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One-pot synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives using β-cyclodextrin as reusable catalyst in water

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ABSTRACT

Various 2-amino-4*H*-chromen-4-yl phosphonate derivatives were synthesized in good yields by condensation of salicylaldehyde, malononitrile or ethylcyanoacetate, and triethyl phosphite using β-cyclodextrin as a reusable catalyst under neutral conditions, in water.

In the past, drug development has been done with iterative manipulation of individual structures with the aid of fundamental chemical reactions. Creation of combinatorial libraries of molecules containing different pharmacophoric components, which are responsible for varied biological activity, is presently required. In this regard, a large number of new and efficient synthetic strategies have been developed by synthetic chemists. Multi-component condensation (MCC) strategy is one such synthetic tool used by scientists all over the world to create new libraries of molecules with diverse biological activities.

Multi-component condensation (MCC) reactions are one-pot procedures in which two or more components react in a single operation to obtain a product, which incorporates all the reactants with elimination of simple molecules like water. These multi-component condensations which differ from multi-step processes are efficient strategies in the modern drug discovery and development.

Phosphonate is a 'bioisostere' of ester moiety and its analogues are found to possess widespread applications as enzyme inhibitors,[1] antibiotics, pharmacological agents,[2] and reaction intermediates in organic synthesis.[3] Numerous properties associated with this bioisostere in organic synthesis and bioorganic chemistry and their derivatization through formation of phosphorus–carbon linkage to form 2-amino-4*H*-chromen-4-yl phosphonate are not much explored.

2-Amino-4*H*-chromenes are important class of compounds found in many natural products[4] and are widely used as cosmetics, pigments,[5] and agrochemicals.[6] Some of these 2-amino-4*H*-chromene derivatives (Fig. 1) are Bcl-2 antagonists that are discovered through fluorescent polarization (FP) and have synergy with various anticancer therapies under diverse mechanism of action.[7] A few synthetic methodologies have been developed till now for the synthesis of 2-amino-4*H*-chromenes by using various catalysts and additives. Recently Perumal and co-workers reported indium(III) chloride as a lewis acid catalyst for the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl) phosphonic acid diethyl ester structural motif.[8] In continuation of our efforts toward the development of new synthetic protocols aided by supramolecular catalysis,[9] we report herein multi-condensation one-pot synthetic strategy involving salicylaldehyde, malononitrile or ethyl cyanoacetate, and triethyl phosphite leading to the formation of 2-amino-4*H*-chromen-4-yl phosphonate derivatives using β-cyclodextrin as a reusable catalyst. To the best of our knowledge this is the first report for the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl)

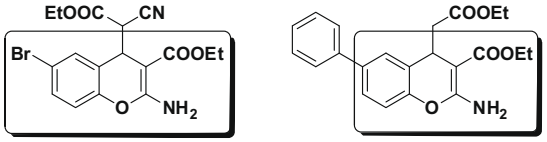

Figure 1. Structures of Bcl-2 protein antagonists.

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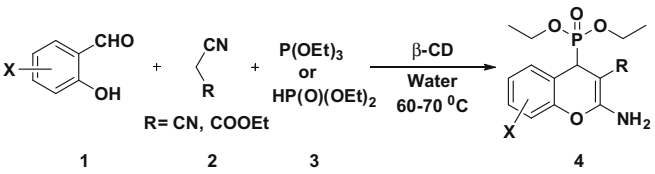


Scheme 1. Synthesis of 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate derivatives.

phosphonic acid diethyl ester structural motif, involving multicondensational approach using β-CD as a recyclable catalyst in water (Scheme 1).

Cyclodextrins and modified cyclodextrins have attracted much attention as aqueous-based hosts for inclusion complex phenomenon with a wide variety of guests. Inclusion complex formation occurs as a result of interaction between hydrophobic cavity of CD and hydrophobic portion of guest. These bind the substrates selectively and catalyze the chemical reactions by supramolecular catalysis involving reversible formation of host–guest complex with the substrate by non-covalent bonding as seen in the enzyme complexation process. These features of CDs attracted us to investigate reactions, under biomimetic conditions.

When we attempted the synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives in water under catalyst-free conditions, we were unsuccessful in getting the desired product. Then we realized the catalytic activity of the β-cyclodextrin to effect this multicomponent condensation by conducting a model reaction. Reacting salicylaldehyde, malononitrile and triethyl phosphite via formation of salicylaldehyde inclusion complex with β-CD at 60–70 °C in water gave corresponding diethyl 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate in 88% yield.[10] The same reaction when carried out by replacing malononitrile with ethylcyanoacetate the corresponding ethyl 2-amino-4-(diethoxyphosphoryl)-4*H*-chromene-3-carboxylate resulted in good yields (Table 1).

Table 1
Synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives with triethyl phosphite[a]

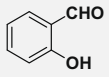
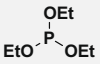
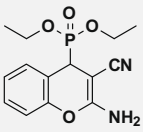
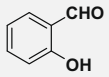
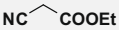
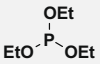
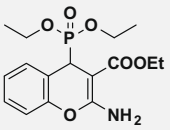
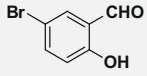
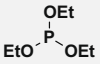
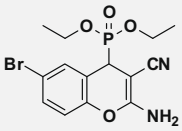
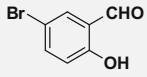
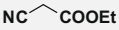
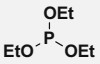
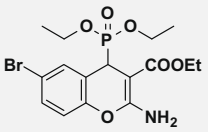
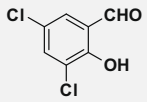
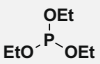
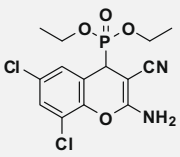
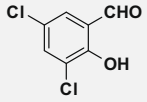
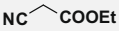
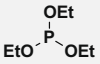
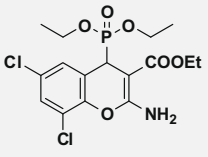
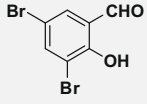
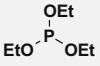
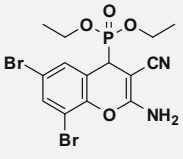
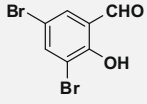
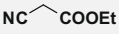
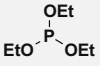
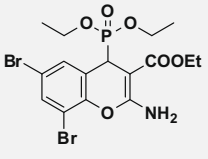
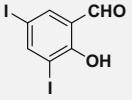
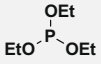
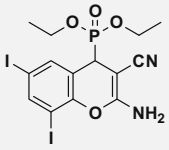
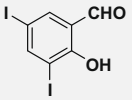
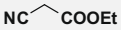
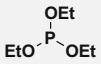
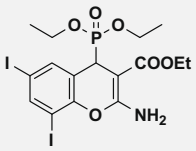
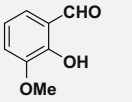
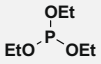
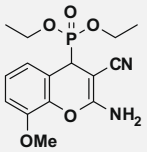
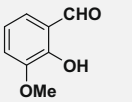
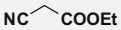
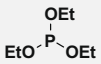
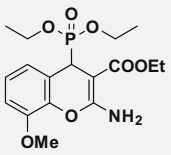
Entry	Salicylaldehyde	**2**	Triethyl phosphite	Product	Time (h)	Yield[b] (%)
1					3.0	88
2					3.5	82
3					3.0	86
4					4.0	79
5					3.0	85
6					3.5	80
7					4.0	87
8					4.5	80

Table 1 (*continued*)

Entry	Salicylaldehyde	**2**	Triethyl phosphite	Product	Time (h)	Yield[b] (%)
9					4.0	85
10					4.5	81
11					3.0	83
12					3.5	78

[a] Reaction conditions: salicylaldehyde (1.0 mmol), malononitrile or ethyl cyanoacetate (1.0 mmol), triethyl phosphate (1.0 mmol), β-CD (1.0 mmol), water (15 mL), 60–70 °C, 3–5 h.
[b] Isolated yield.

Table 2
Synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives with diethyl phosphonate[a]

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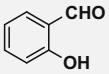
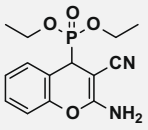
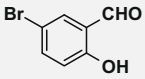
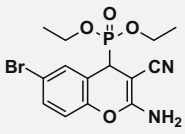
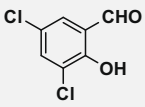
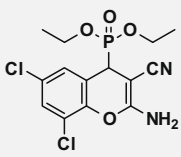
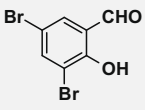
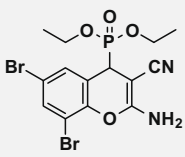
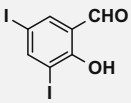
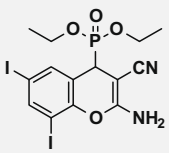
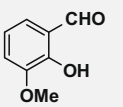
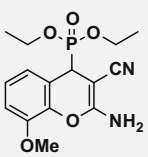
1					4.0	83
2					4.5	81
3					4.5	79
4					4.5	80
5					4.5	78
6					5.0	76

[a] Reaction conditions: salicylaldehyde (1.0 mmol), malononitrile (1.0 mmol), diethyl phosphonate (1.0 mmol), β-CD (1.0 mmol), water (15 mL), 60–70 °C, 4–5 h.
[b] Isolated yield.

The scope of the reaction was studied with various substituted salicylaldehydes keeping triethyl phosphite as a common substrate. In these reactions, substituents on the salicylaldehyde do not have significant effect on the product yields but when we replace malononitrile with ethylcyanoacetate there is a slight decrease in the product yields due to electronic factors. When triethyl phosphite is replaced with diethyl phosphonate as a third component in the reaction, the products are formed in lower yields with longer reaction times as shown in the (Table 2), when compared with the standard reaction. All the products were characterized by ^{1}H, ^{13}C NMR, IR, and Mass spectra.[11]

From a comparative study of ^{1}H NMR spectra (in DMSO-d_6) of salicylaldehyde, β-CD, and β-CD–salicylaldehyde inclusion complex (Fig. 2), it is observed that there is an upfield shift of 3-H (0.012 ppm) and 5-H (0.012 ppm) protons of the cyclodextrin in the β-CD–salicylaldehyde complex, when compared to β-CD, which indicates the formation of an inclusion complex of salicylaldehyde from the secondary side of the β-cyclodextrin.

From this upfield shift of 3-H (0.012 ppm) and 5-H (0.012 ppm) protons of the cyclodextrin in the β-CD–salicylaldehyde inclusion complex we can clearly demonstrate that the reaction was proceeding through an inclusion phenomenon. After the reaction, the mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used with the same substrates as a catalyst and checked for the yields and catalytic activity of recovered catalyst (β-CD). As shown in Table 3, the yields of 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate after two to three recycles were almost the same.

In conclusion, a simple and efficient protocol has been developed in water for the synthesis of 2-amino-3-cyano-4*H*-chromen-4-yl phosphonates under neutral conditions by using β-CD as a supramolecular catalyst through host–guest complexation phenomenon.

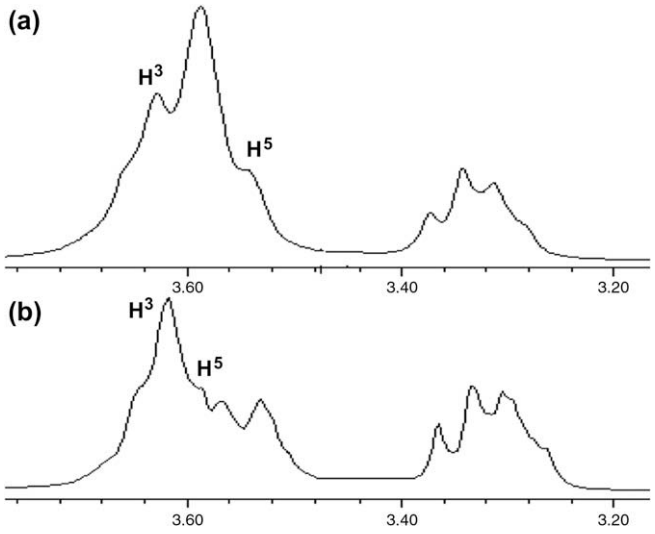


Figure 2. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of (a) β-CD (b) β-CD–salicylaldehyde inclusion complex.

Table 3
Recycling of β-cyclodextrin[a]

Recycles	Yield[b] (%)	β-CD recovery (%)
1	84	96
2	80	92
3	75	89

[a] Reaction conditions: salicylaldehyde (1.0 mmol), malononitrile or ethyl cyanoacetate (1.0 mmol), triethyl phosphate (1.0 mmol), β-CD (1.0 mmol), water (15 mL), 60–70 °C, 3–5 h.
[b] Isolated yield.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.028.

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10. *General procedure for the synthesis of 2-amino-4H-chromen-4-yl phosphonate derivatives:* β-Cyclodextrin (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed. To this clear solution, salicylaldehyde (1.0 mmol) was added and stirred for 10 min, and then malononitrile (1.0 mmol) followed by triethyl phosphite (1.0 mmol) was added, after which the reaction mixture was heated at 60–70 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to the room temperature and β-CD was filtered, the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with water, saturated brine solution, and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (7:3) as eluent to give the corresponding 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate as pure products in good yields.
11. *Data of representative examples: Diethyl 2-amino-3-cyano-4H-chromen-4-ylphosphonate* (Table 1, entry 1). Yield (88%) as white solid; R_f (70% EtOAc/*n*-hexane) 0.23; ν_{max} (KBr) 3319, 3170, 2190, 1647, 1406, 1232, 1023 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.21 (m, 2H), 7.11 (t, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 8.1 Hz), 5.41 (br s, 2H), 4.15–3.15 (m, 4H), 3.89 (d, 1H, $^{2}J_{PH}$ = 17.9 Hz), 1.34 (t, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 6.9 Hz); δ_C (75 MHz, $CDCl_3$)162.1, 149.8, 129.3, 122.8, 124.7, 119.5, 116.4, 116.3, 63.1, 62.8, 50.5, 36.2, 34.3, 16.3, 16.2; MS *m*/*z* (ESI): 309 $(M+H)^+$.
Ethyl 2-amino-4-(diethoxyphosphoryl)-4H-chromene-3-carboxylate (Table 1, entry 2). Yield (82%) as colorless oil; Found: C, 54.08; H, 6.24; N, 3.94. Requires: C, 54.00; H, 6.19; N, 3.89. R_f (70% EtOAc/*n*-hexane) 0.31; ν_{max} (KBr) 3381, 3297, 2982, 2931, 1677, 1483, 1238, 1046 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.30 (m, 1H), 7.23–7.17 (m, 1H), 7.09 (t, 1H, J = 7.5 Hz), 6.95 (d, J = 8.3 Hz), 6.36 (br s, 2H), 4.32 (d, 1H, $^{2}J_{PH}$ = 19.6 Hz), 4.25–4.12 (m, 2H), 4.04–3.95 (m, 2H), 3.89–3.69 (m, 2H), 1.33 (t, 3H, J = 6.7 Hz), 1.25 (t, 3H, J = 6.7 Hz), 1.11 (t, 3H, J = 6.7 Hz); δ_C (75 MHz, $CDCl_3$) 168.4, 162.0, 150.8, 129.4, 128.1, 124.2, 119.7, 115.7, 70.1, 62.5, 62.1, 35.9, 33.9, 16.3, 14.5; MS *m*/*z* (ESI): 356 $(M+H)^+$.
Diethyl 2-amino-6-bromo-3-cyano-4H-chromen-4-ylphosphonate (Table 1, entry 3). Yield (86%) as white solid; R_f (70% EtOAc/*n*-hexane) 0.22; ν_{max} (KBr) 3338, 3298, 3155, 2186, 1649, 1411, 1236, 1019 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43 (m, 1H), 7.37–7.34 (m, 1H), 6.85 (d, 1H, J = 8.3 Hz), 5.34 (br s, 2H), 4.15–4.04 (m, 4H), 3.83 (d, 1H, $^{2}J_{PH}$ = 18.2 Hz), 1.34 (t, 3H, J = 6.7 Hz), 1.28 (t, 3H, J = 7.5 Hz); δ_C (75 MHz, $CDCl_3$) 161.9, 149.2, 132.0, 131.8, 119.2, 118.1, 63.4, 63.1, 50.3, 36.1, 34.1, 16.3. MS *m*/*z* (ESI): 388 $(M+H)^+$.

Ethyl 2-amino-6-bromo-4-(diethoxyphosphoryl)-4H-chromene-3-carboxylate (Table 1, entry 4). Yield (79%) as colorless oil; Found: C, 44.26; H, 4.87; N, 3.23. Requires: C, 44.21; H, 4.80; N, 3.20. R_f (70% EtOAc/*n*-hexane) 0.29; ν_{max} (KBr) 3380, 3291, 2980, 2928, 1669, 1481, 1232, 1040 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (m, 1H), 7.22 (d, 1H, *J* = 8.7 Hz), 6.76 (d, 1H, *J* = 8.7 Hz), 5.39 (br s, 2H), 4.17–4.04 (m, 6H), 3.88 (d, 1H, $^2J_{PH}$ = 19.2 Hz), 1.36–1.20 (m, 9H); δ_C (75 MHz, $CDCl_3$) 162.4, 154.5, 150.1, 132.0, 130.7, 124.9, 119.8, 63.9, 63.5, 49.4, 30.5, 29.7, 16.4, 16.2. MS *m*/*z* (ESI): 435 $(M+H)^+$.

Diethyl 2-amino-6, 8-dichloro-3-cyano-4H-chromen-4-ylphosphonate (Table 1, entry 5). Yield (85%) as yellow solid; R_f (70% EtOAc/*n*-hexane) 0.22; ν_{max} (KBr) 3357, 3162, 2195, 1661, 1413, 1238, 1045 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32 (t, 1H, *J* = 2.2 Hz), 7.20 (t, 1H, *J* = 2.2 Hz), 5.35 (br s, 2H), 4.19–4.03 (m, 4H), 3.83 (d, 1H, $^2J_{PH}$ = 18.8 Hz), 1.39–1.25 (m, 6H); δ_C (300 MHz, $CDCl_3$) 161.4, 129.7, 129.4, 127.7, 120.1, 118.5, 63.5, 63.2, 50.9, 36.8, 34.8, 16.4, 16.2; MS *m*/*z* (ESI): 378 $(M+H)^+$.

Ethyl 2-amino-6,8-dichloro-4-(diethoxyphosphoryl)-4H-chromene-3-carboxylate (Table 1, entry 6). Yield (80%) as colorless oil; Found: C, 45.30; H, 4.75; N, 3.30. Requires: C, 45.28; H, 4.70; N, 3.27. R_f (70% EtOAc/*n*-hexane) 0.29; ν_{max} (KBr) 3217, 2987, 1740, 1464, 1233, 1035 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29–7.25 (m, 1H), 7.18 (t, 1H, *J* = 2.2 Hz), 5.46 (br s, 2H), 4.23–4.01 (m, 6H), 3.87 (d, 1H, $^2J_{PH}$ = 19.0 Hz), 1.38–1.15 (m, 9H); δ_C (75 MHz, $CDCl_3$) 165.4, 160.2, 149.5, 128.7, 126.4, 126.0, 124.6, 122.9, 63.7, 63.5, 57.8, 37.7, 36.1, 16.1, 16.0; MS *m*/*z* (ESI): 425 $(M+H)^+$.

Diethyl 2-amino-6,8-dibromo-3-cyano-4H-chromen-4-ylphosphonate (Table 1, entry 7). Yield (87%) as light yellow solid; R_f (70% EtOAc/*n*-hexane) 0.21; ν_{max} (KBr) 3311, 3153, 2197, 1662, 1415, 1237, 1040 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (d, 1H, *J* = 2.0 Hz), 7.46–7.41 (m, 1H), 5.18 (br s, 2H), 4.17–4.07 (m, 4H), 3.79 (d, 1H, $^2J_{PH}$ = 18.7 Hz), 1.36 (t, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 6.3 Hz); δ_C (75 MHz, $CDCl_3$) 161.5, 146.1, 134.5, 130.9, 120.8, 118.7, 116.0, 62.7, 62.5, 49.2, 36.3, 34.4, 15.8, 15.5; MS *m*/*z* (ESI): 467 $(M+H)^+$.

Ethyl 2-amino-6,8-dibromo-4-(diethoxyphosphoryl)-4H-chromene-3-carboxylate (Table 1, entry 8). Yield (80%) as colorless oil; Found: C, 37.45; H, 3.93; N, 2.73. Requires: C, 37.40; H, 3.91; N, 2.69. R_f (70% EtOAc/*n*-hexane) 0.33; ν_{max} (KBr) 3320, 3172, 2187, 1649, 1401, 1232, 1021 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.56 (t, 1H, *J* = 2.2 Hz), 7.41 (t, 1H, *J* = 2.2 Hz), 5.59 (br s, 2H), 4.23–4.00 (m, 6H), 3.85 (d, 1H, $^2J_{PH}$ = 19.5 Hz), 1.36–1.22 (m, 9H); δ_C (75 MHz, $CDCl_3$ + DMSO) 165.4, 160.2, 150.9, 135.5, 134.2, 129.9, 129.8, 127.2, 126.0, 112.6, 63.8, 63.5, 46.3, 37.4, 36.0, 16.0, 15.7; MS *m*/*z* (ESI): 514 $(M+H)^+$.

Diethyl 2-amino-3-cyano-6,8-diiodo-4H-chromen-4-ylphosphonate (Table 1, entry 9). Yield (85%) as light yellow solid; R_f (70% EtOAc/*n*-hexane) 0.20; ν_{max} (KBr) 3379, 3179, 2191, 1656, 1409, 1233, 1023 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.01–9.79 (m, 1H), 7.57 (t, 1H, *J* = 2.2 Hz), 5.60 (br s, 2H), 4.20–4.04 (m, 4H), 3.78 (d, 1H, $^2J_{PH}$ = 18.2 Hz), 1.39–1.24 (m, 6H); δ_C (75 MHz, $CDCl_3$ + DMSO) 160.5, 147.9, 143.3, 136.0, 119.2, 117.5 86.1, 84.1, 60.8, 60.7, 46.0, 34.2, 32.2, 14.4. MS *m*/*z* (ESI): 561 $(M+H)^+$.

Ethyl 2-amino-4-(diethoxyphosphoryl)-6,8-diiodo-4H-chromene-3-carboxylate (Table 1, entry 10). Yield (81%) as colorless oil; Found: C, 31.65; H, 3.32; N, 2.31. Requires: C, 31.61; H, 3.30; N, 2.29. R_f (70% EtOAc/*n*-hexane) 0.35; ν_{max} (KBr) 3319, 3191, 1448, 1235, 1043 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.12 (m, 1H), 7.90–7.80 (m, 1H), 6.50 (br s, 2H), 4.45–4.17 (m, 6H), 3.82 (d, 1H, $^2J_{PH}$ = 18.7 Hz), 1.56–1.13 (m, 9H); MS *m*/*z* (ESI): 608 $(M+H)^+$.

Diethyl 2-amino-3-cyano-8-methoxy-4H-chromen-4-ylphosphonate (Table 1, entry 11). Yield (83%) as white solid; R_f (70% EtOAc/*n*-hexane) 0.25; ν_{max} (KBr) 3300, 3171, 2189, 1640, 1404, 1215, 1018 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.05 (t, 1H, *J* = 7.8 Hz), 6.88 (d, 2H, *J* = 6.8 Hz), 6.50 (br s, 2H), 4.07 (t, 2H, *J* = 6.8 Hz), 4.05–3.95 (m, 2H), 3.89 (d, 1H, $^2J_{PH}$ = 19.5 Hz), 3.84 (s, 3H), 1.32–1.15 (m, 6H); δ_C (75 MHz, $CDCl_3$ + DMSO) 161.4, 146.0, 138.1, 122.7, 119.3, 118.8, 116.7, 110.0, 61.2, 61.0, 54.3, 46.7, 35.0, 33.1, 14.9, 14.8. MS *m*/*z* (ESI): 339 $(M+H)^+$.

Ethyl 2-amino-4-(diethoxyphosphoryl)-8-methoxy-4H-chromene-3-carboxylate (Table 1, entry 12). Yield (78%) as colorless oil; Found: C, 52.99; H, 6.28; N, 3.63. Requires: C, 52.95; H, 6.26; N, 3.60. R_f (70% EtOAc/*n*-hexane) 0.32; ν_{max} (KBr) 3341, 3199, 2981, 2934, 1681, 1483, 1223, 1040 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.04–6.99 (m, 1H), 6.92–6.89 (m, 1H), 6.84–6.79 (m, 1H), 4.39–3.71 (m, 10H), 1.33–1.20 (m, 6H), 1.10 (t, 3H, *J* = 7.5 Hz); δ_C (75 MHz, $CDCl_3$ + DMSO) 168.2, 161.6, 147.4, 147.1, 143.7, 127.9, 127.4, 123.8, 120.8, 120.6, 119.4, 110.7, 63.0, 62.1, 55.6, 50.7, 35.8, 33.8, 16.0, 14.2; MS *m*/*z* (ESI): 386 $(M+H)^+$.