

## REGIOSELECTIVE SYNTHESIS OF SOME NOVEL PHOSPHONOPYRAZOLE, PHOSPHONOPYRIMIDINE AND PHOSPHONODIAZEPINE COMPOUNDS CONTAINING COUMARIN RING

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**Abstract** – A convenient regioselective synthesis of some novel phosphonopyrazole, phosphonopyrimidine and phosphonodiazepine derivatives containing a coumarin ring, was designed. The methodology involves one-pot reaction of 3-(2-bromoacetyl)-2*H*-chromen-2-one (**1**) with dimethylformamide dimethyl acetal and diethyl phosphite to give diethyl [2-bromo-3-oxo-3-(2-oxo-2*H*-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**). The successful heterocyclization of substrate **2** with 1,2-, 1,3- and 1,4-diamine reagents afforded the target products in moderate to good yields.

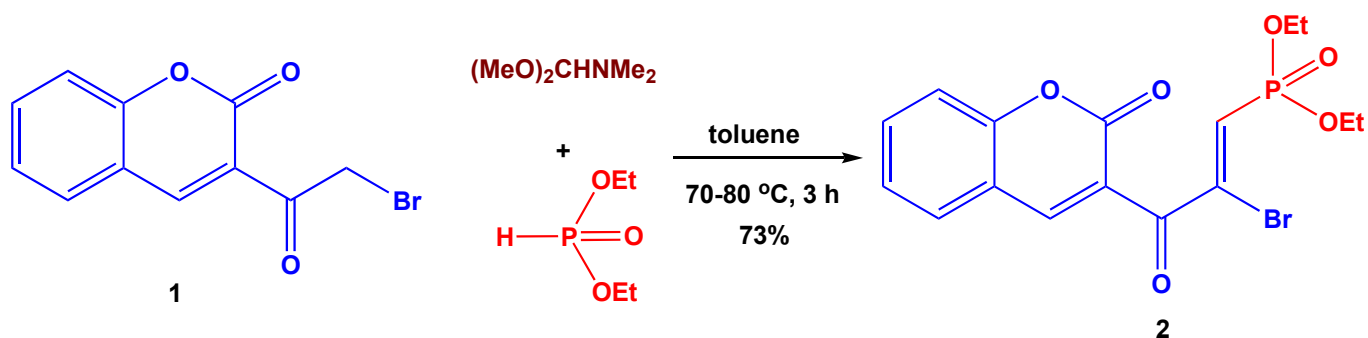
### INTRODUCTION

Coumarin is a naturally occurring substance that may be found in a variety of plants. It was discovered in 1820 and has been utilized in the perfume industry since 1882.<sup>1</sup> Coumarin and its derivatives have exceptional antibacterial<sup>2</sup> and antifungal properties.<sup>3</sup> Coumarin molecules are also the basis for a category of over 40 drugs used in medicine.<sup>4-6</sup> Recently, some novel coumarin-incorporated nitrogen heterocycles with promising medicinal properties have been synthesized.<sup>7-9</sup> Some pyrazolylcoumarin analogues are found to have potential as anticancer<sup>10</sup> and antimicrobial agents.<sup>11</sup> Also, a series of biologically active agents containing both of pyrimidine and diazepine linked to coumarin were synthesized.<sup>12-15</sup> On the other hand, compounds containing phosphonate group are a familiar group possessing chemotherapy, fungicidal and anticancer properties.<sup>16-18</sup> A lot of work was done in the last few decades on heterocyclic containing phosphonate group to find new compounds to act as antimicrobial, antifungal and anticancer agents.<sup>19-21</sup>

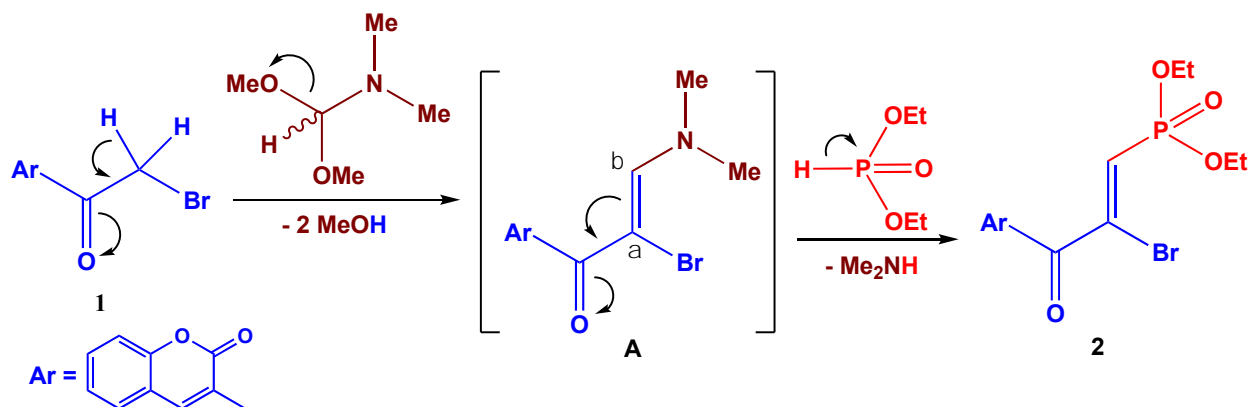
The merging of phosphonate group and coumarin ring linked to nitrogen heterocyclic skeleton in one molecular frame may generate prominent pharmacological potencies. Therefore, in the context of our ongoing studies concerning the synthesis of novel phosphorus compounds,<sup>22-26</sup> herein we describe the synthesis of diethyl [2-bromo-3-oxo-3-(2-oxo-2*H*-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**) as a novel substrate having a reactive  $\beta$ -phosphonyl- $\alpha,\beta$ -unsaturated ketone moiety, which underwent cyclocondensation reactions with a series of 1,2-, 1,3- and 1,4-diamine reagents to design novel coumarin linked to nitrogen heterocycles which bearing phosphonate group.

## RESULTS AND DISCUSSION

Initially, diethyl [2-bromo-3-oxo-3-(2-oxo-2*H*-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**) as a novel starting material was synthesized *via* one-pot three-component reaction (Scheme 1). The method depend on the reaction of 3-(2-bromoacetyl)-2*H*-chromen-2-one (**1**) with dimethylformamide dimethyl acetal (DMFDMA) and diethyl phosphite in dry toluene at 70-80 °C for 3 h (Scheme 1). The reaction proceed through the condensation of compound **1** with DMFDMA giving the enaminone intermediate **A** by elimination of two methanol molecules. The latter intermediate **A** reacted with diethyl phosphite through the nucleophilic attack of phosphorus atom at the C $\beta$  with removal of dimethylamine molecule (Scheme 2). The structure of resulting substrate **2** was elucidated based on spectral data, for example <sup>1</sup>H-NMR spectrum revealed the presence of the protons of two methyl groups of diethyl phosphonate group as two triplet signals at  $\delta$  1.03 and 1.19 ppm, and two quartet signals at  $\delta$  3.96 and 4.22 ppm. Also, it showed a specific doublet signal at  $\delta$  7.34 ppm for H $\beta$  for olefin bond with  $J=22.4$  Hz.<sup>27</sup> Furthermore, its <sup>13</sup>C-NMR spectrum recorded some specific carbon atoms at  $\delta$  13.3, 14.6 (CH<sub>3</sub>), 60.4, 61.6 (OCH<sub>2</sub>), 140.2 (C $\alpha$ , olefin bond) and 138.2 (C $\beta$ , olefin bond,  $J_{PC}=100.4$  Hz) ppm. Its <sup>31</sup>P-NMR spectrum exhibited a singlet at  $\delta$  20.62 ppm. In addition, the mass spectrometry confirmed the structure by recording its molecular ion peaks at  $m/z$  416 (8%) and 414 (9%) due to the bromine atom.

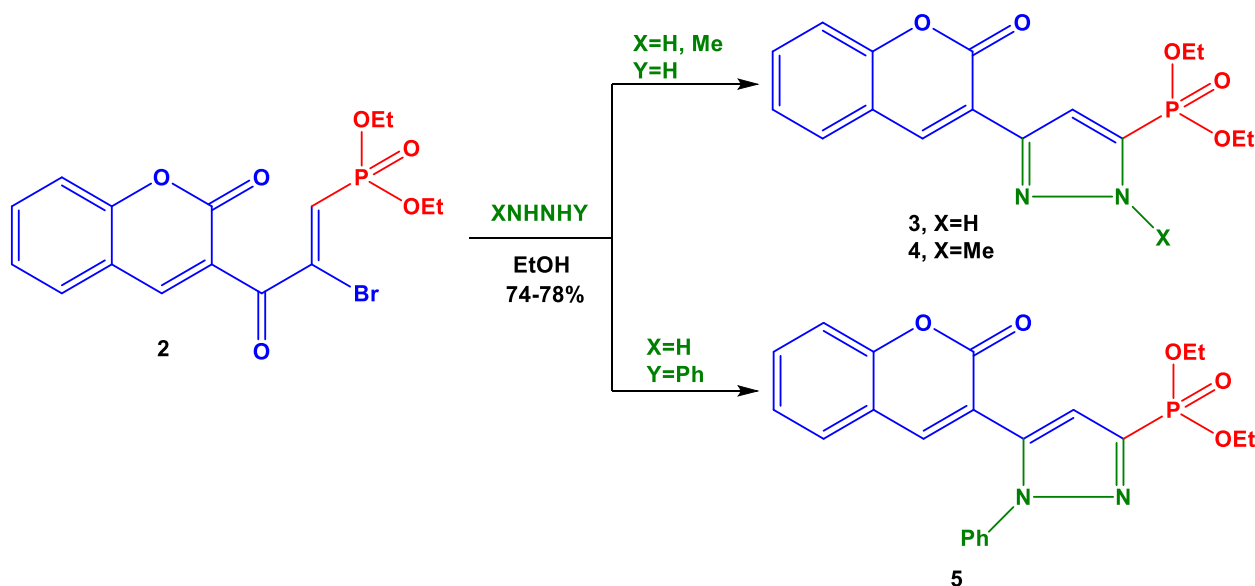


Scheme 1

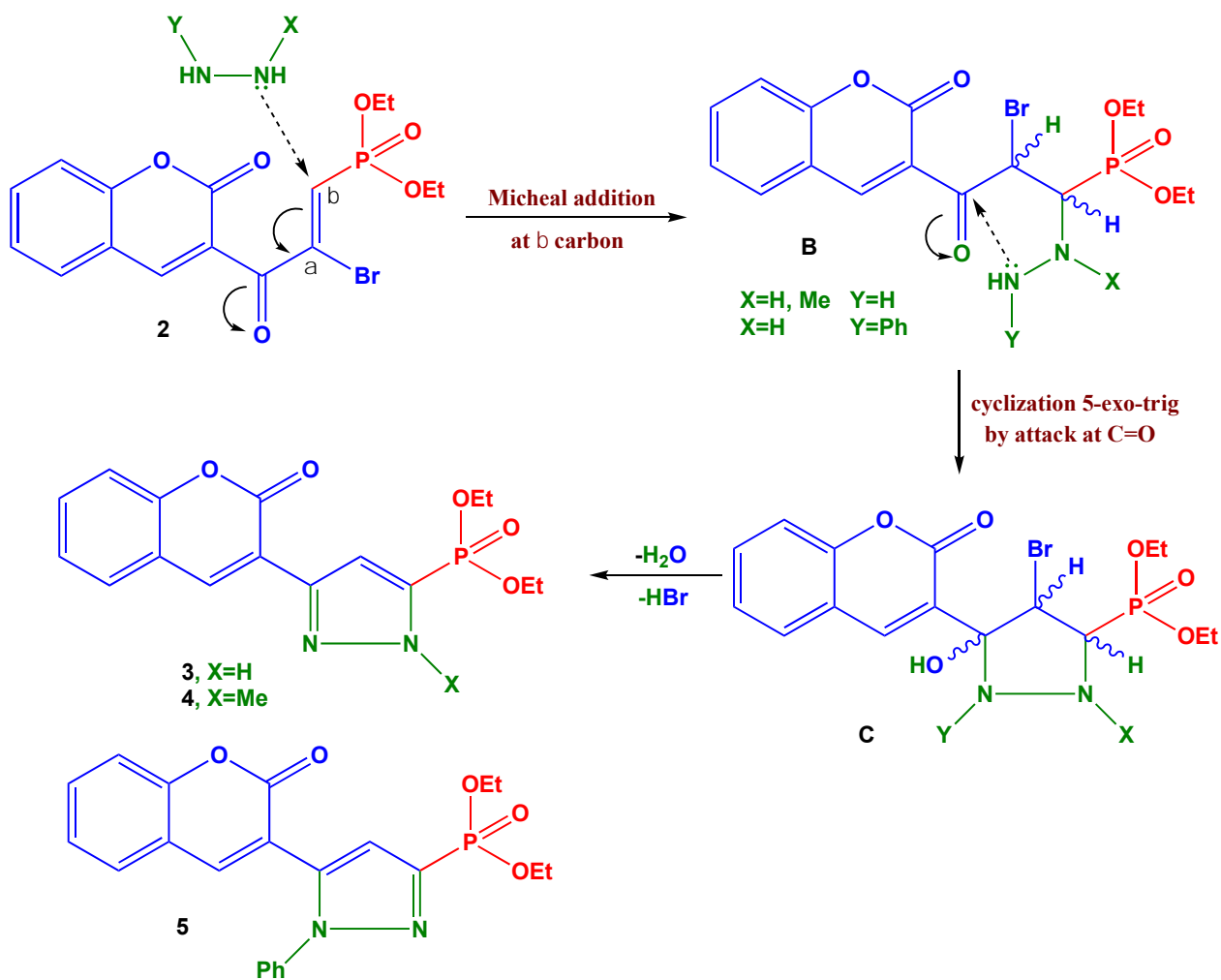


Scheme 2

Basically, diethyl [2-bromo-3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**) has three specific electrophilic sites,  $C_\alpha$ ,  $C_\beta$  and  $C=O$  in  $\alpha,\beta$ -unsaturated ketone system which can undergo nucleophilic attack by 1,2-, 1,3- and 1,4-diamine reagents. Thus, construction of the novel coumarinyl phosphonopyrazole compounds **3–5** was accomplished in one step. The synthetic route involves the reaction of diethyl [2-bromo-3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**) with three examples of hydrazines, namely hydrazine hydrate, methylhydrazine and phenylhydrazine in absolute ethanol (Scheme 3). The reactions proceed through the regioselective nucleophilic attack of  $NH_2$  of hydrazines to  $C_\beta$  of substrate **2** to form the C–N bond, giving an intermediate **B**. Then the nucleophilic attack has occurred selectively at the  $C_\beta$  due to its higher electrophilicity. Then, the other NHR group attacks to the carbonyl group, leading to 5-*exo-trig* cyclization to form the intermediate **C**. The latter intermediate undergoes removal of water and hydrogen bromide molecules to create the isolated products **3–5** (Scheme 4).

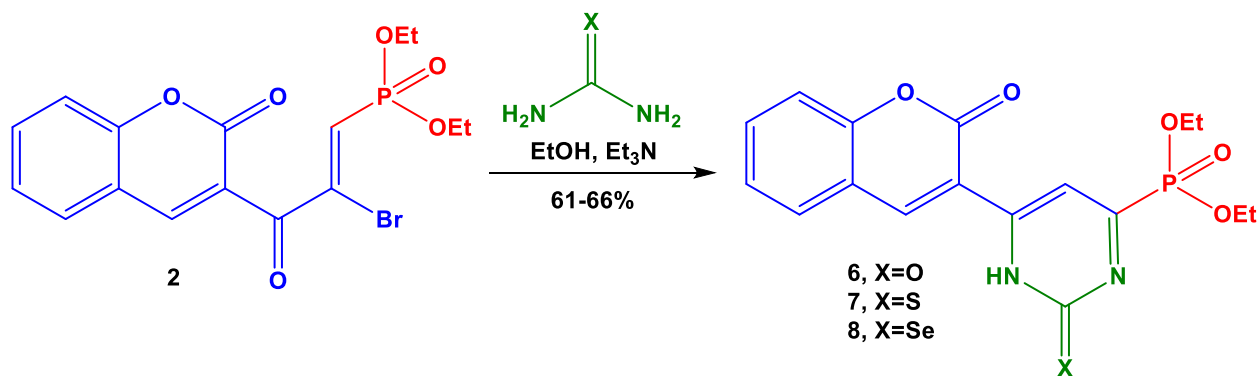


Scheme 3



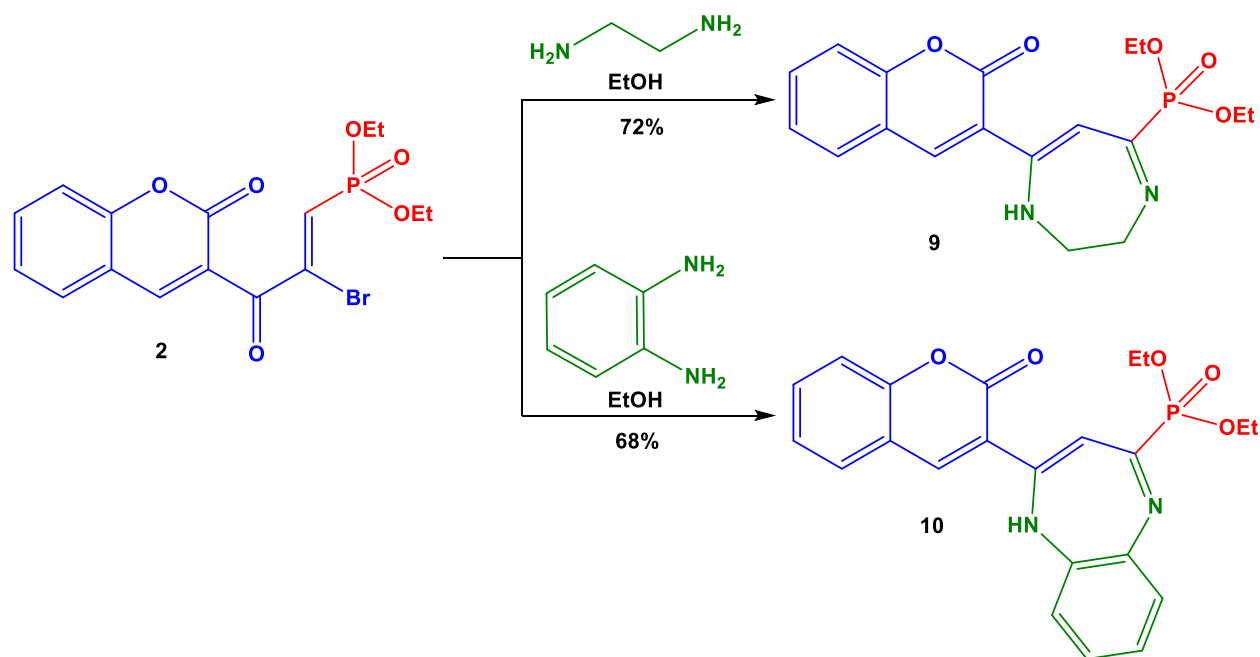
Scheme 4

The previous approaches encouraged us to employ this strategy for designing other various functionalized phosphonyl nitrogen heterocycles. Thus, when the starting material **2** was treated with nitrogen 1,3-diamine reagents, namely urea, thiourea and selenourea in absolute ethanol in the presence of triethylamine as a catalyst, the coumarinyl phosphonopyrimidines **6–8**, respectively, were isolated in moderate yields (Scheme 5).



Scheme 5

Interestingly, the same strategy was used to construct a novel coumarinyl phosphonodiazepine **9** and its benzo analogue **10**. Thus, diethyl [7-(2-oxo-2*H*-chromen-3-yl)-2,3-dihydro-1*H*-1,4-diazepin-5-yl]-phosphonate (**9**) and diethyl [2-(2-oxo-2*H*-chromen-3-yl)-1*H*-1,4-benzodiazepin-4-yl]phosphonate (**10**) were obtained in good yields by reacting the substrate **2** with ethylenediamine and 1,2-phenylenediamine, respectively, in absolute ethanol (Scheme 6).



**Scheme 6**

The structures of all obtained products were confirmed by IR, mass,  $^1\text{H}$ -,  $^{13}\text{C}$ - and  $^{31}\text{P}$ -NMR spectroscopies. The mass spectra of all synthesized compounds showed their expected molecular ion peaks. The IR spectra for all products displayed absorption bands at region 3222–3158, 1259–1212 and 1053–1023  $\text{cm}^{-1}$ , which are respectively, related to the stretching frequencies of NH, P=O and P–O–C groups. Also, the C=O absorption bands were observed at 1736–1721  $\text{cm}^{-1}$ . The  $^1\text{H}$ -NMR spectra of all products exhibited the diethoxy groups in the aliphatic region as a triplet in  $\delta$  0.99–1.31 (Me) and 3.75–4.23 (OCH<sub>2</sub>) ppm.<sup>28</sup> Also, in the region  $\delta$  8.46–8.89 ppm, the hydrogens of C–4 in coumarin ring appeared as singlets. The singlets of the hydrogens C–4<sub>pyrazoles</sub>, C–5<sub>pyrimidines</sub>, and C–6(3)<sub>diazepines</sub> appeared in the region  $\delta$  5.92–6.62, 5.76–5.86 and 5.13–6.21 ppm, respectively. Each product exhibited the distinct signals for carbon atoms. The specific carbon atoms of diethoxy groups were recorded at range  $\delta$  13.4–14.8 (Me) and 59.4–62.6 (OCH<sub>2</sub>) ppm. The signals of the carbon atoms C–3(5)<sub>pyrazoles</sub>, C–4<sub>pyrimidines</sub>, and C–5(4)<sub>diazepines</sub> appeared as doublet in the region  $\delta$  146.2–148.3 ( $J_{\text{PC}}=100.2\text{--}101.4$  Hz), 162.4–163.1 ( $J_{\text{PC}}=102.6\text{--}103.4$  Hz) and 161.2–162.2 ( $J_{\text{PC}}=104.4\text{--}104.6$  Hz) ppm, respectively. In addition, the carbon atom C–4 of coumarin rings were

observed at  $\delta$  143.9–146.4 ppm while C=O carbon atoms were found at  $\delta$  159.3–160.2 ppm. Finally, the  $^{31}\text{P}$ -NMR spectra for the products **3–10** showed at region  $\delta$  19.9–23.2 ppm, respectively.<sup>29</sup>

## EXPERIMENTAL

The melting point was determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on FT-IR (Nicolet IS10) spectrophotometer using KBr disks and Perkin-Elmer 293 spectrophotometer using KBr disks.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were measured a Bruker spectrometer (400 and 100 MHz), using DMSO- $d_6$  as a solvent and TMS ( $\delta$ ) as an internal standard.  $^{31}\text{P}$ -NMR spectra were measured on a Bruker (162 MHz) spectrophotometer using DMSO- $d_6$  as a solvent, TMS as an internal standard and 85%  $\text{H}_3\text{PO}_4$  as an external reference. Mass spectra were recorded on direct probe controller inlet part to single quadropole mass analyzer in (thermo scientific GCMS). Elemental microanalyses were performed Perkin-Elmer 2400II at the Chemical War department, Ministry of Defence. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis.

**Synthesis of diethyl [2-bromo-3-oxo-3-(2-oxo-2*H*-chromen-3-yl)prop-1-en-1-yl]phosphonate (2).** A mixture of 3-(2-bromoacetyl)-2*H*-chromen-2-one (**1**) (1.33 g, 5 mmol), dimethylformamide dimethyl acetal (DMFDMA) (0.67 g, 5 mmol) and diethyl phosphite (0.7 ml, 5 mmol) in dry toluene (50 mL) was heated under reflux for 3 h at 70–80 °C. The solvent was concentrated to its half volume. The formed solid was filtered off and crystallized from benzene to give orange solid in yield 73%, mp 193–194 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3056 (C–H<sub>arom</sub>), 2973 (C–H<sub>aliph</sub>), 1721 (C=O), 1640 (C=O), 1591 (C=C), 1240 (P=O), 1032 (P–O–C).  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ ): 1.03 (t, 3H,  $J=7.6$  Hz, CH<sub>3</sub>), 1.19 (t, 3H,  $J=7.2$  Hz, CH<sub>3</sub>), 3.96 (q, 2H,  $J=7.6$  Hz, CH<sub>2</sub>O), 4.22 (q, 2H,  $J=7.2$  Hz, CH<sub>2</sub>O), 7.34 (d, 1H,  $J=22.4$  Hz, CH <sub>$\beta$</sub>  olefin), 7.21 (t, 1H,  $J=6.8$  Hz, H-6<sub>coumarin</sub>), 7.49 (d, 1H,  $J=7.2$  Hz, H-8<sub>coumarin</sub>), 7.64 (t, 1H,  $J=6.8$  Hz, H-7<sub>coumarin</sub>), 7.91 (d, 1H,  $J=6.8$  Hz, H-5<sub>coumarin</sub>), 8.43 (s, 1H, H-4<sub>coumarin</sub>).  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ ): 13.3 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 60.4 (OCH<sub>2</sub>), 61.6 (OCH<sub>2</sub>), 115.8 (C-8<sub>coumarin</sub>), 120.1 (C-4<sub>a</sub>coumarin), 122.3 (C-3<sub>coumarin</sub>), 124.6 (C-6<sub>coumarin</sub>), 127.6 (C-5<sub>coumarin</sub>), 132.6 (C-7<sub>coumarin</sub>), 138.2 (d, C <sub>$\beta$</sub> ,  $J_{\text{PC}}=100.4$  Hz, C=C<sub>olefin</sub>), 140.2 (C <sub>$\alpha$</sub> , C=C<sub>olefin</sub>), 147.2 (C-4<sub>coumarin</sub>), 154.1 (C-8<sub>a</sub>coumarin), 159.8 (C-2<sub>coumarin</sub>), 169.0 (C=O).  $^{31}\text{P}$ -NMR (162 MHz, DMSO- $d_6$ ): 20.62 ppm. MS (EI,  $m/z$ ): 416 (M+2, 7%) and 414 (M<sup>+</sup>, 8%). Anal. Calcd for C<sub>16</sub>H<sub>16</sub>BrO<sub>6</sub>P (415.18): C, 46.29; H, 3.88%. Found: C, 46.12; H, 3.79%.

**General procedure for synthesis of the target compounds 3–10.** A mixture of diethyl [2-bromo-3-oxo-3-(2-oxo-2*H*-chromen-3-yl)prop-1-en-1-yl]phosphonate (**2**) (0.83 g, 2 mmol) and different diamine reagents (2 mmol) in absolute EtOH (25 mL), was heated under reflux for 4–10 h (Et<sub>3</sub>N was used as a catalyst in case of nitrogen 1,3-diamine reagents). After completion of reaction (monitored by TLC), the formed solid was filtered off and crystallized from the proper solvent.

**Diethyl [3-(2-oxo-2H-chromen-3-yl)-1H-pyrazol-5-yl]phosphonate (3):** Yield 78%, pale yellow solid, mp 173–175 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3204 (br, NH), 3062 ( $\text{C-H}_{\text{arom}}$ ), 2962, 2924 ( $\text{C-H}_{\text{aliph}}$ ), 1735 ( $\text{C=O}$ ), 1616 ( $\text{C=N}$ ), 1594 ( $\text{C=C}$ ), 1246 ( $\text{P=O}$ ), 1041 ( $\text{P-O-C}$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ): 1.05 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 1.10 (t, 3H,  $J=7.6$  Hz,  $\text{CH}_3$ ), 3.88 (q, 2H,  $J=7.2$  Hz,  $\text{CH}_2\text{O}$ ), 4.01 (q, 2H,  $J=7.6$  Hz,  $\text{CH}_2\text{O}$ ), 5.92 (s, 1H,  $\text{H-4}_{\text{pyrazole}}$ ), 7.28 (t, 1H,  $J=7.2$  Hz,  $\text{H-6}_{\text{coumarin}}$ ), 7.43 (d, 1H,  $J=6.8$  Hz,  $\text{H-8}_{\text{coumarin}}$ ), 7.63 (t, 1H,  $J=7.2$  Hz,  $\text{H-7}_{\text{coumarin}}$ ), 7.86 (d, 1H,  $J=7.2$  Hz,  $\text{H-5}_{\text{coumarin}}$ ), 8.89 (s, 1H,  $\text{H-4}_{\text{coumarin}}$ ), 11.19 (s, 1H, NH).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ): 13.4 ( $\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ ), 59.4 ( $\text{OCH}_2$ ), 60.9 ( $\text{OCH}_2$ ), 104.2 ( $\text{C-4}_{\text{pyrazole}}$ ), 116.1 ( $\text{C-8}_{\text{coumarin}}$ ), 119.5 ( $\text{C-4a}_{\text{coumarin}}$ ), 121.2 ( $\text{C-3}_{\text{coumarin}}$ ), 123.4 ( $\text{C-6}_{\text{coumarin}}$ ), 128.3 ( $\text{C-5}_{\text{coumarin}}$ ), 131.5 ( $\text{C-7}_{\text{coumarin}}$ ), 144.5 ( $\text{C-4}_{\text{coumarin}}$ ), 146.2 (d,  $J_{\text{PC}}=100.2$  Hz,  $\text{C-5}_{\text{pyrazole}}$ ), 149.3 ( $\text{C-3}_{\text{pyrazole}}$ ), 153.6 ( $\text{C-8a}_{\text{coumarin}}$ ), 159.3 ( $\text{C-2}_{\text{coumarin}}$ ).  $^{31}\text{P-NMR}$  (162 MHz,  $\text{DMSO-}d_6$ ): 22.1 ppm. MS (EI,  $m/z$ ): 348 ( $\text{M}^+$ , 11%). Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_5\text{P}$  (348.29): C, 55.18; H, 4.92; N, 8.04%. Found: C, 55.01; H, 4.79; N, 7.88%.

**Diethyl [1-methyl-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazol-5-yl]phosphonate (4):** Yield 75%, white solid, mp 192–194 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3058 ( $\text{C-H}_{\text{arom}}$ ), 2959, 2935 ( $\text{C-H}_{\text{aliph}}$ ), 1731 ( $\text{C=O}$ ), 1613 ( $\text{C=N}$ ), 1596 ( $\text{C=C}$ ), 1239 ( $\text{P=O}$ ), 1044 ( $\text{P-O-C}$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ): 1.07 (t, 3H,  $J=6.8$  Hz,  $\text{CH}_3$ ), 1.21 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 3.11 (s, 3H,  $\text{CH}_3$ ), 4.01 (q, 2H,  $J=6.8$  Hz,  $\text{CH}_2\text{O}$ ), 4.22 (q, 2H,  $J=7.2$  Hz,  $\text{CH}_2\text{O}$ ), 6.11 (s, 1H,  $\text{H-4}_{\text{pyrazole}}$ ), 7.31 (t, 1H,  $J=7.6$  Hz,  $\text{H-6}_{\text{coumarin}}$ ), 7.48 (d, 1H,  $J=6.8$  Hz,  $\text{H-8}_{\text{coumarin}}$ ), 7.59 (t, 1H,  $J=7.2$  Hz,  $\text{H-7}_{\text{coumarin}}$ ), 7.99 (d, 1H,  $J=7.6$  Hz,  $\text{H-5}_{\text{coumarin}}$ ), 8.76 (s, 1H,  $\text{H-4}_{\text{coumarin}}$ ).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ): 13.9 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ), 39.1 ( $\text{CH}_3$ ), 59.8 ( $\text{OCH}_2$ ), 61.2 ( $\text{OCH}_2$ ), 103.8 ( $\text{C-4}_{\text{pyrazole}}$ ), 116.3 ( $\text{C-8}_{\text{coumarin}}$ ), 118.8 ( $\text{C-4a}_{\text{coumarin}}$ ), 122.4 ( $\text{C-3}_{\text{coumarin}}$ ), 123.6 ( $\text{C-6}_{\text{coumarin}}$ ), 129.6 ( $\text{C-5}_{\text{coumarin}}$ ), 131.9 ( $\text{C-7}_{\text{coumarin}}$ ), 143.9 ( $\text{C-4}_{\text{coumarin}}$ ), 146.8 (d,  $J_{\text{PC}}=101.4$  Hz,  $\text{C-5}_{\text{pyrazole}}$ ), 148.0 ( $\text{C-3}_{\text{pyrazole}}$ ), 153.4 ( $\text{C-8a}_{\text{coumarin}}$ ), 159.7 ( $\text{C-2}_{\text{coumarin}}$ ).  $^{31}\text{P-NMR}$  (162 MHz,  $\text{DMSO-}d_6$ ): 21.8 ppm. MS (EI,  $m/z$ ): 362 ( $\text{M}^+$ , 8%). Anal. Calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_5\text{P}$  (362.32): C, 56.36; H, 5.29; N, 7.73%. Found: C, 56.19; H, 5.13; N, 7.58%.

**Diethyl [5-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-3-yl]phosphonate (5):** Yield 74%, yellow solid, mp 152–154 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3063 ( $\text{C-H}_{\text{arom}}$ ), 2946, 2921 ( $\text{C-H}_{\text{aliph}}$ ), 1736 ( $\text{C=O}$ ), 1614 ( $\text{C=N}$ ), 1594 ( $\text{C=C}$ ), 1244 ( $\text{P=O}$ ), 1026 ( $\text{P-O-C}$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ): 1.11–1.23 (m, 6H, 2  $\text{CH}_3$ ), 3.81–4.15 (m, 4H, 2  $\text{CH}_2\text{O}$ ), 6.62 (s, 1H,  $\text{H-4}_{\text{pyrazole}}$ ), 7.10–7.16 (m, 3H,  $\text{Ph-H}$ ), 7.28–7.39 (m, 2H,  $\text{H-6}_{\text{coumarin}}$  and  $\text{Ph-H}$ ), 7.46–7.62 (m, 2H,  $\text{H-8}_{\text{coumarin}}$  and  $\text{Ph-H}$ ), 7.72 (t, 1H,  $J=6.8$  Hz,  $\text{H-7}_{\text{coumarin}}$ ), 8.02 (d, 1H,  $J=7.2$  Hz,  $\text{H-5}_{\text{coumarin}}$ ), 8.49 (s, 1H,  $\text{H-4}_{\text{coumarin}}$ ).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ): 14.1 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ), 60.2 ( $\text{OCH}_2$ ), 61.4 ( $\text{OCH}_2$ ), 108.3 ( $\text{C-4}_{\text{pyrazole}}$ ), 113.1 ( $\text{C-2,6}_{\text{phenyl}}$ ), 117.1 ( $\text{C-8}_{\text{coumarin}}$ ), 119.1 ( $\text{C-4a}_{\text{coumarin}}$ ), 120.1 ( $\text{C-4}_{\text{phenyl}}$ ), 122.6 ( $\text{C-3}_{\text{coumarin}}$ ), 124.1 ( $\text{C-6}_{\text{coumarin}}$ ), 129.3 ( $\text{C-3,5}_{\text{phenyl}}$ ), 129.8 ( $\text{C-5}_{\text{coumarin}}$ ), 133.0 ( $\text{C-7}_{\text{coumarin}}$ ), 144.5 ( $\text{C-4}_{\text{coumarin}}$ ), 146.6 ( $\text{C-5}_{\text{pyrazole}}$ ), 148.3 (d,  $J_{\text{PC}}=102.2$  Hz,  $\text{C-3}_{\text{pyrazole}}$ ), 150.3 ( $\text{C-1}_{\text{phenyl}}$ ), 153.8 ( $\text{C-8a}_{\text{coumarin}}$ ), 159.9 ( $\text{C-2}_{\text{coumarin}}$ ).  $^{31}\text{P-NMR}$  (162 MHz,  $\text{DMSO-}d_6$ ): 23.2 ppm. MS (EI,  $m/z$ ): 424 ( $\text{M}^+$ , 15%). Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_5\text{P}$  (424.39): C, 62.26; H, 4.99; N, 6.60%. Found: C,

62.09; H, 4.86; N, 6.45%.

**Diethyl [2-oxo-6-(2-oxo-2H-chromen-3-yl)-1,2-dihydropyrimidin-4-yl]phosphonate (6):** Yield 63%, pale brown solid, mp 182–184 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3211 (NH), 3073 (C–H<sub>arom</sub>), 2963, 2949 (C–H<sub>aliph</sub>), 1725 (C=O), 1660 (C=O), 1605 (C=N), 1584 (C=C), 1212 (P=O), 1023 (P–O–C). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.03 (t, 3H, *J*=7.6 Hz, CH<sub>3</sub>), 1.22 (t, 3H, *J*=7.2 Hz, CH<sub>3</sub>), 3.92 (q, 2H, *J*=7.6 Hz, CH<sub>2</sub>O), 4.19 (q, 2H, *J*=7.2 Hz, CH<sub>2</sub>O), 5.76 (s, 1H, H-5<sub>pyrimidine</sub>), 7.25 (t, 1H, *J*=6.8 Hz, H-6<sub>coumarin</sub>), 7.39 (d, 1H, *J*=6.8 Hz, H-8<sub>coumarin</sub>), 7.61 (t, 1H, *J*=7.2 Hz, H-7<sub>coumarin</sub>), 7.82 (d, 1H, *J*=6.8 Hz, H-5<sub>coumarin</sub>), 8.46 (s, 1H, H-4<sub>coumarin</sub>), 11.92 (s, 1H, NH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>): 14.1 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 60.3 (OCH<sub>2</sub>), 61.4 (OCH<sub>2</sub>), 89.2 (C-5<sub>pyrimidine</sub>), 115.9 (C-8<sub>coumarin</sub>), 117.9 (C-4<sub>a</sub>coumarin), 123.6 (C-3<sub>coumarin</sub>), 124.2 (C-6<sub>coumarin</sub>), 128.3 (C-5<sub>coumarin</sub>), 134.1 (C-7<sub>coumarin</sub>), 142.3 (C-6<sub>pyrimidine</sub>), 143.9 (C-4<sub>coumarin</sub>), 152.8 (C-8<sub>a</sub>coumarin), 158.2 (C-2<sub>pyrimidine</sub>), 160.1 (C-2<sub>coumarin</sub>), 162.4 (d, *J*<sub>PC</sub>=103.4 Hz, C-4<sub>pyrimidine</sub>). <sup>31</sup>P-NMR (162 MHz, DMSO-*d*<sub>6</sub>): 21.6 ppm. MS (EI, *m/z*): 376 (M<sup>+</sup>, 12%). Anal. Calcd for C<sub>17</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub>P (376.30): C, 54.26; H, 4.55; N, 7.44%. Found: C, 54.09; H, 4.39; N, 7.28%.

**Diethyl [6-(2-oxo-2H-chromen-3-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phosphonate (7):** Yield 66%, pale brown solid, mp 222–224 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3196 (NH), 3062 (C–H<sub>arom</sub>), 2955, 2911 (C–H<sub>aliph</sub>), 1722 (C=O), 1609 (C=N), 1589 (C=C), 1232 (P=O), 1153 (C=S), 1028 (P–O–C). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.04 (t, 3H, *J*=7.2 Hz, CH<sub>3</sub>), 1.28 (t, 3H, *J*=7.2 Hz, CH<sub>3</sub>), 3.96 (q, 2H, *J*=7.2 Hz, CH<sub>2</sub>O), 4.23 (q, 2H, *J*=7.2 Hz, CH<sub>2</sub>O), 5.86 (s, 1H, H-5<sub>pyrimidine</sub>), 7.41 (t, 1H, *J*=7.2 Hz, H-6<sub>coumarin</sub>), 7.59 (d, 1H, *J*=6.8 Hz, H-8<sub>coumarin</sub>), 7.72 (t, 1H, *J*=6.8 Hz, H-7<sub>coumarin</sub>), 8.03 (d, 1H, *J*=6.8 Hz, H-5<sub>coumarin</sub>), 8.46 (s, 1H, H-4<sub>coumarin</sub>), 12.04 (s, 1H, NH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>): 13.8 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 60.8 (OCH<sub>2</sub>), 62.6 (OCH<sub>2</sub>), 91.2 (C-5<sub>pyrimidine</sub>), 116.3 (C-8<sub>coumarin</sub>), 118.6 (C-4<sub>a</sub>coumarin), 123.9 (C-3<sub>coumarin</sub>), 125.1 (C-6<sub>coumarin</sub>), 130.1 (C-5<sub>coumarin</sub>), 133.8 (C-7<sub>coumarin</sub>), 145.3 (C-4<sub>coumarin</sub>), 151.6 (C-6<sub>pyrimidine</sub>), 153.2 (C-8<sub>a</sub>coumarin), 159.8 (C-2<sub>coumarin</sub>), 163.1 (d, *J*<sub>PC</sub>=102.6 Hz, C-4<sub>pyrimidine</sub>), 180.6 (C-2<sub>pyrimidine</sub>). <sup>31</sup>P-NMR (162 MHz, DMSO-*d*<sub>6</sub>): 21.4. MS (EI, *m/z*): 392 (M<sup>+</sup>, 19%). Anal. Calcd for C<sub>17</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>PS (392.37): C, 52.04; H, 4.37; N, 7.14; S, 8.17%. Found: C, 51.89; H, 4.21; N, 6.98; S, 8.03%.

**Diethyl [6-(2-oxo-2H-chromen-3-yl)-2-selenoxo-1,2-dihydropyrimidin-4-yl]phosphonate (8):** Yield 61%, brown solid, mp 228–230 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3222 (NH), 3038 (C–H<sub>arom</sub>), 2923, 2903 (C–H<sub>aliph</sub>), 1724 (C=O), 1607 (C=N), 1591 (C=C), 1243 (P=O), 1037 (P–O–C). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.09 (t, 3H, *J*=6.8 Hz, CH<sub>3</sub>), 1.31 (t, 3H, *J*=7.2 Hz, CH<sub>3</sub>), 4.03 (q, 2H, *J*=6.8 Hz, CH<sub>2</sub>O), 4.28 (q, 2H, *J*=7.2 Hz, CH<sub>2</sub>O), 5.82 (s, 1H, H-5<sub>pyrimidine</sub>), 7.32 (t, 1H, *J*=7.2 Hz, H-6<sub>coumarin</sub>), 7.47 (d, 1H, *J*=6.8 Hz, H-8<sub>coumarin</sub>), 7.68 (t, 1H, *J*=6.8 Hz, H-7<sub>coumarin</sub>), 7.99 (d, 1H, *J*=7.2 Hz, H-5<sub>coumarin</sub>), 8.52 (s, 1H, H-4<sub>coumarin</sub>), 11.64 (s, 1H, NH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>): 13.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>), 61.0 (OCH<sub>2</sub>), 62.3 (OCH<sub>2</sub>), 90.8 (C-5<sub>pyrimidine</sub>), 117.4 (C-8<sub>coumarin</sub>), 119.2 (C-4<sub>a</sub>coumarin), 121.8 (C-3<sub>coumarin</sub>), 124.8 (C-6<sub>coumarin</sub>), 130.4 (C-5<sub>coumarin</sub>), 134.2 (C-7<sub>coumarin</sub>), 144.6 (C-4<sub>coumarin</sub>), 152.0 (C-6<sub>pyrimidine</sub>), 154.6



(C-8<sub>coumarin</sub>), 160.2 (C-2<sub>coumarin</sub>), 162.2 (d,  $J_{PC}=103.4$  Hz, C-4<sub>pyrimidine</sub>), 179.6 (C-2<sub>pyrimidine</sub>).  $^{31}\text{P}$ -NMR (162 MHz, DMSO- $d_6$ ): 20.9 ppm. MS (EI,  $m/z$ ): 440, 438, 436 ( $M^+$ , 6%). Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_5\text{PSe}$  (439.27): C, 46.48; H, 3.90; N, 6.38%. Found: C, 46.32; H, 3.76; N, 6.23%.

**Diethyl [7-(2-oxo-2H-chromen-3-yl)-2,3-dihydro-1H-1,4-diazepin-5-yl]phosphonate (9):** Yield 72%, yellow solid, mp 211–213 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3158 (NH), 3049 (C-H<sub>arom</sub>), 2986, 2935, 2869 (C-H<sub>aliph</sub>), 1729 (C=O), 1613 (C=N), 1586 (C=C), 1259 (P=O), 1053 (P-O-C).  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ ): 1.02 (t, 3H,  $J=6.4$  Hz, CH<sub>3</sub>), 1.22 (t, 3H,  $J=6.8$  Hz, CH<sub>3</sub>), 2.85 (br, 2H, NCH<sub>2</sub>), 3.11 (br, 2H, NCH<sub>2</sub>), 3.75–4.06 (m, 4H, 2 CH<sub>2</sub>O), 4.82 (br, 1H, NH), 5.13 (s, 1H, H-6<sub>diazepine</sub>), 7.36 (t, 1H,  $J=7.2$  Hz, H-6<sub>coumarin</sub>), 7.49 (d, 1H,  $J=6.8$  Hz, H-8<sub>coumarin</sub>), 7.66 (t, 1H,  $J=6.8$  Hz, H-7<sub>coumarin</sub>), 7.96 (d, 1H,  $J=7.2$  Hz, H-5<sub>coumarin</sub>), 8.61 (s, 1H, H-4<sub>coumarin</sub>).  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ ): 14.4 (CH<sub>3</sub>), 14.8 (CH<sub>3</sub>), 59.9 (OCH<sub>2</sub>), 60.8 (OCH<sub>2</sub>), 43.6 (NCH<sub>2</sub>), 49.6 (NCH<sub>2</sub>), 89.2 (C-6<sub>diazepine</sub>), 116.8 (C-8<sub>coumarin</sub>), 120.0 (C-4<sub>coumarin</sub>), 124.1 (C-3<sub>coumarin</sub>), 125.9 (C-6<sub>coumarin</sub>), 130.1 (C-5<sub>coumarin</sub>), 134.3 (C-7<sub>coumarin</sub>), 146.2 (C-4<sub>coumarin</sub>), 151.3 (C-7<sub>diazepine</sub>), 153.3 (C-8<sub>coumarin</sub>), 159.7 (C-2<sub>coumarin</sub>), 161.2 (d,  $J_{PC}=104.4$  Hz, C-5<sub>diazepine</sub>).  $^{31}\text{P}$ -NMR (162 MHz, DMSO- $d_6$ ): 19.9 ppm. MS (EI,  $m/z$ ): 376 ( $M^+$ , 13%). Anal. Calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5\text{P}$  (376.35): C, 57.45; H, 5.62; N, 7.44%. Found: C, 57.29; H, 5.46; N, 7.28%.

**Diethyl [2-(2-oxo-2H-chromen-3-yl)-1H-1,4-benzodiazepin-4-yl]phosphonate (10):** Yield 68%, yellow solid, mp 243–245 °C. IR (KBr), ( $\nu$  max,  $\text{cm}^{-1}$ ): 3210 (NH), 3053 (C-H<sub>arom</sub>), 2951, 2919 (C-H<sub>aliph</sub>), 1721 (C=O), 1619 (C=N), 1596 (C=C), 1251 (P=O), 1043 (P-O-C).  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ ): 0.99–1.16 (m, 6H, 2 CH<sub>3</sub>), 3.76–3.99 (m, 4H, 2 CH<sub>2</sub>O), 6.21 (s, 1H, H-3<sub>benzodiazepine</sub>), 6.83–6.94 (m, 2H, Ar-H), 7.24 (t, 1H,  $J=7.2$  Hz, Ar-H), 7.41–7.46 (m, 2H, H-6<sub>coumarin</sub> and Ar-H), 7.68 (t, 1H,  $J=6.8$  Hz, H-8<sub>coumarin</sub>), 7.76 (t, 1H,  $J=6.8$  Hz, H-7<sub>coumarin</sub>), 8.13 (d, 1H,  $J=6.8$  Hz, H-5<sub>coumarin</sub>), 8.63 (s, 1H, H-4<sub>coumarin</sub>), 10.13 (s, 1H, NH).  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ ): 13.7 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 59.8 (OCH<sub>2</sub>), 61.6 (OCH<sub>2</sub>), 99.3 (C-3<sub>benzodiazepine</sub>), 117.8 (C-8<sub>coumarin</sub>), 118.6 (C-9<sub>benzodiazepine</sub>), 119.4 (C-4<sub>coumarin</sub>), 121.2 (C-7<sub>benzodiazepine</sub>), 122.3 (C-3<sub>coumarin</sub>), 123.9 (C-8<sub>benzodiazepine</sub>), 125.3 (C-6<sub>coumarin</sub>), 126.2 (C-6<sub>benzodiazepine</sub>), 130.2 (C-5<sub>coumarin</sub>), 134.2 (C-7<sub>coumarin</sub>), 139.3 (C-9<sub>benzodiazepine</sub>), 146.4 (C-4<sub>coumarin</sub>), 150.2 (C-2<sub>benzodiazepine</sub>), 153.2 (C-8<sub>coumarin</sub>), 156.5 (C-5<sub>benzodiazepine</sub>), 160.1 (C-2<sub>coumarin</sub>), 162.2 (d,  $J_{PC}=104.6$  Hz, C-4<sub>benzodiazepine</sub>).  $^{31}\text{P}$ -NMR (162 MHz, DMSO- $d_6$ ): 20.60 ppm. MS (EI,  $m/z$ ): 424 ( $M^+$ , 6%). Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_5\text{P}$  (424.39): C, 62.26; H, 4.99; N, 6.60%. Found: C, 62.11; H, 4.88; N, 6.42%.

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