Kabachnik–Fields synthesis of novel 2-oxoindolin methyl phosphonate derivatives using CAN.

Anna Pratima G. Nikalje*, Rekha I. Gajare¹, Shailee V. Tiwari¹, Julio A. Seijas², M. Pilar Vazquez-Tato²

¹=Y.B. Chavan College of Pharmacy, Dr. RafiqZakaria Campus, RauzaBaug, Aurangabad, Maharashtra 431001, India;
²=Departamento de Química Orgánica, Facultad de Ciencias, Universidad of Santiago DeCompostela, Alfonso X el Sabio, Lugo 27002, Spain

* Correspondence: annapratimanikalje@gmail.com

Abstract

The work reports ultrasound promoted facile synthesis of novel ten $\alpha$-aminophosphonate derivatives coupled with indole-2,3-dione moiety, namely diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin 3ylidene)hydrazinyl)methylphosphonates derivatives 4(a-j). The derivatives 4(a-j) were synthesized through one-pot three component Kabachnik-Fields reaction, by stirring at room temperature in presence of Cerric Ammonium Nitrate (CAN) as a catalyst, to give the final compounds in better yields and in shorter reaction time. Isatin, chemically known as $H$-indole-2,3-dione, and its derivatives possess a broad range of biological and pharmacological properties. Isatin is widely used as starting material for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. The $\alpha$-amino phosphonate derivatives constitute an important class of organophosphorus compounds on account of their versatile biological activity. The general low mammalian toxicity of these compounds made them attractive for use in agriculture and medicine. Considering the importance of the two pharmacophores, promoted us to club both the pharmacophores in a single molecule using green synthetic protocol. The structures of the ultrasound synthesized compounds were confirmed by spectral analysis like IR, $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR and MS.

Keywords: Kabachnik-Fields reaction; Cerric Ammonium Nitrate; Isatin; $\alpha$-amino phosphonate.
1. Introduction

The basic method for the preparation of α-aminophosphonates, valuable synthetic equivalents and biologically active substrates, involves the condensation of a primary or secondary amine, a carbonyl compound (aldehyde or ketone) and dialkylphosphite[1]. List of various catalysts used for synthesis of various types α-aminophosphonates and the time (minutes) required for synthesis of α-aminophosphonates are shown in Table 1.

Among the synthetic routes towards α-aminophosphonates two main pathways exist. [2]

a) Three-component reactions (Kabachnik-Fields reaction):

In this an aldehyde, an amine and di- or trialkylphosphite are reacted in a one-pot set-up.

b) Pudovik reaction: In this dialkylphosphites are added to compound containing an imino-bond.

α-aminophosphonates are among the most studied bioactive organo phosphorus derivatives and have been used as enzyme inhibitors [3], inhibitors of serine hydrolase [4], peptide mimics [5], antiviral [6], antibacterial [7], antifungal [8], anticancer [9], anti-HIV [10], antibiotics [11], herbicidal [12] etc.

Indole possesses various medicinal properties like antibacterial, antifungal, anti-malarial, anticonvulsant and anti-inflammatory etc. [13]. Isatin, chemically known as 1-\(H\)-indole-2,3-dione, and its derivatives possess a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. It is also used for the inhibition of pro-apoptotic jurkat T cells. In terms of its mode of action, isatin itself is proposed to inhibit cancer cell proliferation via interaction with extracellular signal-related protein kinases (ERKs), thereby promoting apoptosis. These compounds inhibit cancer cell proliferation and tumor growth via interaction with a variety of intracellular targets such as DNA, telomerase, tubulin, P glycoprotein, protein kinases and phosphatases [14]. Isatin-based hydrazones have been identified as inhibitors of the protein tyrosine phosphatase Shp2, which plays an important role in cell signaling, cell proliferation, differentiation and migration [15]. The marketed anticancer drug Sunitinib [16] and Oratinib contains 2-oxoindolin-3-ylidene moiety where as Ilmofosin and Edelfosin contains phosphonate moiety and a recently marketed anticancer drug, Toceranib phosphate [17] contains 2-oxoindol-3-ylidene as well as phosphonates moiety. Considering the
biological importance of 2-oxoindolin-3-ylidene and α-aminophosphonates prompted us to synthesize coupled derivatives containing isatin based hydrazone and α-aminophosphonates with the hope to get novel hybrid derivatives. The designing protocol for the target molecules is as shown in Fig.1.

![Fig.1: The designing protocol for target compounds](image)

Most remarkable pathway to the synthesis of α-aminophosphonates is the Kabachnik-Fields reaction, the one pot three-component reaction of aromatic/heterocyclic aldehyde, amine and triethylphosphite, also known as Kabachnik–Fields reaction [18]. The novel trends in carrying out this reaction are connected with the application of (i) microwave irradiation itself or in combination with catalyst[19], (ii) ionicliquids as solvents[20], (iii) use of appropriate dehydrating agents [21] and, probably most important, (iv) the use of catalysts, was achieved by using various catalyst like ZrOCl₂·8H₂O [22], YbCl₃ [23], lanthanide triflates [24], Mg(ClO₄)₂ [25], LiClO₄ [26] etc. Kabachnik–Fields reaction was promoted by using Ceric (IV) ammonium nitrate (CAN) as a catalyst because of its advantages like high solubility in organic solvent, ease of handling, and low toxicity [27].
2. **Result and Discussion**

*Chemistry*

Diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methyl phosphonates derivatives 4(a-j) were synthesized by Green protocol as outlined in **Scheme 1**. 3-hydrazonoindolin-2-one (1) was synthesized by reacting indole-2,3-dione (isatin) (1mmol) with hydrazine hydrate (1mmol) in the presence of glacial acetic acid as a catalyst by conventional method in methanol using molecular sieves and by **ultrasonication method** by replacing methanol with ethanol. Ultrasound method is better than the conventional method because, methanol being toxic solvent is replaced by benign solvent ethanol. The amount of solvent required is also less than that required for conventional method. Ultrasound assisted method gives better yield in 15-20 minutes against 3-4 hrs required for conventional method. α-Aminophosphonate derivatives 4(a-j) were synthesized by reacting 3-hydrazonoindolin-2-one (1), substituted/heteryl aldehydes 2(a-j) and triethylphosphite(3) via **one pot synthetic step in presence of CAN as a catalyst**. CAN activates the imine formation due to which addition of phosphite is facilitated to give a phosphonium intermediate. This phosphonium intermediate undergoes reaction with water to give the title compounds. CAN catalyst being water soluble can be easily removed after completion of reaction. 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 diethyl (substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl) methyl phosphonates 4(a-j) is shown in **Table 2**.
Scheme 1: Synthesis of the target compounds
3. 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 \(\delta\) 250 to \(\delta\) 250 in CDCl\(_3\) and using Phosphoric acid (H\(_3\)PO\(_4\)) as external standard (chemical shift \(\delta\) 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:

Synthesis of 3-hydrazoneindolin-2-one (1) (Schiff base)

A) Conventional method [28]

A mixture of indole-2,3-dione (isatin) (1 mmol) and hydrazine hydrate (1 mmol) in 15 ml of methanol was refluxed for 3-4 hr in presence of molecular sieves. Microporous 3Å molecular sieves are alumino silicate minerals with chemical composition of \(\frac{2}{3}K_2O\cdot\frac{1}{3}Na_2O\cdot Al_2O_3\cdot 2SiO_2\cdot 9/2H_2O\).[29] Since the 1990’s, these molecular sieves have attracted considerable attention due to their potential use in catalysis, as they absorb water formed in the reaction and drive the reaction to completion. The separated crystals were filtered, washed with a little amount of methanol, dried and recrystallized with chloroform solvent(s), M.P. 284°C, Yield 82%.

B) Ultrasonication Method

Equimolar quantities of indole-2,3-dione (isatin) (1 mmol) and hydrazine hydrate (1 mmol) in the presence of catalytic amount of glacial acetic acid in absolute ethanol (5 ml) was sonicated by keeping the reaction mixture in acoustic box containing Ultrasonic solid probe at 25-40°C and at 25 amplitude for 15 -20 min. The completion of reaction was monitored by TLC. The reaction
mixture was concentrated and cooled. The obtained solid was filtered and dried. The product was recrystallized from ethanol. 3-Hyrazonoinodolin-2-one, C₈H₇O₁N₃, MW: 161.13. Yield: 95%; melting point: 279-284°C. The melting point was uncorrected.

**Step II:**

*Diethyl*(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonates derivatives*4(a-j) [One pot Kabachnik–Fields reaction]*

Equimolar quantity of 3-hyrazonoinodolin-2-one (1) (1mmol), substituted aromatic aldehyde/heteryl aldehydes 2(a-j) (1mmol) and tri-ethyl phosphite(3) (1mmol) was stirred at room temperature in absolute ethanol, in presence of Ceric Ammonium Nitrate (CAN) as a catalyst. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and poured in water, filtered and the solid obtained was dried and recrystallized with ethanol. The time required for completion of reaction varies from 70 min. to 90 min.

**Table 1: Catalyst used for the synthesis of α-aminophosphonate 4(a-j) as compared with other reported time and catalyst used.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst used</th>
<th>Time(minutes)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bismuth salt (10 mol%)</td>
<td>120-360</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Yb (OTf)₃ (10mol%)</td>
<td>270-2160</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>2 mol % HfCl₄</td>
<td>300-2880</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>CBr₄ (5 mol%)</td>
<td>180</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Oxalyl chloride (1.5 mmol)</td>
<td>360</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>AlCl₃ (10 mol%)</td>
<td>570</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>CAN(Reflux)</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>CAN(RT)</td>
<td>180-210</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>CAN</td>
<td>75-90</td>
<td>Present work</td>
</tr>
</tbody>
</table>
Table 2: Physical constant data of diethyl(substituted phenyl/heteryl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate derivatives4(a-j).

<table>
<thead>
<tr>
<th>Code</th>
<th>-Ar</th>
<th>Molecular formula</th>
<th>Molecular weight (gm)</th>
<th>Time required (min)</th>
<th>% Yield</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Phenyl</td>
<td>C₁₉H₂₂N₃O₄P</td>
<td>387.37</td>
<td>75</td>
<td>90</td>
<td>195-196</td>
</tr>
<tr>
<td>4b</td>
<td>p-chloro Phenyl</td>
<td>C₁₉H₂₁ClN₃O₄P</td>
<td>421.81</td>
<td>70</td>
<td>92</td>
<td>150-152</td>
</tr>
<tr>
<td>4c</td>
<td>p-hydroxy Phenyl</td>
<td>C₁₉H₂₁FN₃O₄P</td>
<td>405.36</td>
<td>75</td>
<td>95</td>
<td>176-180</td>
</tr>
<tr>
<td>4d</td>
<td>p-methoxy Phenyl</td>
<td>C₂₀H₂₄N₅O₅P</td>
<td>417.40</td>
<td>85</td>
<td>89</td>
<td>179-180</td>
</tr>
<tr>
<td>4e</td>
<td>3,4-dimethoxy Phenyl</td>
<td>C₂₁H₂₆N₃O₆P</td>
<td>447.42</td>
<td>90</td>
<td>90</td>
<td>189-190</td>
</tr>
<tr>
<td>4f</td>
<td>p-fluoro Phenyl</td>
<td>C₁₉H₂₂N₃O₅P</td>
<td>403.37</td>
<td>80</td>
<td>88</td>
<td>140-142</td>
</tr>
<tr>
<td>4g</td>
<td>4-hydroxy-3-methoxy Phenyl</td>
<td>C₂₀H₂₄N₃O₆P</td>
<td>433.39</td>
<td>75</td>
<td>94</td>
<td>112-114</td>
</tr>
<tr>
<td>4h</td>
<td>4-hydroxy-3-ethoxy Phenyl</td>
<td>C₂₁H₂₆N₃O₆P</td>
<td>447.44</td>
<td>80</td>
<td>92</td>
<td>160-162</td>
</tr>
<tr>
<td>4i</td>
<td>Thiophen-2-yl</td>
<td>C₁₇H₂₀N₃OsPS</td>
<td>393.40</td>
<td>80</td>
<td>87</td>
<td>178-180</td>
</tr>
<tr>
<td>4j</td>
<td>Furan-2-yl</td>
<td>C₁₇H₂₀N₃OsP</td>
<td>377.33</td>
<td>80</td>
<td>84</td>
<td>176-178</td>
</tr>
</tbody>
</table>

Diethyl(phenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate(4a)

Yield 90%; M.P. 195-196°C; ¹H NMR (400 MHz,CDCl₃) δ: 1.20 (t, 6H,2×OCH₂CH₃),4.70 (q, 4H, 2×OCH₂CH₃), 5.05 (d, 1H, -CH), 7.10-7.94 (m, 9H, -CH), 8.61 (s, 1H, -NH), 10.90 (s, 1H, -NH of indole); ¹³C NMR (100 MHz, CDCl₃) δ: 16.31, 60.11, 63.32, 110.32, 119.25, 124.32, 126.25, 126.52, 128.12, 128.32, 129.22, 130.32, 162.11; ³¹PNMR (200 MHz,CDCl₃) δ: 19.90; ESI-MS: m/z calculated for C₁₉H₂₂N₃O₄P (M+H⁺): 388.84; found: 388.88 (M+1); IR (KBr) cm⁻¹: 3340.31 (N-H stretching), 2960.41 (CH stretching of aromatic), 2837.21 (CH stretching of alkyl), 2300.23 (N-H stretching), 1620.33 (C=O stretching of amide), 1466.55 (CH Bending of CH₂); Elemental analysis calculated for C₁₉H₂₂N₃O₄P: C, 58.91; H, 5.72; N, 10.85; P, 7.58; found; C, 58.88; H, 5.75; N, 10.87; P, 7.60.
Diethyl(4-chlorophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate(4b)

Yield 92%; M.P. 150-152°C; \(^1\)HNMR (400 MHz,CDCl\(_3\)) \(\delta\): 1.20 (t, 6H, 2×OCH\(_2\)CH\(_3\)), 4.13 (q, 4H, 2×OCH\(_2\)CH\(_3\)), 5.10 (d, 1H, -CH), 6.98-7.94 (m, 8H, -CH), 8.58 (s, 1H, -NH), 11.55 (s, 1H, -NH of indole); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 16.15, 40.17, 60.25, 78.07, 110.26, 117.96, 127.79, 128.21, 128.83, 129.54, 130.19, 158.78, 164.52; \(^{31}\)PNMR (200 MHz, CDCl\(_3\)) \(\delta\): 18.84; ESI-MS: m/z calculated for C\(_{19}\)H\(_{21}\)ClN\(_3\)O\(_4\)P (M+2): 423.09; found: 423.81(M+2); IR (KBr) cm\(^{-1}\): 3350.41 (N-H stretching), 2970.06 (CH stretching of aromatic), 2800.22 (CH stretching of alkyl), 2350.36 (N-H stretching), 1710.01 (C=O stretching of amide), 1454.75 (CH Bending of CH\(_2\)); Elemental analysis calculated for C\(_{19}\)H\(_{21}\)ClN\(_3\)O\(_4\)P: C, 54.10; H, 5.02; N, 9.96; P, 7.34; found; C, 54.12; H, 5.04; N, 9.99; P, 7.39

Diethyl(4-flurophenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate (4c)

Yield 95%; M.P. 176-180°C; \(^1\)HNMR (400 MHz,CDCl\(_3\)) \(\delta\): 1.31 (t, 6H, 2×OCH\(_2\)CH\(_3\)), 4.23 (q, 4H, 2×OCH\(_2\)CH\(_3\)), 5.21 (d, 1H, -CH), 7.12-8.05 (m, 8H, -CH), 8.84 (s, 1H, -NH), 10.14 (s, 1H, -NH of indole); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 18.12, 65.21, 68.21, 123.32, 114.21, 117.14, 120.85, 127.55, 128.85, 131.36, 144.74, 146.96, 161.11, 164.85; \(^{31}\)PNMR (200 MHz,CDCl\(_3\)) \(\delta\): 18.54; ESI-MS: m/z calculated for C\(_{19}\)H\(_{21}\)FN\(_3\)O\(_4\)P (M+H\(^{+}\)) 406.13; found: 406.20 (M+H\(^{+}\)); IR (KBr) cm\(^{-1}\): 3340.11 (N-H stretching), 2910.16 (CH stretching of aromatic), 2800.48 (CH stretching of alkyl), 2200.50 (N-H stretching), 1620.17 (C=O stretching of amide), 1464.47 (CH Bending of CH\(_2\)); Elemental analysis calculatedfor C\(_{19}\)H\(_{21}\)FN\(_3\)O\(_4\)P: C, 54.10; H, 5.02; N, 9.96; P, 7.34; found; C, 54.12; H, 5.04; N, 9.99; P, 7.67

Diethyl(4-methoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate(4d)

Yield 89%; M.P. 178-179°C; \(^1\)HNMR (400 MHz,CDCl\(_3\)) \(\delta\): 1.25 (t, 6H, 2×OCH\(_2\)CH\(_3\)), 3.54 (s, 3H, OCH\(_3\)), 4.11 (q, 4H, 2×OCH\(_2\)CH\(_3\)), 5.15 (d, 1H, -CH), 7.00-7.99 (m, 8H, -CH), 8.60 (s, 1H, -NH), 10.94 (s, 1H, -NH of indole); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 14.23, 55.13, 78.34, 79.88, 99.49, 110.93, 113.77, 119.25, 122.98, 126.47, 128.23, 129.85, 133.99, 144.85, 160.22, 168.98; \(^{31}\)PNMR (200 MHz,CDCl\(_3\)) \(\delta\): 19.84; ESI-MS: m/z calculated for C\(_{20}\)H\(_{24}\)N\(_3\)O\(_5\)P (M+H\(^{+}\)) 418.15; found: 418.40 (M+H\(^{+}\)); IR (KBr) cm\(^{-1}\): 3350.11 (N-H stretching), 3070.76 (CH stretching of aromatic), 2800.96 (CH stretching of alkyl), 2300.11 (N-H stretching), 1610.47
(C=O stretching of amide), 1025.74 (-O- stretching); Elemental analysis calculated for C$_{20}$H$_{24}$N$_3$O$_5$P: C, 57.55; H, 5.80; N, 10.07; P, 7.42 found; C, 57.58; H, 5.82; N, 10.10; P, 7.45

**Diethyl(3,4-dimethoxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate(4e)**

Yield 90%; M.P. 189-190°C; $^1$HNMR (400 MHz, CDCl$_3$) δ: 1.21 (t, 6H, 2×OCH$_2$CH$_3$), 3.85 (s, 6H, OCH$_3$), 4.21 (q, 4H, 2×OCH$_2$CH$_3$), 5.06 (d, 1H, -CH), 6.87-7.95 (m, 7H, -CH), 8.42 (s, 1H, -NH), 10.03 (s, 1H, -NH of indole); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ: 20.22, 58.69, 60.21, 61.12, 66.32, 111.78, 120.78, 121.36, 131.85, 132.11, 133.25, 141.74, 148.23, 150.41, 151.12, 167.47; $^{31}$PNMR (200 MHz, CDCl$_3$) δ: 18.94; ESI-MS: m/z calculated for C$_{21}$H$_{26}$N$_3$O$_6$P (M+H$^+$): 448.16; found: 448.44 (M+H$^+$); IR (KBr) cm$^{-1}$: 3250 (N-H stretching), 2890.76 (CH stretching of aromatic), 2800.57 (CH stretching of alkyl), 2350.78 (N-H stretching), 1650.23 (C=O stretching of amide), 1002.44 (-O- stretching); Elemental analysis calculated for C$_{21}$H$_{26}$N$_3$O$_6$P: C, 57.55; H, 5.80; N, 10.07; P, 7.42 found; C, 57.58; H, 5.82; N, 10.10; P, 7.45.

**Diethyl(4-hydroxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate(4f)**

Yield 88%; M.P. 140-142°C; $^1$HNMR: (400 MHz, CDCl$_3$) δ: 1.21 (t, 6H, 2×OCH$_2$CH$_3$), 4.14 (q, 4H, 2×OCH$_2$CH$_3$), 5.11 (d, 1H, -CH), 6.77-7.90 (m, 8H, -CH), 8.45 (s, 1H, OH), 8.53 (s, 1H, -NH), 10.44 (s, 1H, -NH of indole); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 17.26, 61.25, 69.74, 115.47, 116.23, 117.63, 123.52, 129.85, 130.47, 134.52, 136.12, 145.32, 156.54, 164.41; $^{31}$PNMR (200 MHz, CDCl$_3$) δ: 19.64; ESI-MS: m/z calculated for C$_{19}$H$_{22}$N$_3$O$_5$P (M+H$^+$): 404.13; found: 404.37 (M+H$^+$); IR (KBr) cm$^{-1}$: 3600.10 (aromatic OH), 3440.4 (N-H stretching), 2980.88 (CH stretching of aromatic), 2350.78 (N-H stretching), 2280.21 (C=O stretching of amide), 1710.22 (C=O stretching of amide); Elemental analysis calculated for C$_{19}$H$_{22}$N$_3$O$_5$P: C, 56.77; H, 5.67; N, 10.42; P, 6.92 found; C, 56.40; H, 5.67; N, 10.44; P, 6.94.

**Diethyl(4-hydroxyphenyl)(2-(1-morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate (4g)**

Yield 94%; M.P. 112-114°C; $^1$HNMR (400 MHz, CDCl$_3$) δ: 1.20 (t, 6H, 2×OCH$_2$CH$_3$), 3.36 (s, 3H, OCH$_3$), 4.14 (q, 4H, 2×OCH$_2$CH$_3$), 5.14 (d, 1H, CH), 6.83-7.73 (m, 7H, CH), 8.12 (s, 1H, OH), 9.77 (s, 1H, -NH), 10.55 (s, 1H, -NH of indole); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 16.05, 40.17, 55.40, 62.57, 110.36, 116.74, 120.48, 125.29, 132.66, 134.25, 136.24, 138.59, 138.90, 144.46, 150.94, 190.22; $^{31}$PNMR (200 MHz,CDCl$_3$) δ: 19.94; ESI-MS: m/z calculated for
C_{20}H_{24}N_{3}O_{6}P (M+H\textsuperscript{+}): 434.14; found: 434.39 (M+H\textsuperscript{+}); IR (KBr) cm\textsuperscript{-1}: 3610.45 (aromatic OH), 3450.64 (N-H stretching), 2830.74 (CH stretching of alkyl), 2310.21 (N-H stretching), 1680.12 (C=O stretching of amide), 1030.14 (-O-stretching); Elemental analysis calculated for C_{20}H_{24}N_{3}O_{6}P: C, 55.43; H, 5.58; N, 9.70; P, 7.15 found; C, 55.45; H, 5.60; N, 9.73; P, 7.18

**Diethyl(3-ethoxy-4-hydroxyphenyl)(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate (4h)**

Yield 92%; M.P. 160-162\degree C; \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \textdelta: 1.15 (t, 6H, 2\times OCH_{2}CH_{3}), 1.43 (t, 3H, OCH_{2}CH_{3}), 4.11 (m, 6H, 3\times OCH_{2}CH_{3}), 5.11 (d, 1H, CH), 6.72-6.95 (m, 3H, CH), 6.96 (s, 1H, OH), 7.10-7.89 (m, 4H, CH), 8.81 (s, 1H, -NH), 10.72 (s, 1H, -NH of indole); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \textdelta: 16.21, 16.52, 18.21, 61.52, 64.85, 68.74, 117.12, 116.41, 119.32, 121.92, 122.74, 130.96, 133.12, 136.24, 141.23, 142.74, 167.74; \textsuperscript{31}PNMR (200 MHz, CDCl\textsubscript{3}) \textdelta: 18.65; ESI-MS: m/z calculated for C_{21}H_{26}N_{3}O_{6}P (M+H\textsuperscript{+}): 448.16; found: 448.40 (M+H\textsuperscript{+}); IR (KBr) cm\textsuperscript{-1}: 3550.50 (aromatic OH), 3420.32 (N-H stretching), 2999.45 (CH stretching of aromatic), 2813.87 (CH stretching of alkyl), 2350.52 (N-H stretching), 1710.72 (C=O stretching of amide), 1020.42 (-O-stretching); Elemental analysis calculated for C_{21}H_{26}N_{3}O_{6}P: C, 56.37; H, 5.86; N, 9.39; P, 6.92 found; C, 56.40; H, 5.88; N, 9.41; P, 6.94.

**Diethyl(2-(2-oxoindolin-3-ylidene)hydrazinyl)(thiophen-2-yl)methylphosphonate (4i)**

Yield 87%; M.P. 179-182\degree C; \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \textdelta: 1.17 (t, 6H, 2\times OCH_{2}CH_{3}), 4.07 (q, 4H, 2\times OCH_{2}CH_{3}), 5.02 (d, 1H, CH), 6.82-7.89 (m, 7H, CH), 8.57 (s, 1H, -NH), 10.77 (s, 1H, -NH of indole); \textsuperscript{13}C NMR: (100 MHz, CDCl\textsubscript{3}) \textdelta: 17.12, 63.52, 69.96, 119.12, 120.35, 124.18, 128.47, 129.96, 130.18, 150.52, 152.74, 155.54, 165.65, 170.65, 174.96; \textsuperscript{31}PNMR (200 MHz, CDCl\textsubscript{3}) \textdelta: 18.45; ESI-MS: m/z calculated for C_{17}H_{26}N_{3}O_{1}PS (M+H\textsuperscript{+}): 394.09; found: 394.48 (M+H\textsuperscript{+}); IR (KBr) cm\textsuperscript{-1}: 3520.72 (N-H stretching), 2912.88 (CH stretching of aromatic), 2813.87 (CH stretching of alkyl), 2350.52 (N-H stretching), 1710.72 (C=O stretching of amide), 1020.42 (-O-stretching); Elemental analysis calculated for C_{17}H_{26}N_{3}O_{1}PS: C, 51.90; H, 5.12; N, 10.68; P, 7.87; S, 8.15 found; C, 51.91; H, 5.14; N, 10.70; P, 7.89; S, 8.17.

**Diethylfuran-2-yl(2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonate (4j)**
Yield 84%; M.P. 176-178°C; $^1$HNMR (400 MHz, CDCl$_3$) δ: 1.25 (t, 6H, 2×OCH$_2$CH$_3$), 4.12 (q, 4H, 2×OCH$_2$CH$_3$), 4.55 (d, 1H, CH), 6.11-7.89 (m, 7H, CH), 8.44 (s, 1H, -NH), 10.45 (s, 1H, -NH of indole); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 22.21, 50.11, 65.52, 112.31, 119.95, 121.36, 128.63, 130.36, 131.21, 133.65, 147.33, 151.25, 153.23, 155.39, 164.21; $^{31}$PNMR (200 MHz, CDCl$_3$) δ: 18.56; ESI-MS: m/z calculated for C$_{17}$H$_{20}$N$_3$O$_5$P (M+H$^+$): 378.12; found: 378.33 (M+H$^+$); IR (KBr)cm$^{-1}$: 3280.32 (NH stretching), 2945.46 (CH aromatic), 2850.63 (CH stretching of alkyl), 2440.85 (C=O stretching), 1710.33 (C=O stretching), 1070.10 (-O-stretching); Elemental analysis calculated for C$_{17}$H$_{20}$N$_3$O$_5$P: C, 54.11; H, 5.34; N, 11.14; P, 8.21 found; C, 54.14; H, 5.36; N, 11.16; P, 8.24.

**Conclusion**

Ultrasound synthesizer have become a promising alternative green tool for various chemical reactions due to their economic status like less time and electricity consumption by faster reaction. Intermediates (1) were synthesized by Green protocol such as by using ultrasound synthesizer, which gives the better yield in 15-20 minutes while conventional method requires 3-4 hrs. Final compounds 4(a-j) were synthesized through a one-pot three-component reaction process, a Kabachnik-Fields reaction in presence of CAN as a Green catalyst. Novel diethyl (substitutedphenyl/heteraryl)(2-(2-oxoindolin-3yldene)hydrazinyl)methylphosphonate derivatives 4(a-j) were synthesized at room temperature in facile one pot reaction using CAN as a green catalyst, which gives faster reaction at room temperature. CAN catalyst being water soluble can be easily removed after completion of reaction. The synthesized compounds were characterized by TLC, IR, NMR, and Mass spectrometry.

**Acknowledgment:**

The authors are thankful to Mrs. Fatima Rafiq Zakaria, Chairman of Maulana Azad Educational Trust and Dr. Zahid Zaheer, Principal of Y. B. Chavan College of Pharmacy, for providing the laboratory facility.

**Conflict of Interest:** The authors declare no conflict of interest.
References


2) Christian V. Stevens *et al.*, Straight forward continuous synthesis of $\alpha$-aminophosphonates under microreactor conditions, General Papers ARKIVOC 2006 (i) 31-45.

3) C. Li, B. Song, K. Yan, G. Xu, D. Hu, S. Yang, L. Jin, W. Xue ,P. Lu, One Pot Synthesis of $\alpha$-Aminophosphonates Containing Bromo and 3,4,5-Trimethoxybenzyl Groups under Solvent-free Conditions, Molecules, 12 (2007), 163-172.


