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SYNTHESIS AND BIOLOGICAL EVALUATIONS OF A SERIES OF NOVEL AZOLYL, AZINYL, PYRANYL, CHROMONYL AND AZEPINYL PHOSPHONATES

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Abstract – A facile synthetic methodology of novel azolyl, azinyl and azepinyl phosphonates as cyclic α-aminophosphonates was described. Chromonyl α-aminophosphonates, γ-pyranyl and γ-pyridinyl phosphonates were also prepared. The methodology depends on reaction of 6-methyl-3-formylchromone, nitrogen and carbon nucleophiles in the presence of diethyl phosphite in one-pot three-components under solvent-free conditions. The products were evaluated for their antimicrobial activities and antioxidant properties.

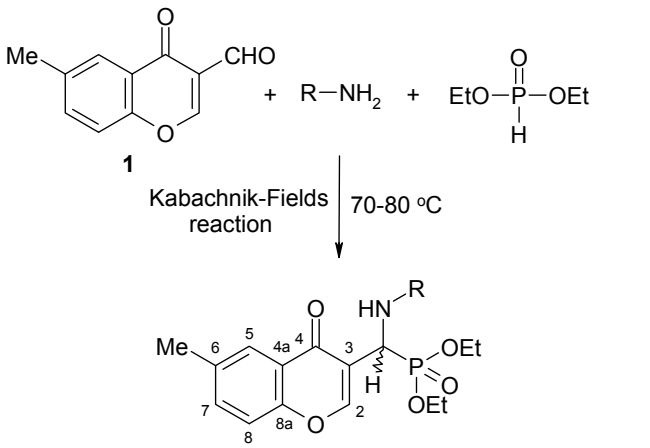
INTRODUCTION

α-Aminophosphonic acid diesters, as phosphorus analogues of α-aminocarboxylic acids, are of great interest due to their reported biological activities.[1] Some representatives of α-aminophosphonates have demonstrated promising enzyme inhibitory activities, as for example, HIV protease antagonists[2] and collagenase inhibitor.[3] Also, they have an important anticancer,[4] antibacterial[5] and antiviral activities.[6] These biological properties are mostly associated with the tetrahedral structure of the phosphonyl group acting as "a transition-state analogue".[7] In the last decades, intensive synthetic articles were performed in the preparation of α-aminophosphonic acids and their esters.[8−13] The Kabachnik−Fields method is the most noteworthy and remarkable, generally using amines, dialkyl phosphites and carbonyl compounds.[14,15] Although, a number of different methods have been reported for the preparation of acyclic α-aminophosphonates,[16−19] there is still a need to search for new methods for the preparation of cyclic α-aminophosphonates which have found promising biological applications.[20,21] As a part of our continuing interest in the preparation of acyclic and cyclic α-aminophosphonates,[22−25] we describe a facile methodology to prepare some novel acyclic and cyclic α-aminophosphonates and also γ-heterocyclic phosphonates. The method is based on the reaction of 6-methyl-3-formylchromone with nitrogen and carbon *mono*- and *bi*-nucleophiles in the presence of diethyl phosphite in one-pot three-components under

solvent-free conditions. The antimicrobial activities and antioxidant properties of the synthesized compounds were also evaluated.

RESULTS AND DISCUSSION

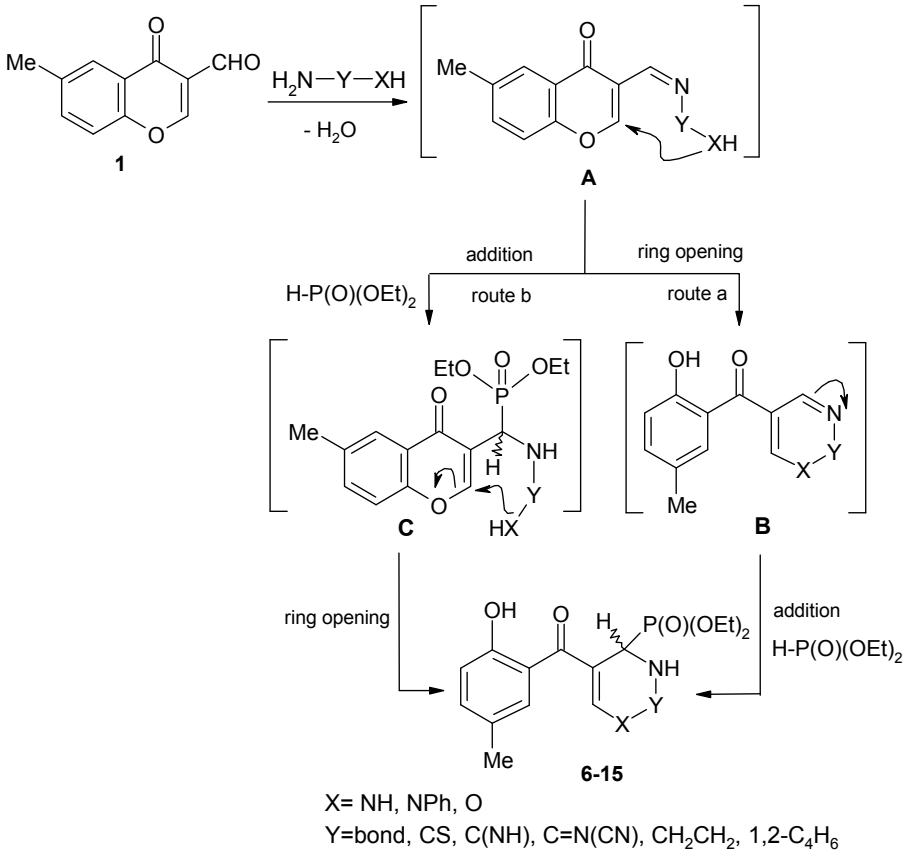
6-Methyl-3-formylchromone (**1**) was allowed to react with some aliphatic and aromatic amines as nitrogen *mono*-nucleophiles namely ethylamine, benzylamine, 4-chloroaniline and 4-hydroxyaniline in the presence of diethyl phosphite at 70−80 °C for 6 h under Kabachnik−Fields reaction conditions[26,27] to produce the corresponding chromonyl α-aminophosphonates **2**−**5** in 62−100% yields (Scheme 1). The IR spectra of the α-aminophosphonates **2**−**5** showed the presence of NH (3289−3443 cm^{-1}), $C{=}O_{pyrone}$ (1640−1646 cm^{-1}) and P=O (1216−1225 cm^{-1}) groups. Moreover, their ^{1}H-NMR spectra recorded the characteristic ethoxy protons at the regions δ 0.93−1.29 ppm (CH_3) and δ 3.60−4.00 ppm (CH_2). The peaks of CH−P protons appeared as doublets at the regions δ 4.39−5.21 ppm with coupling constants in range 15−24 Hz. Furthermore, the protons H−2 of the chromone rings were displayed as singlets at the regions δ 8.20−8.95 ppm. The ^{13}C-NMR spectral data of compounds **3** and **4** supported their structures due to the presence of the characteristic carbon atoms CH_3, CH_2, CH−P and $C{=}O_{pyrone}$ at the regions δ 16.0−16.5, 60.4−62.6, 45.2−45.5 (J_{PC} = 148.5 and 158.5 Hz) and 174.6−174.8 ppm, respectively. Also, the ^{31}P-NMR spectrum of the α-aminophosphonate **5** displayed a singlet at δ 21.6 ppm.



Scheme 1

3-Formylchromones have attracted attention long ago as highly reactive compounds, which can serve as starting substances in the synthesis of a whole series of heterocycles. 3-Formylchromones have useful chemical properties due to presence of three strong electrophilic centers at C−2, $C{=}O_{pyrone}$ and formyl group.[28,29] In the present article, the synthetic utility of 6-methyl-3-formylchromone (**1**) is derived from

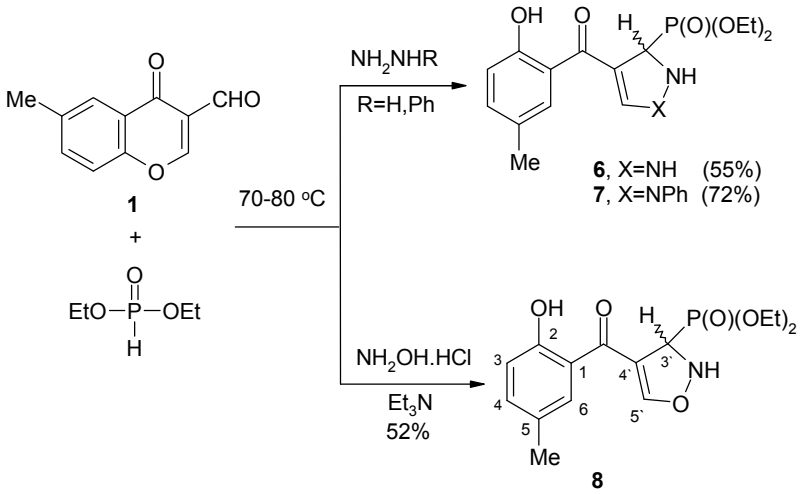
its reaction with nitrogen and carbon *bi*-nucleophiles that starts predominately from the attack on the formyl group to give the nonisolable condensation product **A** then pyrone ring opening at the unsubstituted C−2 forming the intermediate **B**. The latter intermediate **B** undergoes addition of diethyl phosphite at the cyclic azomethine bond to form the target phosphonates (route a, Scheme 2). Also, these phosphonates may be formed *via* addition of diethyl phosphite at the acyclic azomethine bond of the intermediate **A** leading to the formation of the nonisolable intermediate **C**, which undergoes pyrone ring opening (route b, Scheme 2).[30] The resulted compounds gave characteristic red, green and blue colors with an alcoholic ferric chloride solution which support pyrone ring opening.



Scheme 2

When 6-methyl-3-formylchromone (**1**) was treated with some nitrogen 1,2-*bi*-nucleophiles such as hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride in the presence of diethyl phosphite at 70−80 °C for two hours afforded the corresponding novel azolyl phosphonates **6**−**8**, respectively, as cyclic α-aminophosphonates (Scheme 3). Structures of the products **6**−**8** were elucidated from their spectroscopic data and elemental analysis. For example, their IR spectra revealed some characteristic absorption bands at 3132−3407 (NH, OH), 1636−1654 (C=O) and 1212−1216 cm^{-1} (P=O). Also, their ^{1}H-NMR spectra revealed the appearance of the ethoxy protons in the regions δ 1.03−1.21 and 3.90−4.40 ppm while the H−5′ protons of the azole rings appeared as singlets at the region δ 7.30, 8.80

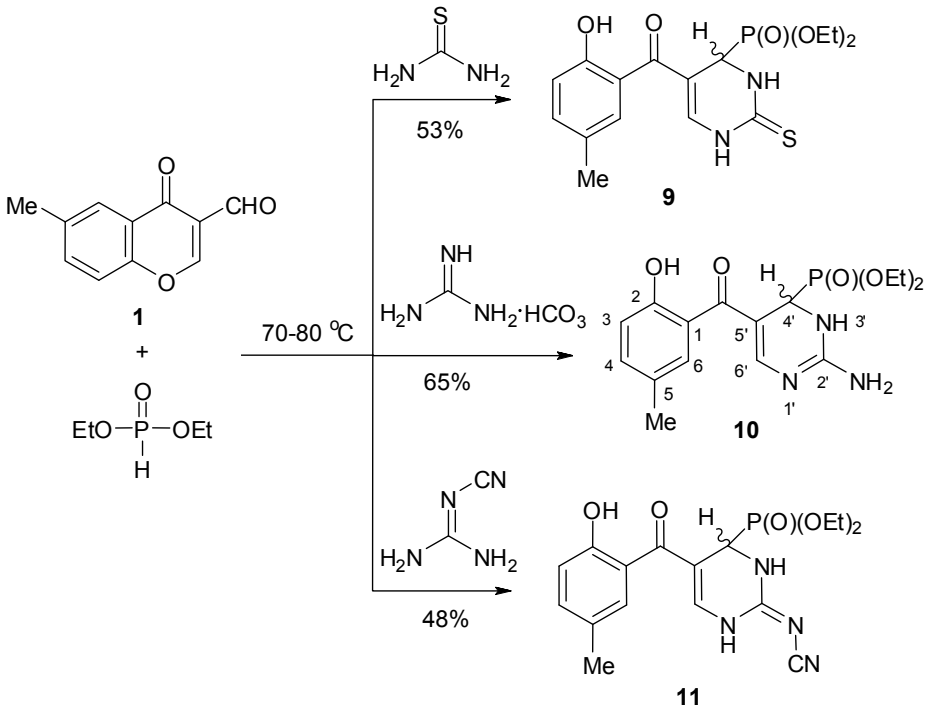
and 9.05 ppm, respectively. Furthermore, characteristic doublets were observed at δ 4.90, 4.94 and 5.65 ppm corresponding to the CH−P protons of compounds **6**−**8**, respectively, besides D_2O-exchangeable signals related to OH and NH protons. The ^{13}C-NMR spectrum of compound **8** recorded the carbon atom of CH−P moiety as doublet at δ 46.0 ppm (J = 155.2 Hz) and the other carbon atoms for the isoxazole ring as singlets at δ 112.3 and 150.9 ppm. Moreover, it also showed highly deshielded carbon atom at δ 193.4 ppm, which indicated to the carbonyl group while the ethoxy carbon atoms appeared at δ 14.4 and 62.0 ppm. The phosphorus atom of phosphonate group resonated at δ 22.4 ppm in ^{31}P-NMR spectrum of compound **6**. The molecular ion peaks of compounds **6** and **7**, were recorded at *m/z* 340 and 416, respectively, in their mass spectra.



Scheme 3

In the present investigation, several subtypes of 1,3-*bi*-nucleophiles were used for recyclization of compound **1**, in the presence of diethyl phosphite leading to the formation of some novel pyrimidinyl phosphonates as cyclic α-aminophosphonates. Thus, fusion of the aldehyde **1** with thiourea, guanidinium carbonate and cyanoguanidine in the presence of diethyl phosphite at 70−80 °C yielded a first type of pyrimidinyl phosphonates **9**−**11**, respectively (Scheme 4). The latter phosphonates showed absorption bands at the regions 3134−3452, 1641−1648 and 1206−1230 cm^{-1} corresponding to OH, NH, C=O and P=O functions, while the nitrile group in compound **11** appeared at 2225 cm^{-1}. The ^{1}H-NMR spectra of compounds **9**−**11** displayed CH_3 (δ 1.00−1.36 ppm) and CH_2 (δ 3.60−4.00 ppm) protons of ethoxy groups in each product, while H−6′ protons of the pyrimidine rings were found in the aromatic region. Also, the doublets that appeared at δ 5.10, 5.20 and 5.03 ppm (J = 20, 19 and 18 Hz) for compounds **9**−**11**, respectively, correspond to the CH−P protons. The ^{13}C-NMR spectrum of compound **10** supported the presence of the carbonyl group which resonated at δ 186.1 ppm, while the carbon atoms of CH−P and C−2′ of the pyrimidine ring appeared at δ 47.0 and 163.6 ppm, respectively. Also, the ^{31}P-NMR spectrum of compound **10** displayed a singlet at δ 26.2 ppm for the phosphonate group. Further confirmation of the

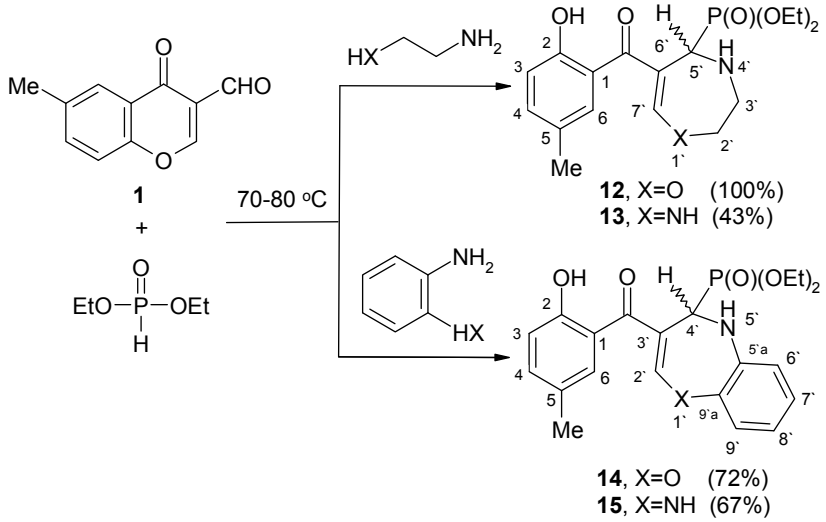
structures **9** and **10** was obtained from their mass spectral data, where both structures showed their molecular ion peaks at *m/z* 384 and 367, in addition to their base peaks at *m/z* 64 and 64, respectively.



Scheme 4

Seven-membered heterocycles with two heteroatoms are known to possess main fold biological activity.[31–33] The present study was extended to investigate the behavior of the aldehyde **1** with classical nitrogen 1,4-*bi*-nucleophiles in the presence of diethyl phosphite with a view to synthesize phosphonates beard on seven-membered heterocyclic systems. Thus, treatment of aldehyde **1** with each one of nitrogen 1,4-*bi*-nucleophiles such as ethanolamine, ethylenediamine, 2-aminophenol and 1,2-phenylenediamine in the presence of diethyl phosphite at 70−80 °C for 4 hours furnished the corresponding phosphonate derivatives of 1,4-oxazepine **12**, 1,4-diazepine **13**, 1,5-benzoxazepine **14** and 1,5-benzodiazepine **15**, respectively (Scheme 5). The IR spectra of the products **12**−**15** showed absorption bands at the regions 3232−3421, 1636−1646 and 1215−1228 cm^{-1} indicating the presence of NH, carbonyl and phosphonyl groups, respectively. The ^{1}H-NMR spectra of compounds **12** and **13** exhibited characteristic broad singlets at δ 3.46, 4.34 and 3.42 ppm for CH_2CH_2 groups, respectively. Also, their ^{1}H-NMR spectra showed characteristic doublets at δ 4.94 (J = 20 Hz) and 5.00 (J = 21 Hz) ppm for the CH−P while H−7′ protons of the seven-membered rings were found in the aromatic region. Furthermore, the ^{1}H-NMR spectra of the benzo analogues **14** and **15** recorded coincident chemical shifts for CH−P protons at δ 5.10 and 5.18 ppm, respectively. In addition, the H−2′ protons of the 1,5-seven-membered rings appeared as singlets at δ 8.44 and 8.30 ppm for compounds **14** and **15**, respectively. The ^{13}C-NMR spectra of compounds **13** and **14** revealed the carbonyl groups at δ 185.0 and 189.6 ppm, respectively. In addition,

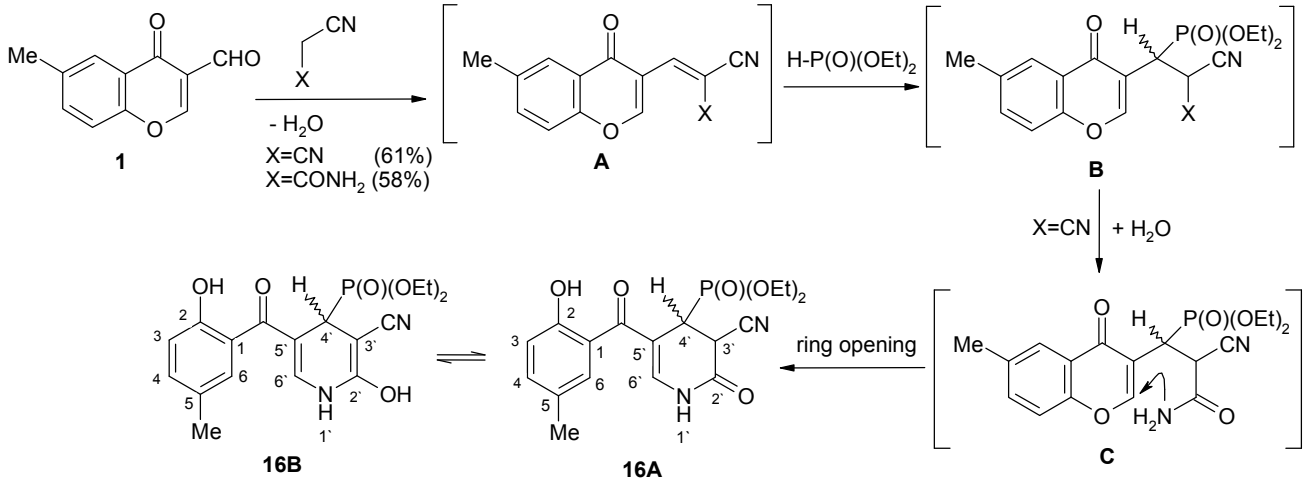
the CH−P carbon atoms for them were recorded as doublets at δ 41.2 (J = 148.0 Hz) and 45.0 (J = 150 Hz) ppm, as well as other characteristic singlets at δ 150.1 and 155.3 ppm for the C−7′ and C−2′ atoms of the azepine rings **13** and **14**, respectively. The mass spectra of compounds **12**, **14** and **15** exhibited their molecular ion peaks at *m/z* 369, 417 and 416, respectively.



Scheme 5

Next, we also studied the effect of acyclic and cyclic carbon nucleophiles which can construct various novel γ-heterocyclic phosphonates in an efficient and economic way. Thus, a simple fusion of 6-methyl-3-formylchromone (**1**) with each one of acyclic carbon nucleophiles namely, malononitrile and cyanoacetamide in the presence of diethyl phosphite and few drops of triethylamine at 70−80 °C for 6 hours afforded the same product **16** in moderate yields (Scheme 6). The latter product existed in two tautomeric forms which named diethyl {3-cyano-5-[(2-hydroxy-5-methylphenyl)carbonyl]-2-oxo-1,2,3,4-tetrahydropyridin-4-yl}phosphonate (**16A**) and diethyl {3-cyano-2-hydroxy-5-[(2-hydroxy-5-methylphenyl)carbonyl]-1,4-dihydropyridin-4-yl}phosphonate (**16B**) (Scheme 6). The suggested mechanism for construction of compound **16** may be the simple Knoevenagel condensation between compound **1** and the methylene compounds to form the condensation products **A**, followed by addition of diethyl phosphite to give the nonisolable intermediates **B**. The water molecules that resulted from condensation process, can hydrolyze the intermediate **B** (X=CN) to yield the corresponding acetamide intermediate **C**, which underwent opening of chromone ring at C−2 affording the stable pyridine ring bearing phosphonate moiety (Scheme 6). The structural elucidation of forms **16A** and **16B** was based on spectral data. The IR spectrum of compound **16** supported the form **16A** which recorded the specific absorption bands at 3411 (br, NH), 2229 (C≡N), 1733 ($C{=}O_{amide}$), 1683 ($C{=}O_{pyrone}$) and 1242 cm^{-1} (P=O) functions. Its ^{1}H-NMR spectrum showed two multiplets at δ 1.08−1.35 and 3.80−3.95 ppm corresponding to CH_3 and CH_2 protons, respectively, while the doublet at δ 4.94 (J = 20 Hz) ppm due to the CH−P

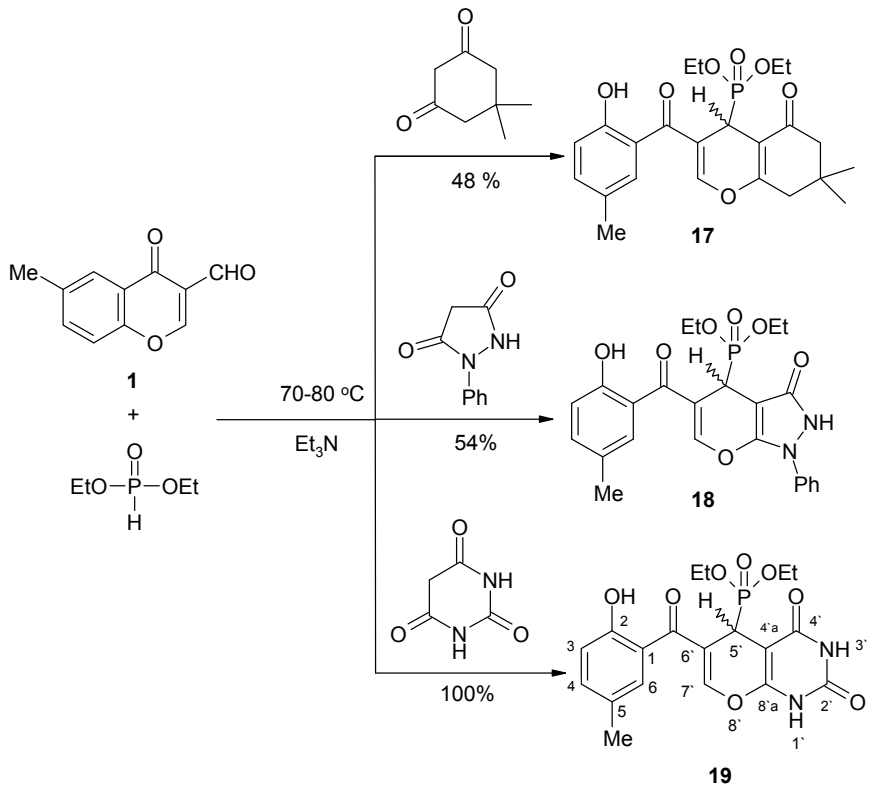
proton. Also, its ^{1}H-NMR spectrum displayed a singlet at δ 8.40 ppm corresponds to H−6′ of pyridine ring, and three D_2O−exchangeable signals at δ 9.60, 10.70 and 11.75 ppm due to two OH and one NH protons, respectively, which supported the form **16B**. Consequently, its ^{13}C-NMR spectrum confirmed the existence of the enol form **16B** through appearance of C−3` atom of the pyridine ring at δ 104.1 ppm, which means that this carbon atom has sp^2 and not sp^3 hybridized. In addition, there are three characteristic signals at δ 110.1, 187.1 and 197.2 ppm due to C≡N, $C{=}O_{pyrone}$ and $C{=}O_{amide}$, respectively. Moreover, its ^{31}P-NMR spectrum displayed one singlet at δ 24.5 ppm. The mass spectrum of **16** recorded the M+1 and M^+ peaks at *m/z* 393 and 392, respectively.



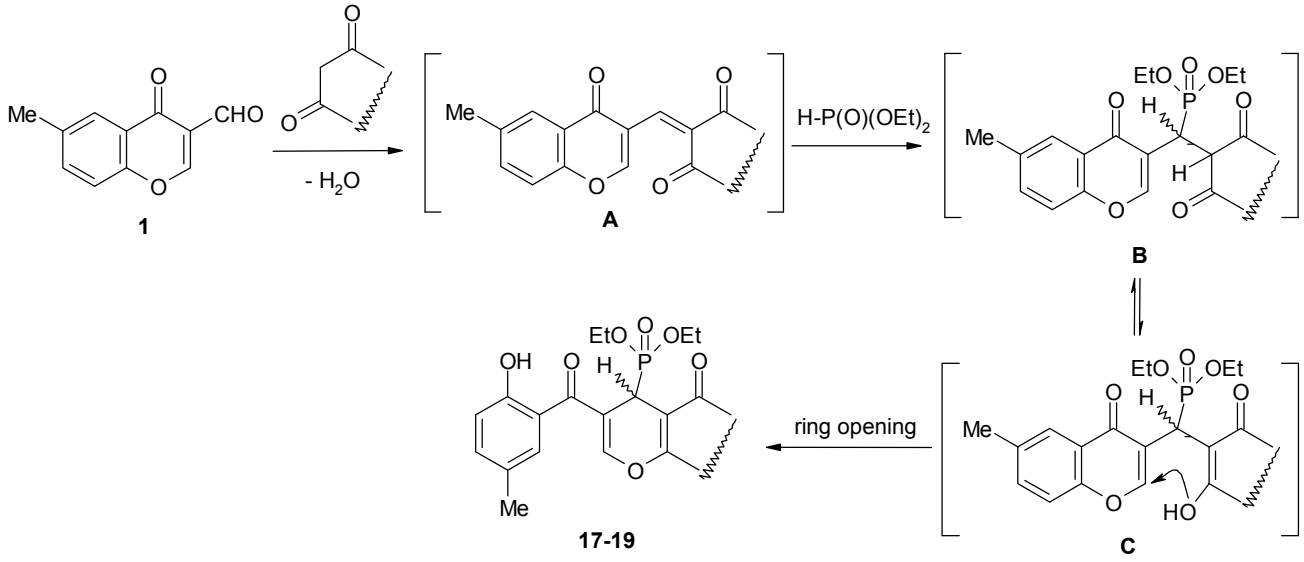
Scheme 6

The high point in this work was the synthesis of some novel fused pyran systems containing phosphonate substrate at γ-position that would expected to have biological properties. Thus, heating of 6-methyl-3-formylchromone (**1**) and each one of cyclic carbon nucleophiles such as dimedone, 1-phenylpyrazolidine-3,5-dione and barbituric acid in the presence of diethyl phosphite and few drops of triethylamine at 70−80 °C for 8 h afforded the γ-pyranyl phosphonates **17**−**19**, respectively (Scheme 7). A plausible mechanism for the formation of compounds **17**−**19** is depicted in Scheme 8. Initially, condensation process occurred between the formyl group and the cyclic active methylene groups forming the intermediate **A**, which underwent addition of diethyl phosphite at the *exo* CH=C bond to yield the phosphonate intermediate **B**. The keto-enol tautomerism between the intermediates **B** and **C** facilitates the nucleophilic attack of OH group on C−2 of chromone ring producing the new pyran ring (Scheme 8). Structures of the latter phosphonates were established from IR, MS and NMR spectral data. The mass spectra of products **18** and **19** recorded their molecular ion peaks at *m/z* 484 and 436, respectively. The IR spectra of compounds **17**−**19** indicated the appearance of the OH groups at 3444, 3392 and 3414 cm^{-1}, respectively, and revealed in each product, two types of C=O bands at 1681, 1655; 1713, 1641 and 1713, 1628, respectively. Also, their ^{1}H-NMR spectra showed characteristic singlets at δ 8.26, 8.40 and 8.60

ppm, respectively, due to α-protons of the pyran rings. Furthermore, each compound displayed a doublet for the CH−P proton at δ 4.51, 4.92 and 5.05 ppm for them with coupling constants 18, 18 and 15.6 Hz, respectively. In addition, the ^{13}C-NMR spectrum of compound **19** confirmed the presence of the pyranopyrimidine system because of three characteristic signals were found at δ 43.0, 150.9 and 162.2 ppm corresponding to CH−P, C−7′ and C=O$_{amide}$ respectively. The ^{31}P-NMR spectrum signal of the phosphonate **18** was found at δ 21.6 ppm.



Scheme 7



Scheme 8

Biological evaluations

1. Antimicrobial activity

All the newly synthesized compounds were evaluated in *vitro* for their antibacterial activities against *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635), as representatives of Gram–positive bacteria and *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028) as examples of Gram–negative bacteria. They were also examined against *Candida albicans* (ATCC 10231) as yeast and *Aspergillus fumigatus* as fungus. Agar diffusion technique was used for the determination of the preliminary antibacterial and antifungal activities.[34,35] The test was performed on medium potato dextrose agar (PDA) which contained infusion of 200 g potatoes, 6 g dextrose and 15 g agar. Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 μL) from the concentrations of 500 and 1000 μg/mL dissolved compounds in dimethylformamide (DMF) and carefully placed on inoculated agar surface. After incubation for 36 hours at 27 °C in the case of bacteria and for 48 h at 24 °C in the case of fungi, the antimicrobial activities were determined by measuring the inhibition zones. Cephalothin, Chloramphenicol and Cycloheximide were used as reference drugs (30 μg/mL) for Gram positive bacteria, Gram negative bacteria and fungi, respectively. The minimum inhibitory concentration (MIC, μg/mL) for some selected compounds against some species of microbes was also determined. The tube dilution technique[36] was applied for the determination of MIC of the tested compounds against microbes. Dilution series were set up with 250, 125, 62.5……3.25 μg/mL of nutrient broth medium to each tube, 100 mL of standardized suspension of the test microbes (107 cell/ mL) were added and incubated at 37 °C for 24 hours. The obtained results on the antimicrobial activities of the compounds and control drugs are given in Table 1. In general, the tested compounds recorded variable antimicrobial activities towards the used microorganism. The most compounds recorded low to moderate inhibitory effects towards all the microorganisms. The antimicrobial spectrum of the synthesized compounds against Gram-negative bacteria demonstrated very low inhibitions. Compound **16** exhibited moderate inhibition against *Staphylococcus aureus* with high MIC value >250 μg/mL. Similarly, compounds **8** and **11** recorded moderate inhibitions against *Bacillus subtilis* with high MIC value >250 μg/mL. All the tested compounds except **2** and **4** exhibited relatively low to high inhibitory activities against *Candida albicans*. Furthermore, compounds **5–9**, **11** and **16** exhibited relatively moderate inhibitory activities against *Candida albicans* especially compounds **8** and **9** which recorded MIC values at 250 μg/mL. Compound **17** is the most effective one against *Staphylococcus aureus* and *Bacillus subtilis* with MIC values of 125 μg/mL. For activity against *Candida albicans* and *Aspergillus fumigatus,* compound **19** recorded the best activity with MIC values of 62.5 and 125 μg/mL, respectively, in comparison to the other synthesized compounds.

2. Antioxidant activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties. The solutions of tested compounds (150, 300 and 450 μmol L^{-1}) were added to DPPH (100 μmol L^{-1}) in DMSO/EtOH. The tubes were kept at an ambient temperature for 20 minutes and the absorbance was measured at λ 517 nm. The difference between the test and the control experiments was taken and expressed as the percent scavenging of the DPPH radical using the following formula % inhibition = (*AB*−*AA*/*AB*) x 100 where *AB*=absorption of blank and *AA*=Absorption of tested compound. The radical scavenging activity of ascorbic acid was also measured and compared with that of the different synthesized compounds.[37,38] The observed data on the antioxidant activities of the compounds and control are shown in Table 2 and illustrated in Figure 1. The results of scavenging the stable DPPH radical recorded variable antioxidant activities towards the synthesized compounds at the different concentrations 150, 300 and 450 μmol L^{-1}. Compounds **2**, **5**, **7**, **11**, **12** and **15** showed moderate activities. In the meantime, compounds **3**, **6**, **8**, **10**, **14**, **16**, **17** and **19** displayed good activities. On the other hand, compounds **4**, **9**, **13** and **18** proved to exhibit potent antioxidative activities. The structure activity relationships of the tested compounds demonstrated that all the synthesized compounds recorded remarkable inhibition activities in range 37.81–78.35% at the different concentrations due to the presence of 4-methylphenol group in all the compounds except compounds **2**–**5** which have other free NH groups attached to phosphonate moieties. The cyclic α-aminophosphonates **6**–**15** and phosphonates **16**–**19** recorded noticeable antioxidative properties more than the acyclic α-aminophosphonates **2**–**5**. This may due to the presence of free phenolic OH groups in compounds **6**–**19** which can scavenge the DPPH radical. The appearance of isoxazole unit in compound **8** exhibited greater activity than those having pyrazole units in compounds **6** and **7**. Similarly, the thioxopyrimidinyl derivative **9** was more active than the other amino/cyanoiminopyrmidinyl derivatives **10** and **11**. Amongst compounds having seven-membered rings **12**–**15**, the diazepinyl derivative **13** exhibited the highest inhibition activity. On the other hand, the pyridine system **16** did not record the hoped antioxidative properties. The pyrazolopyranyl phosphonate **18** was the most active one between the pyranyl phosphonates **17**–**19**. In this study, the systems **4**, **9**, **13** and **18** displayed the higher scavenging activities. However, the result exemplified that compound **13** having the diazepinyl unit in combination with phosphonic diester moiety is the most powerful antioxidant agent.

Table 1. In *vitro* antimicrobial activities of the synthesized compounds **2-19** at 500 and 1000 μg/mL and the MIC values for some selected compounds.

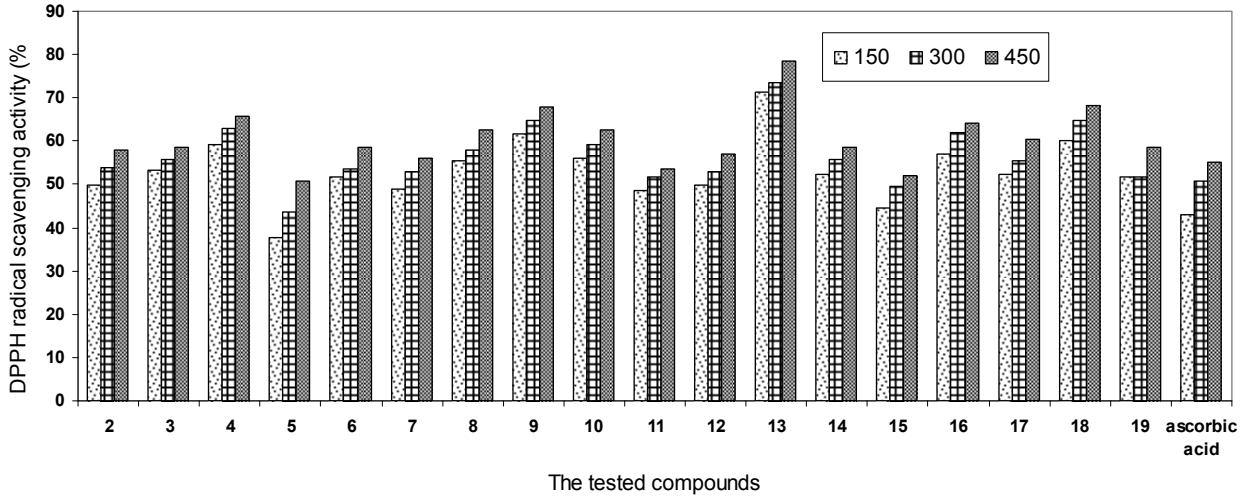
Compd.	Conc. (μg/ml)	Zone of inhibition in mm* and (MIC values in μg/mL)					
		Bacteria Gram (+) ve		Bacteria Gram (−) ve		Yeast	Fungi
		S. aureus	*B. subtilis*	*S. typhimurium*	*E. coli*	*C. albicans*	*A. fumigatus*
2	500	7	7	-	7	-	-
	1000	9	7	-	7	-	-
3	500	-	7	7	8	8	-
	1000	-	7	7	11	9	-
4	500	-	-	-	-	-	-
	1000	-	-	-	-	-	-
5	500	9	9	7	9	15 (>250)	10
	1000	11	10	7	11	19	12
6	500	-	8	-	8	13 (>250)	-
	1000	-	9	-	9	17	-
7	500	-	-	-	-	10 (>250)	-
	1000	-	-	-	-	13	-
8	500	-	9 (>250)	-	-	17 (250)	-
	1000	-	14	-	-	20	-
9	500	-	-	-	-	14 (250)	-
	1000	-	-	-	-	20	-
10	500	7	-	7	8	8	-
	1000	10	-	8	10	9	-
11	500	-	10 (>250)	-	-	13 (>250)	-
	1000	-	12	-	-	18	-
12	500	7	9	9	7	7	7
	1000	8	10	11	10	8	11
13	500	7	8	-	-	8	-
	1000	8	9	-	-	11	-
14	500	-	8	-	-	11	-
	1000	-	9	-	-	15	-
15	500	-	8	-	-	7	-
	1000	-	9	-	-	14	-
16	500	13 (>250)	7	7	8	15 (>250)	9
	1000	15	8	11	9	17	12
17	500	18 (125)	15 (125)	7	9	8	9
	1000	20	17	7	10	12	11
18	500	9	9	7	7	9	10
	1000	13	11	9	10	14	15
19	500	9	9	8	7	20 (62.5)	15 (125)
	1000	10	12	10	11	27	19
Standard drug	500	26	25	28	27	28	26
	1000	35	35	36	38	35	37

* Low active: 6–12 mm; moderately active: 13–19 mm; highly active: 20–30 mm; –: No inhibition or inhibition less than 5 mm.

Table 2. The DPPH radical scavenging activities of the synthesized compounds **2-19** at 150, 300 and 450 μmol L^{-1}.

Compd. No.	DPPH % inhibition antioxidant ± SD		
	150 μmol L^{-1}	300 μmol L^{-1}	450 μmol L^{-1}
2	49.85 ± 0.12	53.74 ± 0.24	57.83 ± 0.24
3	53.29 ± 0.06	55.83 ± 0.06	58.59 ± 0.12
4	59.07 ± 0.12	62.78 ± 0.25	65.84 ± 0.25
5	37.81 ± 0.12	43.71 ± 0.25	50.62 ± 0.06
6	51.79 ± 0.25	53.46 ± 0.12	58.58 ± 0.06
7	48.84 ± 0.12	52.89 ± 0.06	56.16 ± 0.06
8	55.35 ± 0.06	58.02 ± 0.18	62.46 ± 0.06
9	61.53 ± 0.38	64.70 ± 0.25	67.96 ± 0.06
10	56.16 ± 0.12	59.13 ± 0.06	62.69 ± 0.24
11	48.56 ± 0.06	51.79 ± 0.06	53.69 ± 0.06
12	49.97 ± 0.18	52.92 ± 0.06	57.01 ± 0.18
13	71.47 ± 0.12	73.56 ± 0.06	78.35 ± 0.06
14	52.28 ± 0.24	55.79 ± 0.24	58.45 ± 0.25
15	44.68 ± 0.18	49.37 ± 0.06	52.16 ± 0.06
16	56.88 ± 0.38	61.97 ± 0.38	64.28 ± 0.38
17	52.28 ± 0.06	55.55 ± 0.18	60.28 ± 0.06
18	60.20 ± 0.06	64.83 ± 0.06	68.34 ± 0.25
19	51.83 ± 0.18	51.83 ± 0.06	58.62 ± 0.06
ascorbic acid	43.00	50.70	55.20

Figure 1. The DPPH radical scavenging activities (%) for the tested compounds.



CONCLUSION

In conclusion, we have explored one-pot three component's reaction, which furnished novel classes of functionalized heterocyclic analogues of acyclic and cyclic α-aminophosphonates and phosphonates from readily available 6-methyl-3-formylchromone, nitrogen and carbon *mono*- and *bi*-nucleophiles and diethyl phosphite. The procedure is efficient and general. The reactions have been shown to display relatively good functional group tolerance and good yields. We hope that this approach may be value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

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. ^{1}H-NMR spectra were measured on Gemini-300BB spectrometer (300 MHz), using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. ^{13}C-NMR spectra were measured on Mercury-300BB (75 MHz using DMSO-d_6 as a solvent) and Bruker-600 (150 MHz using $CDCl_3$ as a solvent) spectrometer and TMS (δ) as the internal standard. ^{31}P-NMR spectra were registered on a Bruker-600 (242 MHz) spectrometer at room temperature using DMSO-d_6 as a solvent and TMS as internal standard and 85% H_3PO_4 as external reference. Mass spectra recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 ev. Elemental microanalyses were performed Perkin-Elmer 2400 II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC). 6-Methyl-3-formylchromone (**1**) was prepared according to the reported method.[39]

General procedure for the preparation of target compounds 2-19

A mixture of 6-methyl-3-formylchromone (**1**) (5 mmol, 0.94 g), nucleophile (5 mmol) and diethyl phosphite (10 mmol, 1.38 mL) was heated under reflux at 70−80 °C for 2−8 h (in case of **2, 8** and **16**−**19** few drops of triethylamine were added). The reaction mixture was cooled then poured into ice and left for complete precipitation. The precipitate formed was filtered off, dried and crystallized from the proper solvent.

Diethyl [(ethylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonate (2): Brown crystals from EtOH in 100% yield; mp 247−249 °C. IR (KBr), (ν_{max}, cm^{-1}): 3443 (br, NH), 3083 (C–H_{arom}), 2987, 2893 (C–H_{aliph}), 1640 (C=O_{pyrone}), 1621 (C=C), 1228 (P=O), 1059 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 0.93 (t, 3H, J = 6.9 Hz, C***H***$_3$), 1.00–1.15 (m, 6H, OCH_2C***H***$_3$), 2.41 (s, 3H, Ar–C***H***$_3$), 2.92 (brs, 1H, N***H*** exchangeable with D_2O), 3.69 (q, 2H, J = 6.9 Hz, C***H***$_2$), 3.93–4.00 (m, 4H, OC***H***$_2CH_3$), 4.39 (d, 1H, J = 24 Hz, C***H***–P), 7.58–7.66 (m, 2H, ***H***–8 and ***H***–7), 7.89 (s, 1H, ***H***–5), 8.76 (s, 1H, ***H***–2). MS (EI, *m/z*): 353 (M^+). Anal. Calcd for $C_{17}H_{24}NO_5P$ (353.36): C, 57.79; H, 6.85; N, 3.96%. Found: C, 57.70; H, 6.92; N, 4.22%.

Diethyl [(benzylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonate (3): Pale yellow crystals from EtOAc in 75% yield; mp 229−230 °C. IR (KBr), (ν_{max}, cm^{-1}): 3439 (br, NH), 3070, 3032 (C–H_{arom}), 2973, 2932 (C–H_{aliph}), 1640 (C=O_{pyrone}), 1620 (C=C), 1225 (P=O), 1053 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 0.93 (t, 6H, J = 7.5 Hz, OCH_2CH_3), 2.44 (s, 3H, Ar–CH_3), 3.60 (q, 4H, OCH_2CH_3), 3.88 (brs, 1H, N*H* exchangeable with D_2O), 4.22 (d, 2H, CH_2), 4.48 (d, 1H, J = 15 Hz, C*H*–P), 7.29–7.67 (m, 7H, *H*–8, *H*–7 and Ph–*H*), 7.87 (s, 1H, *H*–5), 8.95 (s, 1H, *H*–2). ^{13}C-NMR (75 MHz, DMSO): 16.5 (OCH_2CH_3), 20.4 (CH_3), 45.5 (d, J = 148.5 Hz, *C*H–P), 56.0 (CH_2), 60.4 (OCH_2CH_3), 117.4 (*C*–3), 118.2 (*C*–8), 122.4 (*C*–4a), 124.4 (*C*–4′$_{phenyl}$), 128.1 (*C*–2′, 6′$_{phenyl}$), 128.4 (*C*–3′, 5′$_{phenyl}$), 130.4 (*C*–5), 131.9 (*C*–6), 135.2 (*C*–7), 135.3 (*C*–1′$_{phenyl}$), 153.7 (*C*–2), 157.5 (*C*–8a), 174.6 (*C*=O). Anal. Calcd for $C_{22}H_{26}NO_5P$ (415.43): C, 63.61; H, 6.31; N, 3.37%. Found: C, 63.34; H, 6.49; N, 3.63%.

Diethyl [(4-chlorophenylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonate (4): Pale yellow crystals from EtOH in 70% yield; mp 196–198 °C (lit.,[26] 199–201 °C). IR (KBr), (ν_{max}, cm^{-1}): 3290 (NH), 3064 (C–H_{arom}), 2991, 2897 (C–H_{aliph}), 1646 (C=O_{pyrone}), 1622 (C=C), 1221 (P=O), 1023 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.12 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.28 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.40 (s, 3H, Ar–CH_3), 3.67–3.97 (m, 4H, OCH_2CH_3), 4.56 (brs, 1H, N*H* exchangeable with D_2O), 5.21 (d, 1H, J = 23.2 Hz, C*H*–P), 6.37–7.70 (m, 7H, Ar–*H*), 8.20 (s, 1H, *H*–2). ^{13}C-NMR (75 MHz, DMSO–d_6): 16.0 (OCH_2CH_3), 20.3 (CH_3), 45.2 (d, J = 158.5 Hz, *C*H–P), 62.6 (OCH_2CH_3), 114.6 (*C*–2′,6′$_{aryl}$), 118.2 (*C*–3), 120.1 (*C*–8), 120.9 (*C*–4`$_{aryl}$), 122.3 (*C*–4a), 128.6 (*C*–3′,5′$_{aryl}$), 124.4 (*C*–5), 135.5 (*C*–6), 135.6 (*C*–7), 145.7 (*C*–1′$_{aryl}$), 153.9 (*C*–2), 155.7 (*C*–8a), 174.8 (*C*=O). Anal. Calcd for $C_{21}H_{23}ClNO_5P$ (435.85): C, 57.87; H, 5.32; N, 3.21%. Found: C, 57.52; H, 5.28; N, 3.43%.

Diethyl [(4-hydroxyphenylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonate (5): Brown crystals from aq. DMF in 62% yield; mp 243–245 °C. IR (KBr), (ν_{max}, cm^{-1}): 3393 (br, OH, NH), 3079 (C–H_{arom}), 2982, 2926 (C–H_{aliph}), 1640 (C=O_{pyrone}), 1617 (C=C), 1216 (P=O), 1046 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.02–1.20 (m, 6H, OCH_2CH_3), 2.21 (s, 3H, Ar–CH_3), 3.66–3.81 (m, 4H, OCH_2CH_3), 4.00 (brs, 1H, N*H* exchangeable with D_2O), 5.01 (d, 1H, J = 21.9 Hz, C*H*–P), 6.85–7.81 (m, 6H, Ar–*H*), 7.91 (s, 1H, *H*–5), 8.50 (s, 1H, *H*–2), 10.00 (brs, 1H, O*H* exchangeable with D_2O). ^{31}P-NMR (242 MHz, DMSO–d_6): 21.6 ppm. Anal. Calcd for $C_{21}H_{24}NO_6P$ (417.40): C, 60.43; H, 5.80; N, 3.36%. Found. C, 60.09; H, 5.42; N, 3.54%.

Diethyl {4-[(2-hydroxy-5-methylphenyl)carbonyl]-2,3-dihydro-1*H*-pyrazol-3-yl}phosphonate (6): Yellow crystals from EtOAc in 55% yield; mp 210–212 °C. IR (KBr), (ν_{max}, cm^{-1}): 3407 (br, OH), 3139 (br, NH), 2974, 2940 (C–H_{aliph}), 1636 (C=O), 1614 (C=C), 1212 (P=O), 1046 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.03 (t, 6H, J= 7.2 Hz, OCH_2CH_3), 2.17 (s, 3H, Ar–CH_3), 4.00–4.20 (m, 4H,

OC***H***$_2$CH$_3$), 4.90 (d, 1H, *J* = 20 Hz, C***H***–P), 6.84 (d, 1H, ***H***–4), 7.03 (d, 1H, ***H***–3), 7.30 (s, 1H, ***H***–5′$_{pyrazole}$), 7.65 (s, 1H, ***H***–6), 8.70 (brs, 1H, N***H*** exchangeable with D_2O), 9.50 (brs, 1H, N***H*** exchangeable with D_2O), 10.70 (brs, 1H, O***H*** exchangeable with D_2O). ^{31}P-NMR (242 MHz, DMSO–d_6): 22.4 ppm. MS (EI, *m/z*): 341 (M+1), 340 (M^+). Anal. Calcd for $C_{15}H_{21}N_2O_5P$ (340.32): C, 52.94; H, 6.22; N, 8.23%. Found: C, 52.61; H, 5.87; N, 8.02%.

Diethyl {4-[(2-hydroxy-5-methylphenyl)carbonyl]-1-phenyl-2*H*-pyrazol-3-yl}phosphonate (7): Beige crystals from EtOH in 72% yield; mp 255–256 °C. IR (KBr), (ν_{max}, cm^{-1}): 3334 (br, OH), 3132 (br, NH), 3061 (C–H$_{arom}$), 2982, 2914 (C–H$_{aliph}$), 1654 (C=O), 1598 (C=C), 1212 (P=O), 1084 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.05 (t, 3H, *J* = 6.4 Hz, OCH$_2$C***H***$_3$), 1.20 (t, 3H, *J* = 6.4 Hz, OCH$_2$C***H***$_3$), 2.17 (s, 3H, Ar–C***H***$_3$), 3.91–4.00 (m, 4H, OC***H***$_2$CH$_3$), 4.94 (d, 1H, *J* = 20 Hz, C***H***–P), 6.70–7.71 (m, 7H, Ar–***H***), 7.78 (s, 1H, Ar–***H***), 8.80 (brs, 1H, ***H***–5′$_{pyrazole}$), 9.40 (brs, 1H, N***H*** exchangeable with D_2O), 10.60 (brs, 1H, O***H*** exchangeable with D_2O). MS (EI, *m/z*): 416 (M^+). Anal. Calcd for $C_{21}H_{25}N_2O_5P$ (416.42): C, 60.57; H, 6.05; N, 6.73%. Found: C, 60.28; H, 5.82; N, 6.49%.

Diethyl {4-[(2-hydroxy-5-methylphenyl)carbonyl]-2,3-dihydro-isoxazol-3-yl}phosphonate (8): Brown crystals from EtOH in 52% yield; mp 100–102 °C. IR (KBr), (ν_{max}, cm^{-1}): 3390 (br, OH), 3246 (br, NH), 3020 (C–H$_{arom}$), 2976, 2923 (C–H$_{aliph}$), 1642 (C=O), 1622 (C=C), 1216 (P=O), 1041 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.07–1.21 (m, 6H, OCH$_2$C***H***$_3$), 2.36 (s, 3H, Ar–C***H***$_3$), 4.20–4.40 (m, 4H, OC***H***$_2$CH$_3$), 5.65 (d, 1H, *J* = 18 Hz, C***H***–P), 7.23–7.80 (m, 2H, Ar–***H***), 7.98 (s, 1H, Ar–***H***), 9.05 (s, 1H, ***H***–5′$_{isoxazole}$), 9.66 (s, 1H, N***H*** exchangeable with D_2O), 10.43 (s, 1H, O***H*** exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO–d_6): 14.4 (OCH$_2$***C***H$_3$), 20.4 (***C***H$_3$), 46.0 (d, *J* = 155.2 Hz, ***C***H–P), 62.0 (O***C***H$_2$CH$_3$), 112.3 (***C***–4′$_{isoxazole}$), 116.0 (***C***–3), 121.3 (***C***–1), 134.3 (***C***–6), 135.6 (***C***–5), 137.0 (***C***–4), 150.9 (***C***–5′$_{isoxazol}$), 154.3 (***C***–2), 193.4 (***C***=O). Anal. Calcd for $C_{15}H_{20}NO_6P$ (341.30): C, 52.79; H, 5.91; N, 4.10%. Found: C, 52.53; H, 5.63; N, 3.86%.

Diethyl {5-[(2-hydroxy-5-methylphenyl)carbonyl]-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl}-phosphonate (9): Pale brown crystals from EtOH in 53% yield; mp 196–198 °C. IR (KBr), (ν_{max}, cm^{-1}): 3293 (br, OH, NH), 3050 (C–H$_{arom}$), 2980, 2927 (C–H$_{aliph}$), 1641 (C=O), 1619 (C=C), 1214 (P=O), 1044 (P–O–C), 1165 (C=S). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.08–1.36 (m, 6H, OCH$_2$C***H***$_3$), 2.28 (s, 3H, Ar–C***H***$_3$), 3.80–4.00 (m, 4H, OC***H***$_2$CH$_3$), 5.10 (d, 1H, *J* = 20 Hz, C***H***–P), 7.40–7.80 (m, 3H, Ar–***H*** and ***H***–6′$_{pyrimidine}$), 7.95 (s, 1H, Ar–***H***), 8.40 (brs, 1H, N***H*** exchangeable with D_2O), 9.10 (brs, 1H, O***H*** exchangeable with D_2O), 9.80 (brs, 1H, N***H*** exchangeable with D_2O). MS (EI, *m/z*): 384 (M^+). Anal. Calcd for $C_{16}H_{21}N_2O_5PS$ (384.39): C, 50.00; H, 5.51; N, 7.29; S, 8.33%. Found: C, 49.71; H, 5.24; N, 6.97; S, 7.97%.

Diethyl {2-amino-5-[(2-hydroxy-5-methylphenyl)carbonyl]-3,4-dihydropyrimidin-4-yl}phosphonate

(10): Pale beige crystals from EtOH in 65% yield; mp 303–305 °C. IR (KBr), (ν_{max}, cm^{-1}): 3452 (OH), 3302, 3134 (NH_2, NH), 3020 (C–H_{arom}), 2984, 2920 (C–H_{aliph}), 1648 (C=O), 1600 (C=N), 1583 (C=C), 1206 (P=O), 1028 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.07 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 1.15 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 2.31 (s, 3H, Ar–C***H***$_3$), 3.60–3.95 (m, 4H, OC***H***$_2$$CH_3$), 5.20 (d, 1H, J = 19 Hz, C***H***–P), 6.92 (d, 1H, J = 8.4 Hz, Ar–***H***), 7.25 (d, 1H, J = 6 Hz, Ar–***H***), 7.38 (brs, 2H, N***H***$_2$ exchangeable with D_2O), 7.88 (s, 1H, Ar–***H***), 8.00 (brs, 1H, N***H*** exchangeable with D_2O), 8.24 (s, 1H, ***H***–6′$_{pyrimidine}$), 9.46 (s, 1H, ***OH*** exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO–d_6): 16.0 (OCH_2***C***H_3), 20.3 (***C***H_3), 47.0 (d, J = 148.5 Hz, ***C***H–P), 61.8 (O***C***H_2CH_3), 113.7 (***C***–3), 117.6 (***C***–5′$_{pyrimidine}$), 123.9 (***C***–1), 130.2 (***C***–6), 133.1 (***C***–5), 135.0 (***C***–4), 152.1 (***C***–6′$_{pyrimidine}$), 156.2 (***C***–2), 163.6 (***C***–2′$_{pyrimidine}$), 186.1 (***C***=O). ^{31}P-NMR (242 MHz, DMSO–d_6): 26.2 ppm. MS (EI, *m/z*): 368 (M+1), 367 (M^+). Anal. Calcd for $C_{16}H_{22}N_3O_5P$ (367.34): C, 52.32; H, 6.04; N, 11.44%. Found: C, 52.01; H, 5.81; N, 11.07%.

Diethyl {2-(cyanoimino)-5-[(2-hydroxy-5-methylphenyl)carbonyl]-1,2,3,4-tetrahydro-pyrimidin-4-yl}-phosphonate (11): Beige crystals from EtOH in 48% yield; mp 201–202 °C. IR (KBr), (ν_{max}, cm^{-1}): 3405 (br, OH, NH), 2982, 2928 (C–H_{aliph}), 2225 (C≡N), 1643 (C=O), 1620 (C=N), 1230 (P=O), 1046 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.00–1.20 (m, 6H, OCH_2CH_3), 2.29 (s, 3H, Ar–C***H***$_3$), 3.80–4.00 (m, 4H, OC***H***$_2$$CH_3$), 5.03 (d, 1H, J' = 18 Hz, C***H***–P), 6.96–7.61 (m, 3H, Ar–***H*** and ***H***–6′$_{pyrimidine}$), 7.82 (s, 1H, Ar–***H***), 8.39 (brs, 1H, N***H*** exchangeable with D_2O), 9.42 (brs, 1H, N***H*** exchangeable with D_2O), 10.89 (brs, 1H, O***H*** exchangeable with D_2O). Anal. Calcd for $C_{17}H_{21}N_4O_5P$ (392.35): C, 52.04; H, 5.39; N, 14.28%. Found: C, 51.77; H, 5.30; N, 14.15%.

Diethyl {6-[(2-hydroxy-5-methylphenyl)carbonyl]-2,3,4,5-tetrahydro-1,4-oxazepin-5-yl}-phosphonate (12): Pale yellow crystals from EtOAc in 100% yield; mp 302–303 °C. IR (KBr), (ν_{max}, cm^{-1}): 3417 (br, OH, NH), 3056 (C–H_{arom}), 2974, 2893 (C–H_{aliph}), 1645 (C=O), 1622 (C=C), 1216 (P=O), 1073 (P–O–C). ^{1}H- NMR (300 MHz, DMSO–d_6): 1.00–1.16 (m, 6H, OCH_2CH_3), 2.27 (s, 3H, Ar–C***H***$_3$), 3.46 (brs, 2H, C***H***$_2$), 3.80–4.00 (m, 4H, OC***H***$_2$$CH_3$), 4.34 (brs, 2H, C***H***$_2$), 4.94 (d, 1H, J = 20 Hz, C***H***–P), 7.50–7.68 (m, 3H, Ar–***H*** and ***H***–7′$_{oxazepine}$), 7.90 (s, 1H, Ar–***H***), 8.87 (brs, 1H, N***H*** exchangeable with D_2O), 9.60 (brs, 1H, O***H*** exchangeable with D_2O). MS (EI, *m/z*): 370 (M+1), 369 (M^+). Anal. Calcd for $C_{17}H_{24}NO_6P$ (369.36): C, 55.28; H, 6.55; N, 3.79%. Found: C, 54.98; H, 6.23; N, 3.56%.

Diethyl {6-[(2-hydroxy-5-methylphenyl)carbonyl]-2,3,4,5-tetrahydro-1*H*-1,4-diazepin-5-yl}-phosphonate (13): Brown crystals from EtOAc in 43% yield; mp 210–212 °C. IR (KBr), (ν_{max}, cm^{-1}): 3397 (br, OH, NH), 3030 (C–H_{arom}), 2980, 2920 (C–H_{aliph}), 1646 (C=O), 1622 (C=C), 1228 (P=O), 1045 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 0.91–1.20 (m, 6H, OCH_2CH_3), 2.27 (s, 3H, Ar–C***H***$_3$), 3.42 (brs, 4H, C***H***$_2$C***H***$_2$), 3.80–4.00 (m, 4H, OC***H***$_2$$CH_3$), 5.00 (d, 1H, J = 21 Hz, C***H***–P), 6.08 (brs, 1H, N***H*** exchangeable with D_2O), 6.84–7.62 (m, 3H, Ar–***H*** and ***H***–7′$_{diazepine}$), 7.90 (s, 1H, Ar–***H***), 9.60 (brs, 2H,

O***H*** and N***H*** exchangeable with D_2O). ^{13}C-NMR (150 MHz, $CDCl_3$): 14.9 ($OCH_2\boldsymbol{C}H_3$), 22.1 ($\boldsymbol{C}H_3$), 41.2 (d, J = 148.0 Hz, ***C***H–P), 54.9 ($\boldsymbol{C}H_2N$), 58.5 ($\boldsymbol{C}H_2N$), 59.9 ($O\boldsymbol{C}H_2CH_3$), 115.5 (***C***–3), 117.5 (***C***–6′$_{diazepine}$), 121.1 (***C***–1), 131.2 (***C***–6), 133.5 (***C***–4), 150.1 (***C***–7′$_{diazepine}$), 151.5 (***C***–2), 185.0 (***C***=O). ^{31}P-NMR (242 MHz, DMSO-d_6): 28.8 ppm. Anal. Calcd for $C_{17}H_{25}N_2O_5P$ (368.37): C, 55.43; H, 6.84; N, 7.60%. Found: C, 55.20; H, 6.56; N, 7.32%.

Diethyl {3-[(2-hydroxy-5-methylphenyl)carbonyl]-4,5-dihydro-1,5-benzoxazepin-4-yl}phosphonate (14): Yellow crystals from EtOH in 7% yield; mp 186–187 °C. IR (KBr), (ν_{max}, cm^{-1}): 3417 (br, OH), 3232 (br, NH), 3020 (C–H$_{arom}$), 2981, 2934 (C–H$_{aliph}$), 1641 (C=O), 1617 (C=C), 1228 (P=O), 1026 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.11 (t, 3H, J = 6.9 Hz, $OCH_2C\boldsymbol{H}_3$), 1.22 (t, 3H, J = 6.9 Hz, $OCH_2C\boldsymbol{H}_3$), 2.42 (s, 3H, Ar–C***H***$_3$), 3.94–4.15 (m, 4H, OC***H***$_2$CH$_3$), 5.10 (d, 1H, J = 15 Hz, C***H***–P), 6.44–6.92 (m, 4H, Ar–***H***), 7.53–7.66 (m, 2H, Ar–***H***), 7.88 (s, 1H, Ar–***H***), 8.44 (s, 1H, ***H***–2′$_{benzoxazepine}$), 9.56 (s, 1H, N***H*** exchangeable with D_2O), 10.35 (brs, 1H, O***H*** exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO–d_6): 16.0 ($OCH_2\boldsymbol{C}H_3$), 20.4 ($\boldsymbol{C}H_3$), 45.0 (d, J = 150 Hz, ***C***H–P), 62.5 (OC***H***$_2$CH$_3$), 110.8 (***C***–6′), 113.8 (***C***–3), 117.7 (***C***–3′), 118.2 (***C***–8′), 119.7 (***C***–9′), 122.3 (***C***–1), 124.2 (***C***–7′), 134.5 (***C***–6), 134.7 (***C***–5), 135.4 (***C***–4), 144.7 (***C***–5′a), 145.7 (***C***–9′a), 153.8 (***C***–2′), 155.3 (***C***–2), 189.6 (***C***=O). MS (EI, *m/z*): 417 (M^+). Anal. Calcd for $C_{21}H_{24}NO_6P$ (417.40): C, 60.34; H, 5.80; N, 3.36%. Found: C, 60.10; H, 5.94; N, 3.55%.

Diethyl {3-[(2-hydroxy-5-methylphenyl)carbonyl]-4,5-dihydro-1*H*-1,5-benzo-diazepin-4-yl}-phosphonate (15): Yellow crystals from EtOH in 67% yield; mp 228–230 °C. IR (KBr), (ν_{max}, cm^{-1}): 3421 (br, OH, NH), 3055 (C–H$_{arom}$), 2979, 2917 (C–H$_{aliph}$), 1636 (C=O), 1618 (C=C), 1215 (P=O), 1049 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.04–1.35 (m, 6H, $OCH_2C\boldsymbol{H}_3$), 2.23 (s, 3H, Ar–C***H***$_3$), 4.20–4.40 (m, 4H, OC***H***$_2$CH$_3$), 5.18 (d, 1H, J = 20 Hz, C***H***–P), 6.83–6.96 (m, 4H, Ar–***H***), 7.31–7.65 (m, 2H, Ar–***H***), 7.87 (s, 1H, Ar–***H***), 8.30 (s, 1H, ***H***–2′$_{benzodiazepine}$), 9.57 (brs, 1H, N***H*** exchangeable with D_2O), 11.82 (brs, 2H, O***H*** and N***H*** exchangeable with D_2O). MS (EI, *m/z*): 416 (M^+). Anal. Calcd for $C_{21}H_{25}N_2O_5P$ (416.42): C, 60.57; H, 6.05; N, 6.73%. Found: C, 60.2; H, 5.89; N, 6.41%.

Diethyl {3-cyano-5-[(2-hydroxy-5-methylphenyl)carbonyl]-2-oxo-1,2,3,4-tetrahydropyridin-4-yl}-phosphonate (16A) and diethyl {3-cyano-2-hydroxy-5-[(2-hydroxy-5-methyl-phenyl)carbonyl]-1,4-dihydropyridin-4-yl}phosphonate (16B): Yellow crystals from EtOH in 61 and 58% yields; mp 198–200 °C. IR (KBr), (ν_{max}, cm^{-1}): 3411 (br, OH, NH), 3050 (C–H$_{arom}$), 2982, 2929, 2861 (C–H$_{aliph}$), 2229 (C≡N), 1733 (C=O$_{amide}$), 1683 (C=O), 1622, 1598 (C=C), 1242 (P=O), 1032 (P–O–C). ^{1}H NMR (300 MHz, DMSO–d_6): 1.08–1.35 (m, 6H, $OCH_2C\boldsymbol{H}_3$), 2.27 (s, 3H, Ar–C***H***$_3$), 3.80–3.95 (m, 4H, OC***H***$_2$CH$_3$), 4.94 (d, 1H, J = 20 Hz, C***H***–P), 7.37–7.60 (m, 2H, Ar–***H***), 7.80 (brs, 1H, Ar–***H***), 8.40 (brs, 1H, ***H***–6′$_{pyridine}$), 9.60 (brs, 1H, O***H*** exchangeable with D_2O), 10.70 (brs, 1H, O***H*** exchangeable with

D_2O), 11.75 (brs, 1H, N***H*** exchangeable with D_2O). ^{13}C-NMR (150 MHz, $CDCl_3$): 16.0 (OCH_2***C***H_3), 23.8 (***C***H_3), 43.5 (d, *J* = 147.6 Hz, ***C***H–P), 62.9 (O***C***H_2CH_3), 104.1 (***C***–3′), 110.1 (***C***≡N), 115.3 (***C***–3), 117.9 (***C***–5′), 120.1 (***C***–1), 131.9 (***C***–6), 134.0 (***C***–4), 134.1 (***C***–5), 140.8 (***C***–6′), 155.7 (***C***–2), 187.1 (***C***=O), 197.2 (***C***–2′). ^{31}P-NMR (242 MHz, DMSO–d_6): 24.5 ppm. MS (EI, *m/z*): 393 (M+1), 392 (M^+). Anal. Calcd for $C_{18}H_{21}N_2O_6P$ (392.35): C, 55.10; H, 5.39; N, 7.14%. Found: C, 54.95; H, 5.14; N, 7.42%.

Diethyl {7,7-dimethyl-3-[(2-hydroxy-5-methylphenyl)carbonyl]-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl}phosphonate (17): Pale yellow crystals from EtOH in 48% yield; mp 303–305 °C. IR (KBr), (ν_{max}, cm^{-1}): 3444 (br, OH), 2957, 2867 (C–H_{aliph}), 1681 (C=O), 1655 (C=O), 1622 (C=C), 1203 (P=O), 1003 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 0.83 (s, 3H, C***H***$_3$), 1.00 (s, 3H, C***H***$_3$), 1.33 (t, 6H, *J* = 7.5 Hz, OCH_2C***H***$_3$), 2.04 (s, 2H, C***H***$_2$), 2.28 (s, 3H, Ar–C***H***$_3$), 3.62 (q, 4H, *J* = 7.5 Hz, OC***H***$_2CH_3$), 4.28 (s, 2H, C***H***$_2$), 4.51 (d, 1H, *J* = 18 Hz, C***H***–P), 7.46–7.54 (m, 2H, Ar–***H***), 7.71 (s, 1H, Ar–***H***), 8.26 (brs, 1H, ***H***–2′$_{pyran}$), 9.38 (s, 1H, O***H*** exchangeable with D_2O). Anal. Calcd for $C_{23}H_{29}O_7P$ (448.46): C, 61.60; H, 6.52%. Found: C, 61.24; H, 6.51%.

Diethyl {5-[(2-hydroxy-5-methylphenyl)carbonyl]-1-phenyl-4*H*-3-oxo-pyrano[2,3-*c*]pyrazol-4-yl}-phosphonate (18): Beige crystals from EtOH in 54% yield; mp 252–254 °C. IR (KBr), (ν_{max}, cm^{-1}): 3392 (br, OH, NH), 3064 (C–H_{arom}), 2980, 2980 (C–H_{aliph}), 1713 (C=O_{amide}), 1641 (C=O), 1617 (C=C), 1212 (P=O), 1084 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.00–1.21 (m, 6H, OCH_2C***H***$_3$), 2.16 (s, 3H, Ar–C***H***$_3$), 4.10–4.21 (m, 4H, OC***H***$_2CH_3$), 4.92 (d, 1H, *J* = 18 Hz, C***H***–P), 6.60–7.70 (m, 8H, Ar–***H*** and Ph–***H***), 8.40 (brs, 1H, ***H***–6′$_{pyran}$), 9.52 (brs, 2H, O***H*** and N***H*** exchangeable with D_2O). ^{31}P-NMR (242 MHz, DMSO–d_6): 21.6 ppm. MS (EI, *m/z*): 484 (M^+). Anal. Calcd for $C_{24}H_{25}N_2O_7P$ (484.45): C, 59.50; H, 5.20; N, 5.78%. Found: C, 59.21; H, 4.96; N, 5.38%.

Diethyl {6-[(2-hydroxy-5-methylphenyl)carbonyl]-1,5-dihydro-2*H*-2,4-dioxo-pyrano[2,3-*d*]-pyrimidin-5-yl}phosphonate (19): Brown crystals from DMF in 100% yield; mp 193–195 °C. IR (KBr), (ν_{max}, cm^{-1}): 3414 (br, OH), 3182 (br, NH), 3020 (C–H_{arom}), 2986, 2911 (C–H_{aliph}), 1713 (2 C=O_{amide}), 1628 (C=O), 1212 (P=O), 1011 (P–O–C). ^{1}H-NMR (300 MHz, DMSO–d_6): 1.07 (t, 3H, *J* = 6.6 Hz, OCH_2C***H***$_3$), 1.20 (t, 3H, *J* = 6.6 Hz, OCH_2C***H***$_3$), 2.23 (s, 3H, Ar–C***H***$_3$), 3.42 (q, 2H, *J* = 6.6 Hz, OC***H***$_2CH_3$), 3.86 (q, 2H, *J* = 6.6 Hz, OC***H***$_2CH_3$), 5.05 (d, 1H, *J* = 15.6 Hz, C***H***–P), 6.93–7.27 (m, 2H, Ar–***H***), 7.79 (s, 1H, Ar–***H***), 8.60 (brs, 1H, ***H***–7′$_{pyran}$), 9.23 (brs, 1H, O***H*** exchangeable with D_2O), 10.67, 11.20 (brs, 2H, N***H*** exchangeable with D_2O). ^{13}C-NMR (150 MHz, $CDCl_3$): 15.0 (OCH_2***C***H_3), 21.3 (***C***H_3), 43.0 (d, *J* = 133.5 Hz, ***C***H–P), 60.8 (O***C***H_2CH_3), 95.1 (***C***–4′a), 115.3 (***C***–3), 117.4 (***C***–6′), 121.7 (***C***–1), 132.0 (***C***–6), 135.9 (***C***–4), 150.9 (***C***–7′), 155.0 (***C***–2), 160.5 (***C***–8′a), 162.2 (2 ***C***=O_{amide}), 186.5 (***C***=O). MS (EI, *m/z*): 437 (M+1), 436 (M^+). Anal. Calcd for $C_{19}H_{21}N_2O_8P$ (436.36): C, 52.30; H, 4.85; N, 6.42%. Found: C, 51.98; H, 4.63; N, 6.02%.

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