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Abstract

The work reports facile synthesis of novel ten α-aminophosphonate derivatives coupled with 3-formyl chromone moiety, namely diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl)phosphonate 6(a-j). The derivatives 6(a-j) were synthesized through one-pot three component Kabachnik-Fields reaction, by using ultrasound in presence of zirconium oxychloride (ZrOCl₂) as a catalyst, to give the final compounds in better yields and in shorter reaction time. Thiadiazole and its derivatives possess a broad range of biological and pharmacological properties. 5-substituted phenyl-1,3,4-thiadiazol-2-amine is widely used as starting material for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. Several 3-formylchromone derivatives possess a broad range of biological and pharmacological properties. The α-amino phosphonate derivatives constitute an important class of organophosphorus compounds on account of their versatile biological activity. Considering the importance of the three pharmacophores, promoted us to club all pharmacophores in a single molecule using green protocol. The Principles of Green chemistry are followed while performing the synthesis.

Keywords: Kabachnik-Fields reaction; Ultrasound, thiadiazol; 3-formyl chromone; α-amino phosphonate; zirconium oxychloride.
1. Introduction

In recent years, numerous promising multicomponent reactions have appeared as an innovative synthetic platform in the field of organic chemistry. This boosted not only drug discovery but also the construction of new synthetic skeletons. Multicomponent reactions triggered new synthetic applications in organic chemistry. Among many multicomponent reactions reported so far, we were particularly interested in exploring Kabachnik-Fields reaction because it can afford α-amino phosphonates in good yield. The Kabachnik -Fields reaction is one of the well known multicomponent reaction. The Kabachnik -Fields reaction corresponds to the classical method for the synthesis of organophosphorus compounds. It was discovered in 1952 independently by Kabachnik and Medved' [1] and Fields [2]. The reaction occurs in a three-component system consisting of a hydrophosphoryl compound, a carbonyl compound (aldehyde or ketone), and an amine and results in α-aminoalkylphosphonates commonly named as α-amino phosphonates.

Recently, α-aminophosphonates have attracted the attention of organic chemists due to their biological activities, such as antibiotic, enzyme inhibitor, HIV protease and as anti-tumor agents [3]. α-Aminophosphonic acids, considered as phosphorus analogues of α-amino acids, have attracted much attention in drug research due to their low mammalian toxicity. The α-aminophosphonates are considered to be structural analogues of α-amino acids and transition state mimics of peptide hydrolysis [4]. In agrochemistry α-aminophosphonates are used as plant growth regulators, herbicides, insecticides and fungicides [5]. Several α-aminophosphonates have also been used in organic synthesis. For example, phosphorylated allenles are used as versatile building blocks in organic synthesis [6]. They are important targets in the development of antibiotics, antiviral species, antihypertensives, and antitumour agents based on their effect as inhibitors of GABA-receptors, enzyme inhibitors and anti-metabolites [7–13]. Diaryl α-aminophosphonate derivatives are selective and highly potent inhibitors of serine proteases, and thus can mediate the patho-physical processes of cancer growth, metastasis, osteoarthritis or heart failure [14]. Dialkylglycine decarboxylase [13] and leucine aminopeptidase [15] are also inhibited by α-amino-phosphonates. Cyanoacrylate [16] and amide derivatives [17] of α-aminophosphonates are active antiviral compounds and inactivators of the tobacco mosaic virus. Certain α-aminophosphonates were proved to be suitable for the design of continuous drug
release devices due to their ability to increase the membrane permeability of a hydrophilic probe molecule [18].

Chromone and chromone derivatives are ubiquitous structures that constitute a variety of naturally occurring and synthetic bioactive compounds [19]. Chromones are oxygen-containing heterocycles with a benzoannelated γ-pyrone ring. Several biological activities have been ascribed to simple chromones and their analogues such as anti-inflammatory [20], antiplatelet [21], anticancer [22], antimicrobial [23], antiulcers [24], antioxidants [25], antiarrhythmic and hypotensive agents [26], aldose reductase and calpain inhibitors [27-29], MAO inhibition [30]. Due to potential pharmacological properties, chromones are topic of great interest among a number of research groups.

Five membered aromatic systems having three hetero atoms at symmetrical position have interesting physiological properties [31, 32]. Sulphur-nitrogen heterocycles are important compounds due to their significant and versatile biological activity [33], and therefore these compounds have retained the interest of the researchers. Among these, 1,3,4-thiadiazoles represent one of the most promising class of heterocycles in drug discovery. During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [34, 35, 36], anti-inflammatory [37, 38, 39], anticonvulsants [40], antioxidant [41], anticancer [42] and antifungal [43] activities. The activity of 1,3,4-thiadiazoles is possibly due to the presence of the N–C–S moiety [44]. In view of these facts, we have synthesized novel 1,3,4-thiadiazole with spliced chromone and α-amino-phosphonate under ultrasound irradiation using Green protocol. Ultrasound assisted techniques were reported to be more effective in perspective of environment, reaction time, high yields, ease of work-up and isolation of products [45].

**Result and Discussion**

**Chemistry**

Here in we report the ultrasound promoted green synthesis of ten novel 3-Formyl Chromone Spliced Thiadiazole, α-Amino Phosphonate derivatives 6(a-j) from three component reactions of an 3-formyl chromone (4), 5-substituted phenyl-1,3,4-thiadiazole-2-amine 3(a-j) and triethyl phosphite (5) in presence of ethanol as an solvent and ZrOCl₂ catalyst under ultrasound
irradiation as shown in Scheme 1. 5-Substituted phenyl-1,3,4-thiadiazol-2-amine derivatives 3(a-j) were synthesized by reacting thiosemicarbazide (1) (0.05 mol) with various substituted benzoic acid 2(a-j) (0.05 mol) in ethanolic solvent in presences of catalytic amount of sulfuric acid under ultrasound irradiation. The synthesized compounds were characterized and confirmed by FTIR, $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR, MS and elemental analyses. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes and are uncorrected. Physical constant data for synthesized compounds diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate 6(a-j) is as shown in Table 1.

![Scheme 1](image-url)

Scheme 1: Synthesis of diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives 6(a-j) under ultrasound irradiation.
Table 1. Physical characterization data of the synthesized compounds 6(a-j).

<table>
<thead>
<tr>
<th>Code</th>
<th>R</th>
<th>Molecular formula</th>
<th>Molecular weight (gm)</th>
<th>% Yield</th>
<th>Rr value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td></td>
<td>C_{22}H_{22}N_{3}O_{5}PS</td>
<td>471.47</td>
<td>90</td>
<td>0.45</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>C_{22}H_{21}ClN_{3}O_{5}PS</td>
<td>505.91</td>
<td>92</td>
<td>0.35</td>
</tr>
<tr>
<td>6c</td>
<td></td>
<td>C_{22}H_{22}N_{3}O_{6}PS</td>
<td>487.47</td>
<td>95</td>
<td>0.35</td>
</tr>
<tr>
<td>6d</td>
<td></td>
<td>C_{23}H_{24}N_{3}O_{5}PS</td>
<td>485.49</td>
<td>90</td>
<td>0.35</td>
</tr>
<tr>
<td>6e</td>
<td></td>
<td>C_{22}H_{22}N_{3}O_{6}PS</td>
<td>487.47</td>
<td>89</td>
<td>0.50</td>
</tr>
<tr>
<td>6f</td>
<td></td>
<td>C_{22}H_{21}N_{4}O_{7}PS</td>
<td>516.46</td>
<td>88</td>
<td>0.40</td>
</tr>
<tr>
<td>6g</td>
<td></td>
<td>C_{22}H_{21}BrN_{3}O_{5}</td>
<td>550.36</td>
<td>94</td>
<td>0.35</td>
</tr>
<tr>
<td>6h</td>
<td></td>
<td>C_{24}H_{24}N_{3}O_{5}PS</td>
<td>497.50</td>
<td>92</td>
<td>0.40</td>
</tr>
<tr>
<td>6i</td>
<td></td>
<td>C_{24}H_{24}N_{3}O_{7}PS</td>
<td>529.50</td>
<td>87</td>
<td>0.35</td>
</tr>
<tr>
<td>6j</td>
<td></td>
<td>C_{22}H_{20}N_{5}O_{9}PS</td>
<td>561.46</td>
<td>84</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Experimental Chemistry**

All the chemicals used for synthesis were of Merck, Sigma, Research lab, Qualigens make and Himedia. The FTIR spectra were obtained using JASCO FTIR-4000 and peaks were expressed in terms of wave number (cm\(^{-1}\)). The \(^1\)H NMR and \(^{13}\)C NMR spectra of synthesized compounds were recorded on Bruker Avance II 400 NMR Spectrometer at 400 MHz Frequency in CDCl\(_3\) and using TMS as internal standard (chemical shift \(\delta\) in ppm). The Mass spectra were
scanned on Water’s Micromass Q-Tof system. The $^{31}$P NMR of compounds was recorded at δ 250 to δ 250 in CDCl$_3$ and using Phosphoric acid (H$_3$PO$_4$) as external standard (chemical shift δ in ppm). Ultrasound synthesizer Vibra Cell VCX-500(Sonics, Newtown, CT, USA) with solid probe was used for synthesis of intermediates (1).

**Procedures:**

**Step I:**

**General Procedures for the Synthesis of 3(a-j) using Ultra sound method**

To the equimolar quantity of differently substituted benzoic acids 2(a-j) (0.05 mol), thiosemicarbazide (1) (0.05 mol) in 5-8 ml of ethanol, catalytic amount of sulphuric acid was added and the reaction mixture was subjected to Ultrasound irradiation for 30-40 min at room temperature. The completion of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was poured into the ice cold water, filtered, dried and recrystallized from ethanol.

**Step II:**

**General procedure for synthesis of diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives 6(a-j) under ultrasound irradiation.**

A mixture of substituted thiadiazole derivatives 3(a–j) (0.05mol), 3-formyl chromone (4) (0.05mol), triethyl phosphite (5) (0.05mol) and the catalytic amount of zirconium oxychloride in absolute ethanol, was sonicated at a 25 °C temperature and frequency 20 kHz for a specified time as shown in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into the ice-cold water and filtered under suction; the precipitate thus obtained was washed with water and recrystallized from ethanol.
Table 2: Details of synthesis of diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives 6(a-j) under ultrasound irradiation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Time required for ultrasound method (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>40</td>
</tr>
<tr>
<td>6b</td>
<td>30</td>
</tr>
<tr>
<td>6c</td>
<td>35</td>
</tr>
<tr>
<td>6d</td>
<td>45</td>
</tr>
<tr>
<td>6e</td>
<td>50</td>
</tr>
<tr>
<td>6f</td>
<td>40</td>
</tr>
<tr>
<td>6g</td>
<td>35</td>
</tr>
<tr>
<td>6h</td>
<td>40</td>
</tr>
<tr>
<td>6i</td>
<td>35</td>
</tr>
<tr>
<td>6j</td>
<td>40</td>
</tr>
</tbody>
</table>

**Diethyl (4-oxo-4H-chromen-3-yl)(5-phenyl-1,3,4-thiadiazol-2-ylamino)methylphosphonate 6a**

Yield 90%; M. P.: 165-168°C; IR (KBr \( \nu_{max} \) in cm\(^{-1}\)): 3363.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1725.02 (C-O stretching), 1665.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 663.39(C-S Stretching); \(^1\)HNMR (400 MHz, DMSO, \( \delta_H \) ppm): 1.29 (t, 6H, 2×OCH\(_2\)CH\(_3\)), 4.70 (q, 4H, 2×OCH\(_2\)CH\(_3\)), 5.05 (d, 1H, -CH), 7.41-8.08 (m, 10H, aromatic), 8.61 (s, 1H, -NH); \(^13\)CNMR: (DMSO)\( \delta_{ppm} \): 16.3, 16.3, 62.3, 62.3, 61.0, 128.7, 123.4, 129.2, 135.2, 125.8, 130.9, 116.9, 123.9, 133.5, 183.0, 150.6, 157.2, 174.1, 164.2; \(^31\)PNMR (200 MHz,CDCl\(_3\)) \( \delta \): 19.90; Molecular formula: C\(_{22}\)H\(_{22}\)N\(_3\)O\(_5\)PS; Elemental Analysis: calculated: (C,H,N): 56.05, 4.70, 8.91; found: (C,H,N): 56.17, 4.82, 8.87

**Diethyl(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6b**

Yield 92%; M. P.:135-137°C; IR (KBr \( \nu_{max} \) in cm\(^{-1}\)): 3303.25 (N-H stretching), 3096.12 (C-H stretching of aromatic), 2783.14 (C-H stretching of alkyl), 2241.73 (C=N Stretching), 1715.02 (C-O stretching), 1685.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 660.39(C-S Stretching); \(^1\)HNMR (400 MHz, DMSO, \( \delta_H \) ppm): 1.28 (t, 6H, 2×OCH\(_2\)CH\(_3\)), 4.71 (q, 4H, 2×OCH\(_2\)CH\(_3\)), 5.05 (d, 1H, -CH), 7.47-8.08 (m, 9H, aromatic), 8.61 (s, 1H, -NH); \(^13\)C
NMR: (DMSO) δ ppm: 16.3, 16.3, 62.3, 62.3, 61.6, 123.4, 135.2, 125.8, 128.9, 116.1, 129.3, 128.9, 129.3, 116.9, 123.9, 131.6, 183.0, 150.6, 157.2, 134.3, 174.1, 164.2; \(^{31}\)PNMR (200 MHz, CDCl\(_3\)) δ: 19.84; Molecular formula: C\(_{22}\)H\(_{21}\)ClN\(_3\)O\(_5\)PS; Elemental Analysis: calculated: (C,H,N): 54.21, 4.98, 8.66; found: (C,H,N): 54.32, 5.10, 8.62

**diethyl (5-(4-hydroxyphenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6c**

Yield 95%; M. P.: 158-160°C; IR (KBr \(v_{max}\) in cm\(^{-1}\)): 3303.25 (N-H stretching), 3106.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1709.02 (C-O stretching), 1675.10 (C=O stretching), 1527.35 (C-N Stretching), 1051.37 (O-stretching), 698.39 (C-S Stretching); \(^1\)HNMR (400 MHz, DMSO, δ\(_H\) ppm): 1.29 (t, 6H, 2\(\times\)OCH\(_2\)CH\(_3\)), 4.71 (q, 4H, 2\(\times\)OCH\(_2\)CH\(_3\)), 5.09 (d, 1H, -CH), 5.35 (s, 1H, OH), 6.87-8.08 (m, 9H, aromatic), 8.60 (s, 1H, -NH); \(^{13}\)CNMR: (DMSO) δ ppm: 16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 128.9, 116.4, 116.4, 116.9, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; \(^{31}\)PNMR (200 MHz, CDCl\(_3\)) δ: 19.54; Molecular formula: C\(_{22}\)H\(_{21}\)N\(_3\)O\(_5\)PS; Elemental Analysis: calculated: (C,H,N): 54.21, 4.55, 8.62; found: (C,H,N): 54.32, 4.67, 8.58

**Diethyl (4-oxo-4H-chromen-3-yl)(5-p-tosyl-1,3,4-thiadiazol-2-ylamino)methylphosphonate 6d**

Yield 90%; M. P.: 159-161°C; IR (KBr \(v_{max}\) in cm\(^{-1}\)): 3357.25 (N-H stretching), 3016.82 (C-H stretching of aromatic), 2763.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1705.02 (C-O stretching), 1695.10 (C=O stretching), 1597.35 (C-N Stretching), 1041.37 (O-stretching), 676.39 (C-S Stretching); \(^1\)HNMR (400 MHz, DMSO, δ\(_H\) ppm): 1.29 (t, 6H, 2\(\times\)OCH\(_2\)CH\(_3\)), 2.34 (s, 3H, aromatic C-CH\(_3\)), 4.71 (q, 4H, 2\(\times\)OCH\(_2\)CH\(_3\)), 5.09 (d, 1H, -CH), 5.35 (s, 1H, OH), 7.40-8.09 (m, 9H, aromatic), 8.60 (s, 1H, -NH); \(^{13}\)CNMR:(DMSO) δ ppm: 16.3, 16.3, 21.3, 62.3, 61.0, 123.4, 135.2, 129.5, 125.8, 127.4, 116.1, 129.5, 127.4, 131.7, 123.9, 116.9, 123.9, 130.5, 183.0, 150.6, 157.2, 174.1, 164.2; \(^{31}\)PNMR (200 MHz, CDCl\(_3\)) δ: 19.54; Molecular formula: C\(_{23}\)H\(_{24}\)N\(_3\)O\(_5\)PS; Elemental Analysis: calculated: (C,H,N): 56.90, 4.98, 8.66; found: (C,H,N): 57.02, 5.10, 8.62

**diethyl (5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6e**

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8
Yield 89%; M. P.:169-170°C ; IR (KBr $v_{max}$ in cm$^{-1}$): 3363.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2753.14 (C-H stretching of alkyl), 2281.73 (C=N Stretching), 1710.02 (C-O stretching), 1685.10 (C=O stretching), 1617.35 (C-N Stretching), 1081.37 (O-H stretching), 663.39(C-S Stretching); $^1$HNMR (400 MHz, DMSO, $\delta$ ppm): 1.29 (t, 6H, 2×OCH$_2$CH$_3$), 4.70 (q, 4H, 2×OCH$_2$CH$_3$), 5.08 (d, 1H, -CH), 5.35 (s, 1H, OH), 7.01-8.08 (m, 9H, aromatic), 8.55 (s, 1H, -NH); $^{13}$CNMR: (DMSO) $\delta$ ppm: 16.3, 16.3, 62.3, 62.3, 61.60, 123.4, 135.2, 125.8, 128.9, 116.4, 116.1, 128.9, 116.4, 116.9, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; $^{31}$PNMR (200 MHz,CDCl$_3$) $\delta$: 19.04; Molecular formula: C$_{22}$H$_{22}$N$_3$O$_6$PS; Elemental Analysis: calculated: (C,H,N): 54.21, 4.55, 8.62; found: (C,H,N): 54.32, 4.67, 8.58

**Diethyl(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6f**

Yield 88%; M. P.: 130-132°C ; IR (KBr $v_{max}$ in cm$^{-1}$): 3293.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1725.02 (C-O stretching), 1715.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O-H stretching), 689.39(C-S Stretching); $^1$HNMR (400 MHz, DMSO, $\delta$ ppm): 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 7.47-8.38 (m, 9H, aromatic), 8.61 (s, 1H, -NH); $^{13}$CNMR: (DMSO) $\delta$ ppm: 16.3, 16.3, 62.3, 62.3, 61.60, 123.4, 135.2, 125.8, 128.9, 116.4, 116.1, 128.9, 116.4, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; $^{31}$PNMR (200 MHz,CDCl$_3$) $\delta$: 19.04; Molecular formula: C$_{22}$H$_{21}$N$_4$O$_7$PS; Elemental Analysis: calculated: (C,H,N): 51.16, 4.10, 10.85; found: (C,H,N): 51.28, 4.22, 10.81

**Diethyl (5-(4-bromophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6g**

Yield 94%; M. P.: 138-140°C; IR (KBr $v_{max}$ in cm$^{-1}$): 3293.25 (N-H stretching), 3096.12 (C-H stretching of aromatic), 2763.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1715.02 (C-O stretching), 1675.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O-H stretching), 668.39(C-S Stretching); $^1$HNMR: (DMSO) $\delta$ ppm: 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.05 (d, 1H, -CH), 7.40-8.08 (m, 9H, aromatic), 8.56 (s, 1H, -NH); $^{13}$CNMR: (DMSO) $\delta$ ppm: 16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 129.7, 116.1, 132.1, 129.7, 132.1, 116.9, 123.9, 132.5, 183.0, 150.6, 151.2, 123.1, 174.1, 164.2; $^{31}$PNMR (200
MHz, CDCl$_3$) $\delta$: 19.94; Molecular formula: C$_{22}$H$_{21}$BrN$_3$O$_5$PS; Elemental Analysis: calculated: (C,H,N): 48.01, 3.85, 7.63; found: (C,H,N): 48.13, 3.97, 7.59

(E)-diethyl (4-oxo-4H-chromen-3-yl)(5-styryl-1,3,4-thiadiazol-2-ylamino)methylphosphonate 6h

Yield 92%; M. P.: 150-152°C; IR (KBr vmax in cm$^{-1}$): 3293.25 (N-H stretching), 3116.12 (C-H stretching of aromatic), 2703.14 (C-H stretching of alkyl), 2298.73 (C=N Stretching), 1710.02 (C-O stretching), 1705.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O-stretching), 653.39 (C-S Stretching); $^1$HNMR (400 MHz, DMSO, $\delta_H$ ppm): 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 7.33-8.10 (m, 9H, aromatic), 8.55 (s, 1H, -NH); $^{13}$CNMR:(DMSO) $\delta$ ppm: 16.3, 16.3, 133.4, 116.9, 62.3, 62.3, 61.0, 127.9, 128.6, 128.6, 123.4, 135.29, 128.5, 125.8, 116.1, 128.5, 137.5, 116.9, 123.9, 183.0, 150.6, 157.2, 158.9, 164.2; $^{31}$PNMR (200 MHz, CDCl$_3$) $\delta$: 19.65; Molecular formula: C$_{24}$H$_{24}$N$_3$O$_5$PS; Elemental Analysis: calculated: (C,H,N): 57.94, 4.86, 8.45; found: (C,H,N): 58.06, 4.98, 8.41

2-(5-((diethoxyphosphoryl)(4-oxo-4H-chromen-3-yl)methylamino)-1,3,4-thiadiazol-2-yl)phenyl acetate 6i

Yield 87%; M. P.: 168-170°C; IR (KBr vmax in cm$^{-1}$): 3283.25 (N-H stretching), 3056.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1715.02 (C-O stretching), 1695.10 (C=O stretching), 1598.35 (C-N Stretching), 1089.37 (O-stretching), 679.39 (C-S Stretching); $^1$HNMR (400 MHz, DMSO, $\delta_H$ ppm): 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 2.28 (s, 3H, -CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 7.33-8.10 (m, 9H, aromatic), 8.55 (s, 1H, -NH); $^{13}$CNMR:(DMSO) $\delta$ ppm: 16.3, 16.3, 20.3, 62.3, 62.3, 169.0, 61.0, 129.4, 126.0, 129.1, 135.2, 125.8, 127.9, 123.2, 116.1, 116.9, 123.9, 129.4, 151.1, 183.0, 150.6, 157.2, 174.1, 164.2; $^{31}$PNMR (200 MHz, CDCl$_3$) $\delta$: 19.45; Molecular formula: C$_{24}$H$_{24}$N$_3$O$_7$PS; Elemental Analysis: calculated: (C,H,N): 54.44, 4.57, 7.94; found: (C,H,N): 54.56, 4.69, 7.90

Diethyl (5-(3,4-dinitrophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methylphosphonate 6j

Yield 84%; M. P.: 165-168°C; IR (KBr vmax in cm$^{-1}$): 3303.25 (N-H stretching), 3056.12 (C-H stretching of aromatic), 2771.14 (C-H stretching of alkyl), 2225.73 (C=N Stretching), 1710.02
(C-O stretching), 1685.10 (C=O stretching), 1587.35 (C-N Stretching), 1091.37 (O- stretching), 673.39(C-S Stretching); $^1$H NMR (400 MHz, DMSO, $\delta_H$ ppm): 1.29 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.05 (d, 1H, -CH), 7.10-8.08 (m, 5H, aromatic), 8.49 (s, 1H, -NH), 8.52-8.99 (m, 3H, aromatic); $^{13}$C NMR:(DMSO) $\delta_{ppm}$:16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 116.1, 134.5, 125.3, 123.7, 116.9, 123.9, 140.5, 144.8, 145.3, 183.0, 150.6, 157.2, 174.1, 164.2; $^{31}$P NMR (200 MHz,CDC$_3$) $\delta$: 19.56; Molecular formula: C$_{22}$H$_{20}$N$_5$O$_9$PS; Elemental Analysis: calculated: (C,H,N): 47.06, 3.59, 12.47; found:(C,H,N):47.18, 3.71, 12.43

**Conclusion**

The novel ten diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives 6(a-j) were synthesized under ultrasound irradiation. The present protocol is also extendable to a wide variety of substrates. The advantages of this protocol are the use of eco-friendly catalyst, short reaction time, easy work-up, ease of product isolation, and high yield. The present protocol is also extendable to a wide variety of substrates.
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