1$, $J_{\text{HH}} = 7.1$, $J_{\text{HH}} = 2.$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 4.71 (d, $^2J_{\text{HP}} = 21.4$, 1H, CHP), 7.34 (d, $J_{\text{HH}} = 8.6$, 1H, C_8H), 7.46 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.4$, 1H, C_7H), 7.98 (d, $J_{\text{HH}} = 2.4$, 1H, C_2H), 8.15 (d, $J_{\text{HH}} = 3.5$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 408.1864$, $\text{C}_{21}\text{H}_{31}\text{NO}_5\text{P}$ requires 408.1862.

Diethyl ((benzylamino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (14). Yield: 69% (0.29 g), yellow oil; ^{31}P (CDCl_3) δ 23.5; ^{13}C NMR (CDCl_3) δ 16.3 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.4 (d, $^3J_{\text{CP}} = 5.8$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 20.9 (ArCH_3), 29.6 (C_1'), 49.5 (d, $^1J_{\text{CP}} = 157.5$, CHP), 52.0 (d, $^3J_{\text{CP}} = 15.2$, CH_2N), 62.7 (d, $^2J_{\text{CP}} = 7.1$, $\text{CH}_2\text{O}^{\text{I}}$), 63.3 (d, $^2J_{\text{CP}} = 6.6$, $\text{CH}_2\text{O}^{\text{II}}$), 117.9 (C_8), 119.7 (d, $J_{\text{CP}} = 2.2$, C_3), 123.2 (C_{4a}), 125.2 (C_5), 127.1 (C_3'), 128.3 (d, $J_{\text{CP}} = 6.6$, C_2'), 134.9 (C_7), 135.3 (C_6), 154.4 (C_{8a}), 155.7 (d, $^3J_{\text{CP}} = 6.5$, C_2), 176.4 (d, $^3J_{\text{CP}} = 4.7$, C_4); ^1H NMR (CDCl_3) 1.24 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.33 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.28 (brs, NH), 2.48 (s, 3H, ArCH_3), 3.77 (q, $J_{\text{HH}} = 13.1$, 2H, CH_2N), 4.08 (tq, $J_{\text{HH}} = 7.3$, $J_{\text{HH}} = 3.5$, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.23 (q, $J_{\text{HH}} = 7.1$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 4.60 (d, $^2J_{\text{HP}} = 20.0$, 1H, CHP), 7.21–7.26 (m, 1H, $\text{C}_4'\text{H}$), 7.30 (d, $J_{\text{HH}} = 4.3$, 4H, $\text{C}_2'\text{H}$, $\text{C}_6'\text{H}$, $\text{C}_3'\text{H}$, $\text{C}_5'\text{H}$), 7.38 (d, $J_{\text{HH}} = 8.5$, 1H, C_8H), 7.50 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.3$, 1H, C_7H), 8.03 (d, $J_{\text{HH}} = 2.2$, 1H, C_2H), 8.21 (d, $J_{\text{HH}} = 3.4$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 416.1549$, $\text{C}_{22}\text{H}_{27}\text{NO}_5\text{P}$ requires 416.1545.

Diethyl (((2-hydroxyethyl)amino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (15). Yield: 81% (0.30 g), light yellow oil; ^{31}P (CDCl_3) δ 23.9; ^{13}C NMR (CDCl_3) δ 16.3 (d, $^3J_{\text{CP}} = 5.6$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.4 (d, $^3J_{\text{CP}} = 5.7$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 20.9 (ArCH₃), 49.2 (d, $^1J_{\text{CP}} = 158.4$, C₂), 49.8 (d, $J_{\text{CP}} = 12.9$, CH₂N), 61.0 (CH₂OH), 62.8 (d, $^2J_{\text{CP}} = 7.3$, CH₂O^I), 63.3 (d, $^2J_{\text{CP}} = 6.7$, CH₂O^{II}), 117.9 (C₈), 120.1 (C_{4a}), 123.2 (C₃), 125.2 (C₅), 135.1 (C₇), 135.4 (C₆), 154.5 (C_{8a}), 155.6 (d, $^1J_{\text{CP}} = 5.9$, C₂), 176.6 (d, $J_{\text{CP}} = 5.5$, C₄); ^1H NMR (CDCl_3) δ 1.4 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.35 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.57 (brs, 2H, NH, OH), 2.81 (ddt, $J_{\text{HH}} = 8.8$, $J_{\text{HH}} = 7.0$, $J_{\text{HH}} = 3.1$, 2H, CH₂OH), 3.57–3.75 (m, 2H), 4.09 (td, $J_{\text{HH}} = 7.4$, $J_{\text{HH}} = 1.9$, 2H, CH₂O^I), 4.24 (td, $J_{\text{HH}} = 7.3$, $J_{\text{HH}} = 1.9$, 2H CH₂O^{II}), 4.59 (d, $^2J_{\text{HP}} = 20.1$, 1H, CHP), 7.38 (d, $J_{\text{HH}} = 8.6$, 1H, C₈H), 7.51 (dd, $J_{\text{HH}} = 8.5$, $J_{\text{HH}} = 2.3$, 1H, C₇H), 8.01 (d, $J_{\text{HH}} = 2.2$, 1H, C₂H), 8.25 (d, $J_{\text{HH}} = 3.1$, 1H, C₅H); $[\text{M}+\text{H}]^+_{\text{found}} = 370.1343$, requires: C₁₇H₂₅NO₆P 370.1341.

Diethyl (((4-hydroxybutyl)amino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (16). Yield: 78% (0.31 g), light yellow oil; ^{31}P (CDCl_3) δ 23.6; ^{13}C NMR (CDCl_3) δ 16.4 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.5 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 21.0 (ArCH₃), 29.7 (CH₂(CH₂)₂OH), 31.3 (CH₂CH₂OH), 47.2 (d, $^3J_{\text{CP}} = 14.1$, CH₂NH), 49.9 (d, $^1J_{\text{CP}} = 158.6$, CHP) 62.8 (d, $^2J_{\text{CP}} = 7.1$, CHO^I), 63.1 (CH₂OH), 63.3 (d, $^2J_{\text{CP}} = 6.8$, CHO^{II}), 118.0 (C₈), 119.6 (C₃), 123.2 (C_{4a}), 125.3 (C₅), 135.2 (C₇), 135.5 (C₆), 154.5 (C_{8a}), 155.5 (d, $^1J_{\text{CP}} = 6.7$, C₂), 176.6 (d, $^2J_{\text{CP}} = 5.4$, C₄); ^1H NMR (CDCl_3) δ 1.24 (d, $J_{\text{HH}} = 7.0$, 2H, CH₂(CH₂)₃NH), 1.27 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$) 1.35 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 1.72 (dddd, $J_{\text{HH}} = 16.9$, $J_{\text{HH}} = 10.0$, $J_{\text{HH}} = 6.4$, $J_{\text{HH}} = 3.3$, 2H, CH₂(CH₂)₂NH), 2.47 (s, 3H, ArCH₃), 2.62 (bs, 2H, NH, OH), 2.85 (td, $J_{\text{HH}} = 7.1$, $J_{\text{HH}} = 6.6$, 2H, CH₂CH₂NH), 3.77 (td, $J_{\text{HH}} = 5.4$, $J_{\text{HH}} = 4.5$, $J_{\text{HH}} = 1.8$, 2H, CH₂NH), 4.07 (q, $J_{\text{HH}} = 8.4$, $J_{\text{HH}} = 7.7$, 2H, CH₂O^I), 4.23 (p, $J_{\text{HH}} = 7.2$, 2H, CH₂O^{II}), 4.57 (d, $J_{\text{HH}} = 20.2$, 1H, NH), 7.39 (d, $J_{\text{HH}} = 8.5$, 1H, C₈H), 7.51 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.3$, 1H, C₇H), 8.02 (d, $J_{\text{HH}} = 2.2$, 1H, C₂H), 8.21 (d, $J_{\text{HH}} = 3.2$, 1H, C₅H); $[\text{M}+\text{H}]^+_{\text{found}} = 398.1651$, requires: C₁₉H₂₉NO₆P 398.1654.

Diethyl ((pheylamino)(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (17). Yield: 89% (0.36 g), light yellow solid; Mp.: 140–142 °C; ^{31}P (CDCl_3) δ 22.8; ^{13}C NMR (CDCl_3) δ 16.1 (d, $^3J_{\text{CP}} = 5.7$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.4 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 20.9 (ArCH₃), 45.1 (d, $^1J_{\text{CP}} = 156.0$, CHP), 63.4 (d, $^2J_{\text{CP}} = 7.4$, CH₂O^I), 63.7 (d, $^2J_{\text{CP}} = 6.9$, CH₂O^{II}), 113.6 (C₃'), 118.0 (C₈), 118.7 (C₄'), 119.9 (d, $^2J_{\text{CP}} = 1.4$, C₃), 123.2 (C_{4a}), 125.2 (C₅), 129.3 (C₂'), 135.0 (C₇), 135.4 (C₆), 145.5 (d, $^3J_{\text{CP}} = 13.7$, C₁'), 154.5 (C_{8a}), 155.0 (d, $^3J_{\text{CP}} = 5.8$, C₂), 176.3 (d, $^3J_{\text{CP}} = 3.9$, C₄); ^1H NMR (CDCl_3) 1.19 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.33 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.46 (s, 3H, ArCH₃), 4.07 (ddd, $J_{\text{HH}} = 15.2$, $J_{\text{HH}} = 7.7$, $J_{\text{HH}} = 5.8$, 2H, CH₂O^I), 4.25 (p, $J_{\text{HH}} = 7.2$, 2H, CH₂O^{II}), 5.36 (d, $^2J_{\text{HP}} = 23.8$, 1H, CHP), 5.58–6.71 (m, 3H, C₂'H, C₆'H, C₄'H), 7.13 (t, $J_{\text{HH}} = 7.9$, 2H, C₃'H, C₅'H), 7.32 (d, $J_{\text{HH}} = 8.6$, 1H, C₈H), 7.47 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.3$, 1H, C₇H), 8.04 (d, $J_{\text{HH}} = 2.2$, 1H, C₂H), 8.13 (d, $J_{\text{HH}} = 3.6$, 1H, C₅H); $[\text{M}+\text{H}]^+_{\text{found}} = 402.1390$, C₂₁H₂₅NO₅P requires 402.1392.

Dibutyl ((6-methyl-4-oxo-4H-chromen-3-yl)(phenylamino)methyl)phosphonate (18). Yield: 85% (0.39 g), light yellow solid; Mp.: 158–160 °C; ^{31}P (CDCl_3) δ 22.7; ^{13}C NMR (CDCl_3) δ 13.4 (CH₃(CH₂)₃O^I), 13.6 (CH₃(CH₂)₃O^{II}), 18.5 (CH₂(CH₂)₂O^I), 18.7 (CH₂(CH₂)₂O^{II}), 20.9 (ArCH₃), 32.4 (d, $^3J_{\text{CP}} = 5.9$, CH₂CH₂O^I), 32.5 (d, $^3J_{\text{CP}} = 5.9$, CH₂CH₂O^{II}), 45.0 (d, $^1J_{\text{CP}} = 156.0$, CHP), 66.9 (d, $^2J_{\text{CP}} = 7.5$, CH₂O^I), 67.4 (d, $^2J_{\text{CP}} = 7.1$, CH₂O^{II}), 113.6 (C₃'), 118.0 (C₈), 118.7 (C₄') 120.2 (d, $^2J_{\text{CP}} = 1.3$, C₃), 123.1 (C_{4a}), 125.2 (C₅), 129.3 (C₂'), 135.1 (C₇), 135.4 (C₆), 145.6 (d, $^3J_{\text{CP}} = 13.6$, C₁'), 154.6 (C_{8a}), 155.0 (d, $^3J_{\text{CP}} = 5.6$, C₂), 176.2 (d, $^3J_{\text{CP}} = 3.9$, C₄); ^1H NMR (CDCl_3) 0.78 (t, $J_{\text{HH}} = 7.4$, 3H, CH₃(CH₂)₃O^I), 0.91 (t, $J_{\text{HH}} = 7.4$, 3H, CH₃(CH₂)₃O^{II}), 1.24 (h, $J_{\text{HH}} = 7.4$, 2H, CH₂(CH₂)₂O^I), 1.39 (h, $J_{\text{HH}} = 7.4$, 2H, CH₂(CH₂)₂O^{II}), 1.50 (dq, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 6.6$, 2H, CH₂CH₂O^I), 1.66 (ddd, $J_{\text{HH}} = 13.4$, $J_{\text{HH}} = 7.6$, $J_{\text{HH}} = 4.4$, 2H, CH₂CH₂O^{II}), 2.47 (s, 3H, ArCH₃), 3.94–4.08 (q, $J_{\text{HH}} = 6.7$, 2H, CH₂O^I), 4.19 (q, $J_{\text{HH}} = 6.8$, 2H, CH₂O^{II}), 4.85 (brs, 1H, NH), 5.40 (d, $^2J_{\text{HP}} = 23.8$, 1H, CHP), 6.68 (d, $J_{\text{HH}} = 7.5$, 2H, C₂'H, C₆'H), 6.73 (t, $J_{\text{HH}} = 7.3$, 1H, C₄'H), 7.14 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 7.3$, 2H, C₃'H, C₅'H), 7.33 (d, $J_{\text{HH}} = 8.6$, 1H, C₈H), 7.48 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.2$, 1H, C₇H), 8.05 (d, $J_{\text{HH}} = 2.3$, 1H, C₂H), 8.15 (d, $J_{\text{HH}} = 3.5$, 1H, C₅H); $[\text{M}+\text{H}]^+_{\text{found}} = 457.2018$, C₂₅H₃₂NO₅P requires 457.2016.

Dibutyl ((4-methoxyphenyl)amino(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (19). Yield: 74% (0.36 g), light yellow solid; Mp.: 190–192 °C; ^{31}P (CDCl_3) δ 22.9; ^{13}C NMR (CDCl_3) δ 13.4 (CH₃(CH₂)₃O^I), 13.6 (CH₃(CH₂)₃O^{II}), 18.5 (CH₂(CH₂)₂O^I), 18.7 (CH₂(CH₂)₂O^{II}), 20.9 (ArCH₃), 32.4 (d, $^3J_{\text{CP}} = 5.9$, CH₂CH₂O^I), 32.5 (d, $^3J_{\text{CP}} =$

5.9, CH₂CH₂O^{||}), 45.9 (d, ¹J_{CP} = 155.9, CHP), 55.7 (CH₃O), 66.8 (d, ²J_{CP} = 7.4, CH₂O^{||}), 67.4 (d, ²J_{CP} = 7.0, CH₂O^{||}), 114.9 (C_{3'}), 115.0 (C_{2'}), 118.0 (C₈), 120.2 (d, ²J_{CP} = 1.4, C₃), 123.2 (C_{4a}), 125.2 (C₅), 135.0 (C₇), 135.4 (C₆), 139.2 (d, ³J_{CP} = 13.6, C_{1'}), 152.9 (C_{4'}), 154.6 (C_{8a}), 155.1 (d, ³J_{CP} = 5.8, C₂), 176.4 (d, ³J_{CP} = 4.0, C₄); ¹H NMR (CDCl₃) 0.78 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 0.91 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 1.24 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.39 (dq, J_{HH} = 14.8, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.51 (dq, J_{HH} = 15.4, J_{HH} = 6.7, 2H, CH₂CH₂O^{||}), 1.66 (dt, J_{HH} = 15.6, J_{HH} = 6.4, 2H, CH₂CH₂O^{||}), 2.48 (s, 3H, CH₃O), 3.70 (s, 3H, ArCH₃), 3.94–4.08 (m, 2H, CH₂O^{||}), 4.19 (q, J_{HH} = 6.7, 2H, CH₂O^{||}), 4.52 (brt, J_{HH} = 8.9, 1H, NH), 5.40 (d, ²J_{HP} = 23.8, 1H, CHP), 6.63 (d, J_{HH} = 9.0, 2H, C_{2'}H, C_{6'}H), 6.73 (d, J_{HH} = 9.0, 2H, C_{3'}H, C_{5'}H), 7.14 (dd, J_{HH} = 8.6, J_{HH} = 7.3, 1H, C_{4'}H), 7.34 (d, J_{HH} = 8.5, 1H, C₈H), 7.48 (dd, J_{HH} = 8.6, J_{HH} = 2.2, 1H, C₇H), 8.04 (d, J_{HH} = 2.3, 1H, C₂H), 8.13 (d, J_{HH} = 7.5, 1H, C₅H); [M+H]⁺_{found} = 488.2124, C₂₆H₃₅NO₆P requires 488.2126.

Dibutyl ((4-chlorophenyl)amino(6-methyl-4-oxo-4H-chromen-3-yl)methyl)phosphonate (20). Yield: 70% (0.34 g), yellow solid; Mp.: 182–184 °C; ³¹P (CDCl₃) δ 22.4; ¹³C NMR (CDCl₃) δ 13.4 (CH₃(CH₂)₃O^{||}), 13.6 (CH₃(CH₂)₃O^{||}), 18.5 (CH₂(CH₂)₂O^{||}), 18.7 (CH₂(CH₂)₂O^{||}), 20.9 (ArCH₃), 32.4 (d, ³J_{CP} = 5.9, CH₂CH₂O^{||}), 32.5 (d, ³J_{CP} = 5.7, CH₂CH₂O^{||}), 45.1 (d, ¹J_{CP} = 156.6, CHP), 67.0 (d, ²J_{CP} = 7.6, CH₂O^{||}), 67.5 (d, ²J_{CP} = 7.1, CH₂O^{||}), 114.8 (C_{3'}), 118.0 (C₈), 119.9 (d, ²J_{CP} = 1.3, C₃), 123.1 (C_{4a}), 123.4 (C_{4'}), 125.2 (C₅), 129.1 (C_{2'}), 135.2 (C₇), 135.5 (C₆), 144.4 (d, ³J_{CP} = 13.5, C_{1'}), 154.6 (C_{8a}), 155.1 (d, ³J_{CP} = 5.6, C₂), 176.2 (d, ³J_{CP} = 4.1, C₄); ¹H NMR (CDCl₃) 0.77 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 0.90 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 1.23 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.38 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.50 (dq, J_{HH} = 8.6, J_{HH} = 6.6, 2H, CH₂CH₂O^{||}), 1.65 (ddd, J_{HH} = 13.5, J_{HH} = 7.6, J_{HH} = 4.5, 2H, CH₂CH₂O^{||}), 2.47 (s, 3H, ArCH₃), 3.94–4.07 (m, 2H, CH₂O^{||}), 4.19 (q, J_{HH} = 6.7, 2H, CH₂O^{||}), 4.99 (brt, J_{HH} = 9.0, 1H, NH), 5.34 (dd, ²J_{HP} = 23.8, J_{HH} = 6.6, 1H, CHP), 6.61 (d, J_{HH} = 8.9, 2H, C_{3'}H, C_{5'}H), 7.07 (d, J_{HH} = 8.8, 2H, C_{2'}H, C_{6'}H), 7.33 (d, J_{HH} = 8.5, 1H, C₈H), 7.49 (dd, J_{HH} = 8.6, J_{HH} = 2.2, 1H, C₇H), 8.04 (d, J_{HH} = 2.3, 1H, C₂H), 8.17 (d, J_{HH} = 3.5, 1H, C₅H); [M+H]⁺_{found} = 492.1628, C₂₅H₃₂ClN₂O₅P requires 492.1630.

Dibutyl ((6-methyl-4-oxo-4H-chromen-3-yl)(naphthalen-1-ylamino)methyl)phosphonate (21). Yield: 85% (0.34 g), light yellow solid; Mp.: 221–223 °C; ³¹P (CDCl₃) δ 22.6; ¹³C NMR (CDCl₃) δ 13.4 (CH₃(CH₂)₃O^{||}), 13.6 (CH₃(CH₂)₃O^{||}), 18.6 (CH₂(CH₂)₂O^{||}), 18.7 (CH₂(CH₂)₂O^{||}), 21.0 (ArCH₃), 32.4 (d, ³J_{CP} = 5.8, CH₂CH₂O^{||}), 32.5 (d, ³J_{CP} = 5.9, CH₂CH₂O^{||}), 45.3 (d, ¹J_{CP} = 155.9, CHP), 67.0 (d, ²J_{CP} = 7.6, CH₂O^{||}), 67.5 (d, ²J_{CP} = 7.0, CH₂O^{||}), 106.2 (C_{3'}), 117.9 (C_{6'}), 118.0 (C₈), 120.0 (d, ²J_{CP} = 1.4, C₃), 122.6 (C_{8'}), 123.2 (C_{4a}), 125.2 (C₅), 126.3 (d, J_{CP} = 6.0, C_{7'}), 127.5 (C_{3'}), 128.1 (C_{5'}), 129.1 (C_{4a'}), 134.8 (C_{8a'}), 135.1 (C₇), 135.4 (C₆), 143.3 (d, ³J_{CP} = 13.6, C_{2'}), 154.6 (C_{8a}), 154.9 (d, ³J_{CP} = 5.5, C₂), 176.4 (d, ³J_{CP} = 3.8, C₄); ¹H NMR (CDCl₃) 0.80 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 0.89 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 1.27 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.39 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.53 (dq, J_{HH} = 8.6, J_{HH} = 6.7, 2H, CH₂CH₂O^{||}), 1.67 (dq, J_{HH} = 8.7, J_{HH} = 6.7, 2H, CH₂CH₂O^{||}), 2.49 (s, 3H, ArCH₃), 4.03–4.09 (m, 2H, CH₂O^{||}), 4.23 (q, J_{HH} = 6.7, 2H, CH₂O^{||}), 5.09 (brs, 1H, NH), 5.54 (d, ²J_{HP} = 23.8, 1H, CHP), 6.88 (d, J_{HH} = 2.5, 1H, C_{3'}H), 7.01 (dt, J_{HH} = 8.9, J_{HH} = 2.3, 1H, C_{1'}H), 7.20 (ddd, J_{HH} = 8.1, J_{HH} = 6.9, J_{HH} = 1.2, 1H, C₇H), 7.33 (td, J_{HH} = 8.4, J_{HH} = 1.7, 2H, C_{6'}H, C_{7'}H), 7.47 (dd, J_{HH} = 8.6, J_{HH} = 2.3, 1H, C_{8'}H), 7.59 (d, J_{HH} = 8.2, 1H, C₈H), 7.65 (dd, J_{HH} = 8.7, J_{HH} = 6.9, 1H, C_{5'}H), 8.09 (d, J_{HH} = 1.6, 1H, C₂H), 8.20 (d, J_{HH} = 3.2, 1H, C₅H); [M+H]⁺_{found} = 508.2175, C₂₉H₃₅NO₅P requires 508.2178.

Dibutyl ((6-methyl-4-oxo-4H-chromen-3-yl)(pyridin-4-ylamino)methyl)phosphonate (22). Yield: 45% (0.21 g), yellow oil; ³¹P (CDCl₃) δ 22.3; ¹³C NMR (CDCl₃) δ 13.5 (CH₃(CH₂)₃O^{||}), 13.6 (CH₃(CH₂)₃O^{||}), 18.6 (CH₂(CH₂)₂O^{||}), 18.7 (CH₂(CH₂)₂O^{||}), 20.9 (ArCH₃), 32.4 (d, ³J_{CP} = 5.9, CH₂CH₂O^{||}), 32.6 (d, ³J_{CP} = 5.6, CH₂CH₂O^{||}), 44.9 (d, ¹J_{CP} = 159.3, CHP), 66.7 (d, ²J_{CP} = 7.4, CH₂O^{||}), 67.2 (d, ²J_{CP} = 7.0, CH₂O^{||}), 108.2 (C_{3'}), 114.0 (C_{3''}), 118.0 (C₈), 119.9 (d, ²J_{CP} = 1.2, C₃), 123.5 (C_{4a}), 125.2 (C₅), 135.0 (C₇), 135.3 (C₆), 137.6 (C_{2'}), 147.8 (C_{2''}), 154.5 (C_{8a}), 155.0 (d, ³J_{CP} = 7.6, C₂), 156.8 (d, ³J_{CP} = 10.4, C_{1'}), 176.6 (d, ³J_{CP} = 3.4, C₄); ¹H NMR (CDCl₃) 0.80 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 0.88 (t, J_{HH} = 7.4, 3H, CH₃(CH₂)₃O^{||}), 1.26 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.35 (h, J_{HH} = 7.4, 2H, CH₂(CH₂)₂O^{||}), 1.53 (dt, J_{HH} = 14.3, J_{HH} = 6.6, 2H, CH₂CH₂O^{||}), 1.62 (dt, J_{HH} = 13.9, J_{HH} = 6.4, 2H, CH₂CH₂O^{||}), 2.46 (s, 3H, ArCH₃), 4.04 (dddd,

$J_{\text{HH}} = 17.0$, $J_{\text{HH}} = 10.0$, $J_{\text{HH}} = 6.9$, $J_{\text{HH}} = 3.3$, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.15 (qt, $J_{\text{HH}} = 6.7$, $J_{\text{HH}} = 3.8$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 5.80 (d, $^2J_{\text{HP}} = 20.4$, 1H, CHP), 5.89 (brt, $J_{\text{HH}} = 8.9$, 1H, NH), 6.52 (d, $J_{\text{HH}} = 8.4$, 1H, $\text{C}_6'\text{H}$), 6.60 (dd, $J_{\text{HH}} = 6.9$, $J_{\text{HH}} = 5.3$, 1H, $\text{C}_3'\text{H}$), 7.34 (d, $J_{\text{HH}} = 8.5$, 1H, C_8H), 7.39 (ddd, $J_{\text{HH}} = 8.7$, $J_{\text{HH}} = 7.1$, $J_{\text{HH}} = 1.9$, 1H, C_7H), 7.48 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.2$, 1H, $\text{C}_2'\text{H}$), 8.02 (d, $J_{\text{HH}} = 2.9$, 1H, C_2H), 8.09 (dd, $J_{\text{HH}} = 5.3$, $J_{\text{HH}} = 1.3$, 1H, $\text{C}_5'\text{H}$), 8.16 (d, $J_{\text{HH}} = 3.2$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 459.1971$, $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5\text{P}$ requires 459.1968.

Dibutyl ((6-ethyl-4-oxo-4H-chromen-3-yl)(phenylamino)methyl)phosphonate (23). Yield: 83% (0.39 g), light yellow solid; Mp.: 165–167 °C; ^{31}P (CDCl_3) δ 22.8; ^{13}C NMR (CDCl_3) δ 13.4 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 13.6 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 15.5 (ArCH_2CH_3), 18.5 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$), 18.7 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$), 28.4 (ArCH_3), 32.4 (d, $^3J_{\text{CP}} = 5.8$, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 32.5 (d, $^3J_{\text{CP}} = 5.8$, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 45.1 (d, $^1J_{\text{CP}} = 155.9$, CHP), 67.0 (d, $^2J_{\text{CP}} = 7.6$, $\text{CH}_2\text{O}^{\text{I}}$), 67.5 (d, $^2J_{\text{CP}} = 6.9$, $\text{CH}_2\text{O}^{\text{II}}$), 113.6 (C_3'), 118.1 (C_8), 118.7 (C_4'), 120.1 (d, $^2J_{\text{CP}} = 1.2$, C_3), 123.2 (C_{4a}), 124.0 (C_5), 129.3 (C_2'), 134.1 (C_7), 141.7 (C_6), 145.6 (d, $^3J_{\text{CP}} = 13.6$, C_1'), 154.7 (C_{8a}), 155.0 (d, $^3J_{\text{CP}} = 5.6$, C_2), 176.4 (d, $^3J_{\text{CP}} = 4.0$, C_4); ^1H NMR (CDCl_3) 0.77 (t, $J_{\text{HH}} = 7.4$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 0.91 (t, $J_{\text{HH}} = 7.4$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 1.24 (h, $J_{\text{HH}} = 7.4$, 2H, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$), 1.30 (t, $J_{\text{HH}} = 7.6$, 3H, ArCH_2CH_3), 1.39 (h, $J_{\text{HH}} = 7.4$, 2H, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$), 1.50 (dq, $J_{\text{HH}} = 8.8$, $J_{\text{HH}} = 6.6$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 1.65 (ddd, $J_{\text{HH}} = 13.4$, $J_{\text{HH}} = 7.6$, $J_{\text{HH}} = 4.3$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 2.78 (q, $J_{\text{HH}} = 7.6$, 2H, ArCH_2), 3.97–4.06 (m, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.20 (q, $J_{\text{HH}} = 6.8$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 4.84 (brs, 1H, NH), 5.40 (d, $^2J_{\text{HP}} = 23.8$, 1H, CHP), 6.68 (d, $J_{\text{HH}} = 7.6$, 2H, $\text{C}_2'\text{H}$, $\text{C}_6'\text{H}$), 6.73 (tt, $J_{\text{HH}} = 7.3$, $J_{\text{HH}} = 1.1$, 1H, $\text{C}_4'\text{H}$), 7.14 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 7.3$, 2H, $\text{C}_3'\text{H}$, $\text{C}_5'\text{H}$), 7.36 (d, $J_{\text{HH}} = 8.6$, 1H, C_8H), 7.51 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 2.3$, 1H, C_7H), 8.08 (d, $J_{\text{HH}} = 2.0$, 1H, C_2H), 8.15 (d, $J_{\text{HH}} = 3.6$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 472.2175$, $\text{C}_{26}\text{H}_{35}\text{NO}_5\text{P}$ requires 472.2173.

Dibutyl ((6-fluoro-4-oxo-4H-chromen-3-yl)(phenylamino)methyl)phosphonate (24). Yield: 77% (0.35 g), light yellow solid; Mp: 170–172 °C; ^{31}P (CDCl_3) δ 22.4; ^{13}C NMR (CDCl_3) δ 13.4 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 13.6 ($\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 18.5 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$), 18.7 ($\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$), 32.4 (d, $^3J_{\text{CP}} = 5.9$, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 32.5 (d, $^3J_{\text{CP}} = 5.7$, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 45.1 (d, $^1J_{\text{CP}} = 155.8$, CHP), 67.0 (d, $^2J_{\text{CP}} = 7.6$, $\text{CH}_2\text{O}^{\text{I}}$), 67.6 (d, $^2J_{\text{CP}} = 7.2$, $\text{CH}_2\text{O}^{\text{II}}$), 110.7 (d, $^2J_{\text{CP}} = 23.8$, C_7), 113.6 (C_3'), 118.8 (C_4'), 119.9 (d, $^2J_{\text{CP}} = 1.3$, C_3), 120.4 (d, $^2J_{\text{CP}} = 8.0$, C_{4a}), 122.1 (d, $^2J_{\text{CP}} = 25.6$, C_5), 124.6 (d, $^2J_{\text{CP}} = 7.2$, C_8), 129.4 (C_2'), 145.5 (d, $^3J_{\text{CP}} = 13.6$, C_1'), 152.5 (C_{8a}), 155.3 (d, $^3J_{\text{CP}} = 5.7$, C_2), 159.7 (d, $J_{\text{CP}} = 247.3$, C_6), 175.5 (d, $^3J_{\text{CP}} = 3.9$, C_4); ^1H NMR (CDCl_3) 0.79 (t, $J_{\text{HH}} = 7.4$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{I}}$), 0.91 (t, $J_{\text{HH}} = 7.4$, 3H, $\text{CH}_3(\text{CH}_2)_3\text{O}^{\text{II}}$), 1.25 (h, $J_{\text{HH}} = 7.4$, 2H, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{I}}$), 1.39 (h, $J_{\text{HH}} = 7.4$, 2H, $\text{CH}_2(\text{CH}_2)_2\text{O}^{\text{II}}$), 1.51 (dq, $J_{\text{HH}} = 8.8$, $J_{\text{HH}} = 6.6$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{I}}$), 1.65 (dq, $J_{\text{HH}} = 8.8$, $J_{\text{HH}} = 7.0$, 2H, $\text{CH}_2\text{CH}_2\text{O}^{\text{II}}$), 3.98–4.08 (m, 2H, $\text{CH}_2\text{O}^{\text{I}}$), 4.19 (q, $J_{\text{HH}} = 6.8$, 2H, $\text{CH}_2\text{O}^{\text{II}}$), 4.83 (brs, 1H, NH), 5.37 (d, $^2J_{\text{HP}} = 23.8$, 1H, CHP), 6.67 (d, $J_{\text{HH}} = 7.3$, 2H, $\text{C}_2'\text{H}$, $\text{C}_6'\text{H}$), 6.74 (t, $J_{\text{HH}} = 7.4$, 1H, $\text{C}_4'\text{H}$), 7.15 (dd, $J_{\text{HH}} = 8.6$, $J_{\text{HH}} = 7.3$, 2H, $\text{C}_3'\text{H}$, $\text{C}_5'\text{H}$), 7.38–7.43 (m, 1H, C_8H), 7.46 (dd, $J_{\text{HH}} = 9.1$, $J_{\text{HH}} = 4.3$, 1H, C_7H), 7.91 (dd, $J_{\text{HH}} = 8.2$, $J_{\text{HH}} = 3.0$, 1H, C_2H), 8.18 (d, $J_{\text{HH}} = 3.5$, 1H, C_5H); $[\text{M}+\text{H}]^+_{\text{found}} = 462.1767$, $\text{C}_{24}\text{H}_{30}\text{FNO}_5\text{P}$ requires 462.1764.

Ethyl ((6-ethyl-4-oxo-4H-chromen-3-yl)(phenylamino)methyl)(phenyl)phosphinate (25). Yield: 72% (0.32 g), yellow solid; 184–186 °C; characterized as a mixture; **isomer A**: ^{31}P (CDCl_3) δ 37.8; ^{13}C NMR (CDCl_3) δ 15.39 (d, $^3J_{\text{CP}} = 3.2$, $\text{CH}_3\text{CH}_2\text{O}$), 16.3 (d, $J_{\text{CP}} = 5.8$, ArCH_2CH_3), 28.3 (ArCH_2), 47.1 (d, $^1J_{\text{CP}} = 111.3$, CHP), 62.0 (d, $^2J_{\text{CP}} = 7.1$, CH_2O), 113.5 (C_3'), 117.9 (C_8), 118.4 (C_4'), 119.81 (d, $^2J_{\text{CP}} = 1.4$, C_3), 122.9 (C_{4a}), 123.8 (C_5), 128.1 (d, $J_{\text{CP}} = 132.1$, C_1''), 128.2 (d, $J_{\text{CP}} = 12.8$, C_2''), 129.2 (C_2'), 132.2 (d, $J_{\text{CP}} = 10.1$, C_3''), 132.7 (d, $J_{\text{CP}} = 2.8$, C_4''), 133.8 (C_7), 141.5 (C_6), 145.5 (d, $^3J_{\text{CP}} = 13.2$, C_1'), 154.5 (C_{8a}), 154.7 (d, $^3J_{\text{CP}} = 5.0$, C_2), 175.9 (d, $^3J_{\text{CP}} = 3.3$, C_4); ^1H NMR (CDCl_3) 1.11 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.35 [dt, $J_{\text{HH}} = 15.1$, $J_{\text{HH}} = 7.3$, 6H, ArCH_2CH_3 (**A**) and (**B**)], 2.71 (q, $J_{\text{HH}} = 7.6$, 2H, ArCH_2), 3.85–3.98 (m, 2H, CH_2O), 4.93 (brs, 1H, NH) 5.51 (d, $^2J_{\text{HP}} = 17.5$, 1H, CHP), 6.59 (d, $J_{\text{HH}} = 7.4$, 2H, $\text{C}_2'\text{H}$, $\text{C}_6'\text{H}$), 6.66 (t, $J_{\text{HH}} = 7.3$, 1H, $\text{C}_4'\text{H}$), 7.07 (dd, $J_{\text{HH}} = 8.7$, $J_{\text{HH}} = 7.3$, 2H, $\text{C}_3'\text{H}$, $\text{C}_5'\text{H}$), 7.28 (d, $J_{\text{HH}} = 8.6$, 1H, $\text{C}_5'\text{H}$), 7.35 (td, $J_{\text{HH}} = 7.6$, $J_{\text{HH}} = 3.6$, 1H, $\text{C}_3''\text{H}$), 7.50 (d, $J_{\text{HH}} = 3.6$, 1H, $\text{C}_5''\text{H}$), 7.52 (dd, $J_{\text{HH}} = 7.3$, $J_{\text{HH}} = 3.0$, 1H, $\text{C}_4''\text{H}$), 7.78 (dt, $J_{\text{HH}} = 6.9$, $J_{\text{HH}} = 1.4$, 1H, $\text{C}_2''\text{H}$), 7.80 (dt, $J_{\text{HH}} = 6.9$, $J_{\text{HH}} = 1.4$, 1H, $\text{C}_6''\text{H}$), 7.84 (d, $J_{\text{HH}} = 2.2$, 1H, C_2H), 8.08 (d, $J_{\text{HH}} = 3.5$, 1H, C_5H); **isomer B**: ^{31}P (CDCl_3) δ 39.0; ^{13}C NMR (CDCl_3) δ 15.41 (d, $^3J_{\text{CP}} = 3.1$, $\text{CH}_3\text{CH}_2\text{O}$), 16.6 (d, $J_{\text{CP}} = 5.9$, ArCH_2CH_3), 28.4 (ArCH_2), 47.4 (d, $^1J_{\text{CP}} = 106.1$, CHP), 62.4 (d, $^2J_{\text{CP}} = 7.1$, $\text{CH}_2\text{O}^{\text{I}}$), 113.8 (C_3'), 118.2 (C_8), 118.6 (C_4'), 119.93 (d, $^2J_{\text{CP}} = 1.4$, C_3), 123.1 (C_{4a}), 123.9 (C_5), 128.7 (d, $J_{\text{CP}} = 12.8$, C_2''), 129.2 (d, $J_{\text{CP}} = 147.7$, C_1''), 129.3

(C₂'), 132.4 (d, $J_{CP} = 9.8$, C₃''), 132.7 (d, $J_{CP} = 2.8$, C₄''), 132.9 (C₇), 141.7 (C₆), 145.8 (d, $^3J_{CP} = 11.1$, C₁'), 154.8 (C_{8a}), 155.3 (d, $^3J_{CP} = 5.6$, C₂), 176.8 (d, $^3J_{CP} = 3.0$, C₄); ¹H NMR (CDCl₃) 1.25 (t, $J_{HH} = 7.6$, 3H, CH₃CH₂O), 2.80 (q, $J_{HH} = 7.6$, 2H, ArCH₂), 4.14–4.32 (m, 2H, CH₂O), 4.93 (brs, 1H, NH), 5.52 (d, $^2J_{HP} = 16.8$, 1H, CHP), 6.70 (d, $J_{HH} = 7.5$, 2H, C₂'H, C₆'H), 6.73 (t, $J_{HH} = 7.3$, 1H, C₄'H), 7.14 (dd, $J_{HH} = 8.5$, $J_{HH} = 7.3$, 2H, C₃'H, C₅'H), 7.39 (d, $J_{HH} = 8.5$, 1H, C₅'H), 7.43 (ddd, $J_{HH} = 7.6$, $J_{HH} = 3.7$, $J_{HH} = 1.3$, 1H, C₃''H), 7.54 (d, $J_{HH} = 2.3$, 1H, C₅''H), 7.57 (dd, $J_{HH} = 7.4$, $J_{HH} = 1.6$, 1H, C₄''H), 8.01 (dt, $J_{HH} = 6.8$, $J_{HH} = 1.5$, 1H, C₂''H), 8.03 (dt, $J_{HH} = 7.0$, $J_{HH} = 1.4$, 1H, C₆''H), 8.12 (d, $J_{HH} = 2.2$, 1H, C₂H), 8.21 (d, $J_{HH} = 3.2$, 1H, C₅H); [M+H]⁺_{found} = 448.1599, C₂₆H₂₇NO₄P requires 448.1596.

Ethyl ((6-fluoro-4-oxo-4H-chromen-3-yl)(phenylamino)methyl)(phenyl)phosphinate (26). Yield: 65% (0.28 g), yellow solid; Mp: 178–180 °C; characterized as a mixture; **isomer A:** ³¹P (CDCl₃) δ 37.6; ¹³C NMR (CDCl₃) δ 16.3 (d, $^3J_{CP} = 5.9$, CH₃CH₂O), 47.1 (d, $^1J_{CP} = 111.3$, CHP), 62.0 (d, $^2J_{CP} = 7.0$, CH₂O), 110.5 (d $J_{CP} = 23.6$, C₅) 113.5 (C₃'), 118.6 (C₄'), 119.56 (d, $^2J_{CP} = 1.3$, C₃), 120.2 (d, $J_{CP} = 7.9$, C_{4a}), 121.9 (d, $J_{CP} = 23.2$, C₇) 124.2 (d, $J_{CP} = 7.4$, C₅), 127.9 (d, $^1J_{CP} = 132.3$, C₁''), 128.3 (d, $^3J_{CP} = 13.1$, C₃''), 128.9 (C₂'), 132.2 (d, $^2J_{CP} = 10.1$, C₂''), 132.9 (d, $J_{CP} = 2.9$, C₄''), 145.4 (d, $^3J_{CP} = 12.9$, C₁'), 152.2 (C_{8a}), 154.9 (d, $^3J_{CP} = 4.9$, C₂), 159.5 (d, $J_{CP} = 247.3$, C₆), 175.1 (d, $^3J_{CP} = 2.7$, C₄); ¹H NMR (CDCl₃) 1.11 (t, $J_{HH} = 7.0$, 3H, CH₃CH₂O), 3.83–4.00 (m, 2H, CH₂O), 4.93 (brs, 1H, NH), 5.48 (d, $^2J_{HP} = 17.4$, 1H, CHP), 6.57 (d, $J_{HH} = 8.6$, 1H, C₅'H), 6.66 (d, $J_{HH} = 7.5$, 1H, C₄'H), 6.68 (d, $J_{HH} = 1.1$, 1H, C₆'H), 7.08 (dd, $J_{HH} = 8.6$, $J_{HH} = 7.3$, 2H, C₃'H, C₅'H), 7.34 (dd, $J_{HH} = 7.9$, $J_{HH} = 3.8$, 3H, C₅, C₇, C₈), 7.41 (dd, $J_{HH} = 9.2$, $J_{HH} = 3.1$, 2H, C₃''H, C₅''H), 7.64 (dd, $J_{HH} = 8.2$, $J_{HH} = 3.0$, 1H, C₄''H), 7.77 (ddt, $J_{HH} = 11.7$, $J_{HH} = 6.9$, $J_{HH} = 1.4$, 2H, C₂''H, C₆''H), 8.11 (d, $J_{HH} = 3.5$, 1H, C₂H); **isomer B:** ³¹P (CDCl₃) δ 38.7; ¹³C NMR (CDCl₃) δ 16.6 (d, $^3J_{CP} = 6.0$, CH₃CH₂O), 47.4 (d, $^1J_{CP} = 105.8$, CHP), 62.6 (d, $^2J_{CP} = 7.0$, CH₂O), 110.7 (d $J_{CP} = 23.7$, C₅) 113.7 (C₃'), 118.7 (C₄'), 119.59 (d, $^2J_{CP} = 1.5$, C₃), 120.2 (d, $J_{CP} = 8.0$, C_{4a}), 122.1 (d, $J_{CP} = 23.3$, C₇) 124.5 (d, $J_{CP} = 7.4$, C₅), 128.8 (d, $^3J_{CP} = 12.9$, C₃''), 128.9 (d, $^1J_{CP} = 132.3$, C₁''), 129.4 (C₂'), 132.4 (d, $^2J_{CP} = 9.7$, C₂''), 133.0 (d, $J_{CP} = 3.0$, C₄''), 145.7 (d, $^3J_{CP} = 10.9$, C₁'), 152.6 (C_{8a}), 155.5 (d, $^3J_{CP} = 5.8$, C₂), 159.7 (d, $J_{CP} = 247.2$, C₆), 176.0 (d, $^3J_{CP} = 2.9$, C₄); ¹H NMR (CDCl₃) 1.31 (t, $J_{HH} = 7.1$, 3H, CH₃CH₂O), 4.12–4.33 (m, 2H, CH₂O), 4.93 (brs, 1H, NH), 5.49 (d, $^2J_{HP} = 17.4$, 1H, CHP), 6.59 (d, $J_{HH} = 8.7$, 1H, C₅'H), 6.70 (d, $J_{HH} = 1.2$, 1H, C₄'H), 6.74 (t, $J_{HH} = 7.4$, 1H, C₆'H), 7.15 (dd, $J_{HH} = 8.6$, $J_{HH} = 7.3$, 2H, C₃'H, C₅'H), 7.52 (dd, $J_{HH} = 7.7$, $J_{HH} = 3.6$, 3H, C₅, C₇, C₈), 7.59 (dd, $J_{HH} = 7.3$, $J_{HH} = 1.4$, 2H, C₃''H, C₅''H), 7.94 (dd, $J_{HH} = 8.2$, $J_{HH} = 3.1$, 1H, C₄''H), 8.01 (ddt, $J_{HH} = 12.0$, $J_{HH} = 6.9$, $J_{HH} = 1.4$, 2H, C₂''H, C₆''H), 8.24 (d, $J_{HH} = 3.1$, 1H, C₂H); [M+H]⁺_{found} = 438.1192, C₂₄H₂₂FNO₄P requires 438.1190.

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Supplementary Material

The supporting information is available free of charge on the website and contains proof of structures, ¹H NMR, ¹³C NMR and ³¹P NMR spectra for all compounds.

References

1. Bálint, E.; Tripolszky A.; Tajti, Á. *Synthesis of α -aminophosphonates by the Kabachnik–Fields reaction and by the Pudovik reaction*, In: Keglevich, G. Ed. *Organophosphorus Chemistry – Novel Developments*, Germany: Walter de Gruyter GmbH, **2018**; pp 108-147.
<https://doi.org/10.1515/9783110535839-006>
2. Allen, D. W.; Loakes, D.; Tebby, J. C. Eds., *Organophosphorus Chemistry, The Royal Society of Chemistry*: London, **2016**.
<https://doi.org/10.1039/9781849732819>
3. Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anticancer. Agents* **2001**, *1*, 301.
<https://doi.org/10.2174/1568011013354543>
4. Zhang, B., Hu, X.-T., Gu, J., Yang, Y.-S., Duan, Y.-T., and Zhu, H.-L. *Bioorg. Chem.* **2020**, *105*, 104390.
<https://doi.org/10.1016/j.bioorg.2020.104390>
5. Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. *Bioorg. Med. Chem.* **2012**, *20*, 2252.
<https://doi.org/10.1016/j.bmc.2012.02.015>
6. Mucha, A.; Kafarski, P.; Berlicki, Ł. *J. Med. Chem.* **2011**, *54*, 5955.
<https://doi.org/10.1021/jm200587f>
7. Heymann, D. *Curr Pharm Des.* **2010**, *16*, 2948.
<https://doi.org/10.2174/138161210793563572>
8. Gudipati, R.; Kandula, V.; Raghavulu, K.; Basavaiah, K.; Yennam, S.; Behera, M. *ChemistrySelect* **2020**, *5*, 7093.
<https://doi.org/10.1002/slct.202001749>
9. Balakrishna, C.; Gudipati, R.; Kandula, V.; Yennam, S.; Devi, B. U.; Behera, M. *New J. Chem.* **2019**, *43*, 2458.
<https://doi.org/10.1039/c8nj05554h>
10. Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. *Eur. J. Med. Chem.* **2014**, *78*, 340.
<https://doi.org/10.1016/j.ejmech.2014.03.047>
11. Chohan, Z. H.; Iqbal, M. S.; Aftab, S. K. *Appl. Organomet. Chem.* **2010**, *24*, 47.
<https://doi.org/10.1002/aoc.1587>
12. Reis, J.; Gaspar, A.; Milhazes N.; Borges, F. *J. Med. Chem.*, **2017**, *60*, 7941.
<https://doi.org/10.1021/acs.jmedchem.6b01720>
13. Ibrahim, M. A.; El-Sayed Ali, T.; El-Gohary, N. M.; El-Kazak, A. M. *Eur. J. Chem.* **2013**, *4*, 311.
<https://doi.org/10.5155/eurjchem.4.3.311-328.815>
14. Mohsin, N. A.; Irfan, M.; Hassan, S.; Saleem, U. *Pharm. Chem. J.* **2020**, *54*, 241.
<https://doi.org/10.1007/s11094-020-02187-x>
15. Kostka, K. *Roczniki Chem.* **1966**, *40*, 1683.
16. Lacova, M.; Puchala, A.; Soleanyova, E.; Lac, J.; Kois, P.; Chovancova, J.; Rasala, D. *Molecules* **2005**, *10*, 809.
<https://doi.org/10.3390/10070809>
17. Al-Rashida, M.; Batool, G.; Sattar, A.; Ejaz, S.; Khan, S.; Lecka, J.; Sévigny, J.; Hameed, A.; Iqbal, J. *Eur. J. Med. Chem.* **2016**, *115*, 484.
<https://doi.org/10.1016/j.ejmech.2016.02.073>
18. Murugesh, N.; Haribabu, J.; Arumugam, K.; Balachandran, C.; Swaathy, R.; Aoki, S.; Sreekanth, A.; Karvembu, R.; Vedachalam, S. *New J. Chem.* **2019**, *43*, 13509.
<https://doi.org/10.1039/C9NJ02650A>

19. Assiri, M. A.; Ali, T. E.; Ali, M. M.; Yahia, I. S. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2018**, *193*, 668.
<https://doi.org/10.1080/10426507.2018.1487969>
20. Ma, C.; Li, J. *Compos. B. Eng.* **2019**, *178*, 107471.
<https://10.1016/j.compositesb.2019.107471>
21. Kabachnik, M.I.; Medved, T.Y. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689.
22. Fields, E.K. *J. Am. Chem. Soc.* **1952**, *74*, 1528.
<https://doi.org/10.1021/ja01126a054>
23. Keglevich, G.; Bálint, E. *Molecules* **2012**, *17*, 12821.
<https://doi.org/10.3390/molecules171112821>
24. Müller, T.J.J. Ed. *Multicomponent Reactions 1*. In *Science of Synthesis*; Thieme: Stuttgart, Germany, 2014.
<https://doi.org/10.1002/anie.201408144>
25. Baral, E.R.; Sharma, K.; Akhtar, M.S.; Lee, Y.R. *Org. Biomol. Chem.* **2016**, *14*, 10285.
<https://doi.org/10.1039/C6OB02015A>
26. Jaiyeola, A. O.; Anand, K.; Kasumbwe, K.; Ramesh, M.; Gengan, R. M. *J. Photochem. Photobiol., B: Biology* **2017**, *166*, 136.
<https://doi.org/10.1016/j.jphotobiol.2016.11.014>
27. Ramalingam, S.; Kumar, P. *Catal. Lett.*, **2008**, *125*, 315.
<https://doi.org/10.1007/s10562-008-9562-x>
28. Ali, T. E.; Abdel-Aziz, S. A.; El-Edfawy, S. M.; Mohamed, El-Hossain A.; Abdel-Kariem, S. M. *Heterocycles*, **2013**, *87*, 2513.
<https://doi.org/10.3987/COM-13-12836>
29. Shaikh, S.; Dhavan, P.; Ramana, M. M. V.; Jadhav, B. L. *Mol. Divers.*, **2021**, *25*, 811.
<https://doi.org/10.1007/s11030-020-10060-y>
30. Lang, S.-Y.; Wang, D.-Z.; Cao, L.-H. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009**, *184*, 2560.
<https://doi.org/10.1080/10426500802529127>
31. Consiglio, G. A.; Failla, S.; Finocchiaro, P.; Siracusa, V. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1998**, *143*, 159.
<https://doi.org/10.1080/10426509808045494>
32. Ali, T. E.; Abdel-Aziz, S. A.; El-Edfawy, S. M.; Mohamed, E.-H. A.; Abdel-Kariem, S. M. *Synth. Commun.* **2014**, *44*, 3610.
<https://doi.org/10.1080/00397911.2014.948965>

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