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Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one-phosphonates by the Microwave-Assisted Biginelli Reaction

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Abstract: The synthesis of novel 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates was elaborated by the microwave (MW)-assisted three-component Biginelli reaction of β -ketophosphonates, aromatic or aliphatic aldehydes and urea derivatives. The condensation was optimized on a selected model reaction in respect of the reaction parameters, such as the heating method, the type of the catalyst and solvent, the temperature, the reaction time and the molar ratio of the starting materials. The fast and solvent-free MW-assisted procedure was then extended for the preparation of further new 3,4-dihydropyrimidin-2(1*H*)-one-phosphonate derivatives starting from different aromatic aldehydes, β -ketophosphonates and urea derivatives to prove the wide scope of the process. As a novel by-product of the Biginelli-type synthesis of 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates, the 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-one was also isolated and characterized. Our MW-assisted method made also possible the condensation of aliphatic aldehydes, diethyl (2-oxopropyl)phosphonate and urea, which reaction was previously reported to be impossible in the literature.

Keywords: heterocyclic phosphonates; 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates; multicomponent reactions; Biginelli reaction; microwave

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1. Introduction

A wide number of organophosphorus compounds play an important role in different fields of life; in organic- and medicinal chemistry, as well as in the agriculture and plastic industries [1]. Organic phosphonates may be considered as one of the most important subgroups. Among them, α -aminophosphonates are the bioisosteres of natural α -amino acids, and due to this structural similarity, they were proved to be effective as antibiotics, antiviral, or antitumor agents, as well as pesticides [2–6]. Over the last decade, due to their structural diversity, heterocyclic phosphonates have received an intensively growing interest [7,8]. A few biologically active examples can be seen in Figure 1. α -Aminophosphonates containing a piperidine ring (1) showed activity as an insecticide against *Plutella xylostella* [9]. A few 1,2,3-triazol-5-yl-phosphonates (2) were identified as promising cytotoxic and antibacterial agents [10]. Similarly, to the 1,4-dihydropyridine-3,5-dicarboxylates, several 1,4-dihydropyridine-5-phosphonates (3) showed significant antihypertensive activity [11–13].

Over the last decades, a number of biologically active 3,4-dihydropyrimidin-2(1*H*)-one carboxylates were utilized as anticancer-, antihypertensive-, anti-inflammatory-, antibacterial-, antiviral- or antifungal agents (Figure 2) [14,15]. Monastrol (4), a cell-permeable small molecule inhibitor, was introduced in 1999 [16]. Another important derivative is Piperastrol (5), which was proved to be effective against cancer cell lines [17]. As for the closely related 3,4-dihydropyrimidin-2(1*H*)-one phosphonate derivatives (6), the anti-inflammatory effect was investigated [18].

Figure 1. Biologically active heterocyclic phosphonates.

Figure 2. 3,4-Dihydropyrimidin-2(1H)-one derivatives.

One of the most useful tools for the preparation of heterocyclic phosphonates is their synthesis via multicomponent reactions (MCR) [19]. These transformations have several benefits, such as the high atom economy, the fast and simple accomplishment, and the ability to save time and energy [20]. In addition, they usually mean a suitable way for creating large molecular libraries. The efficiency of the MCRs can be further improved by the microwave (MW) technique [21,22]. In most cases, applying MW irradiation, the reactions are faster and more selective, and it allows to reach higher yields as compared to the conventionally heated experiments [23,24]. Moreover, it is usually suitable for carrying out solvent- and/or catalyst-free reactions. Due to these advantages, MW-assisted MCRs may be ideal for the rapid and efficient synthesis of new chemical libraries.

One of the well-known examples of MCRs is the three-component Biginelli reaction, in which a β -ketocarboxylic ester (7), an aldehyde and a urea derivative react in a one-pot manner to form dihydropyrimidin-2(1H)-ones (8) (Scheme 1).

Scheme 1. Biginelli reaction of β -ketocarboxylic esters, aldehydes, and urea derivatives.

Although the Biginelli reaction of regular β -ketocarboxylic acid esters is a widely investigated process [25,26], there are only a few examples for the condensation of β -ketophosphonates [18,27,28]. In order to compare the reactivity of the two different CH-acidic moieties, Chebil and co-workers studied the reaction of β -keto- α -carbethoxyphosphonate derivatives (9), aldehydes and urea in the presence of acetic acid in ethanol (Scheme 2) [29].

It was found that only the carboxyl CH-acidic function was reactive, resulting in 5-carbethoxy-6-phosphonomethyl-3,4-dihidropirimidin-2(1*H*)-ones (**10**) as the products. These experiments predicted a significant reactivity difference between β -ketophosphonates and β -ketocarboxylic esters.

Scheme 2. Condensation of β -keto- α -carbethoxyphosphonates (**9**), aldehydes and urea.

In the literature, only three examples were reported on the Biginelli reaction of β -ketophosphonates. The condensation of diethyl or dimethyl (2-oxopropyl)phosphonate, aromatic aldehydes and urea was carried out in the presence of 50 mol% of *p*-toluene sulfonic acid (PTSA) in acetonitrile [27], 5 mol% of $Yb(OTf)_3$ in toluene [28], or 15 mol% of $Zn(OTf)_2$ in toluene [18]. In all cases, urea was used in excess of 1.5 equivalents. The current literature methods only enable the synthesis of dihydropyrimidin-2(1*H*)-one phosphonate derivatives applying long reaction times (3–24 h) and a solvent. It should also be noted that a comprehensive study on the reaction parameters is still missing.

Based on the literature data, aliphatic aldehydes were found to be inactive in the three-component reaction [27,28]. The condensation of (2-oxopropyl)phosphonate and urea was carried out with propionaldehyde or butyraldehyde, and no product was detected [28].

In this paper, our aim was to study and optimize the Biginelli reaction of diethyl (2-oxopropyl)phosphonate, benzaldehyde and urea in respect of the reaction conditions (e.g., the heating method, the catalyst type, the solvent type, the temperature, the reaction time and the molar ratio of the starting materials). Other goals were to extend the synthesis for further β -ketophosphonates, aromatic aldehydes and urea derivatives, and the characterization on the novel dihydropyrimidin-2(1*H*)-one phosphonates by NMR spectroscopy and HRMS. We also aimed at elaborating the analogous condensation starting from aliphatic aldehydes as novel substrates.

2. Results and Discussion

At first, the model reaction of diethyl (2-oxopropyl)phosphonate, benzaldehyde and urea was investigated (Table 1). The condensation was followed by ^{31}P NMR spectroscopy, the crude products were analyzed by High Performance Liquid Chromatography Mass Spectrometry (HPLC-MS). The first experiments were performed reacting the three components at a molar ratio of 1:1:1.5 in an oil bath at the boiling point of acetonitrile (MeCN) (82 °C) for 4 h (Table 1/Entries 1–6). Applying 50 mol% of PTSA as a catalyst, only 9% of the desired 5-diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**11a**) was obtained, and a by-product containing a styryl group at the position of six (**12a**) was detected in 2% (Table 1/Entry 1). The by-product formation will be discussed later in details. In the next series of experiments, 15 mol% of scandium-, ytterbium- or zinc triflate was tried out as a catalyst (Table 1/Entries 2–4). Among them, $Zn(OTf)_2$ was the most efficient, the proportion of the target compound (**11a**) was 45% (Table 1/Entry 4). In case of $Sc(OTf)_3$ and $Yb(OTf)_3$, 5% and 24% of the dihydropyrimidin-2(1*H*)-one (**11a**) was formed, respectively (Table 1/Entries 2 and 3). After that, the effect of the $Zn(OTf)_2$ amount was investigated (Table 1/Entries 2, 5 and 6). Carrying out the reaction in the presence of 10 mol% of $Zn(OTf)_2$, the conversion was only 35% (Table 1/Entry 5), while 20 mol% of the catalyst did not change the composition as compared to the condensation catalyzed by 15 mol% of $Zn(OTf)_2$ (Table 1/Entry 6). Then, the model reaction was studied at a higher temperature of 100 °C (Table 1/Entry 7). After 3 h, 47% of product **11a** and 10%

of by-product **12a** were formed. Performing the condensation in toluene (PhMe) under the same conditions, the ratio of product **11a** and by-product **12a** increased to 52% and 16%, respectively (Table 1/Entry 8). A solvent-free variation was also carried out at 100 °C for 3 h, when 27% of diethyl (2-oxopropyl)phosphonate (**A**), 59% of dihydropyrimidin-2(1H)-one (**11a**) and 14% of 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-one (**12a**) were present in the reaction mixture (Table 1/Entry 9). Based on the results, the reaction was more efficient in the absence of solvent. After that, the three-component reaction was studied under MW irradiation (Table 1/Entries 9–16). Performing the condensation in the presence of 15 mol% of Zn(OTf)₂ at 100 °C for 2 h without any solvent in a MW reactor, the conversion was already 72%, and the mixture comprised 66% of product **11a** and 6% of by-product **12a** (Table 1/Entry 10). In order to study the influence of the MW irradiation, the reaction was also carried out in the absence of any catalyst, and the formation of 33% of product **11a** was observed (Table 1/Entry 11). However, the catalyst-free MW-assisted variation did not reach the conversion value of the catalyzed reaction, the influence of the MW irradiation was significant, which also confirms the efficiency of the MW heating for MCRs as described in the Literature part. Increasing the reaction time from 2 h to 4 h, and using 15 mol% of Zn(OTf)₂, the proportion of the desired compound (**11a**) (66% and 71%, respectively) did not increase significantly (Table 1/Entry 10 and Entry 12). After that, the molar ratio of the starting materials was optimized (Table 1/Entry 13–16). Applying 2 equivalents of urea, the ratio of the dihydropyrimidin-2(1H)-one phosphonate (**11a**) increased to 73% (Table 1/Entry 13), while with 2.5 equivalents of urea, the composition remained almost the same (74%) (Table 1/Entry 14). Then the molar ratio of benzaldehyde was increased using 2 equivalents of the urea (Table 1/Entries 15 and 16). Carrying out the reaction with 1.2 equivalents of benzaldehyde, the conversion was almost complete, and the proportion of the target product (**11a**) was 82% (Table 1/Entry 15). Using 1.5 equivalents of benzaldehyde, a conversion of 100% was achieved (Table 1/Entry 16), and 89% of product **11a** and 11% of by-product **12a** were formed. The desired dihydropyrimidin-2(1H)-one phosphonate (**11a**) was isolated in a yield of 75% after column chromatography. The optimized conditions include using 1.5 equivalents of benzaldehyde and 2 equivalents of urea in the presence of 15 mol% of Zn(OTf)₂ at 100 °C for 2 h under solvent-free MW conditions (Table 1/Entry 16).

In most of the experiments, formation of the 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-one (**12a**) was observed, which can probably be considered as a by-product of the Biginelli reaction of β -ketophosphonates, however, it was not known in the literature. The mechanism of its formation may be similar to the by-product formation in the regular Biginelli condensation reported by Zang and co-workers [30]. The proposed mechanism of the formation can be seen in Scheme 3. As the first step, the Zn(OTf)₂ catalyst initiates the formation of intermediate **I**, which goes into an aldol condensation with the remaining benzaldehyde in the reaction mixture to form intermediate **II**. After losing a water molecule from intermediate **II**, the 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-one (**12a**) by-product is formed.

Table 1. Biginelli reaction of diethyl (2-oxopropyl)phosphonate, benzaldehyde and urea.

Entry	Mode of Heating	A:B:C [equiv.]	Catalyst	Solvent	T [°C]	t [h]	Composition [%] ^a		
1	Δ	1:1:1.5	50% PTSA	MeCN	82	4	89	9	2
2	Δ	1:1:1.5	15% Sc(OTf) ₃	MeCN	82	4	95	5	0
3	Δ	1:1:1.5	15% Yb(OTf) ₃	MeCN	82	4	76	24	0
4	Δ	1:1:1.5	15% Zn(OTf) ₂	MeCN	82	4	54	45	1
5	Δ	1:1:1.5	10% Zn(OTf) ₂	MeCN	82	4	65	35	0
6	Δ	1:1:1.5	20% Zn(OTf) ₂	MeCN	82	4	54	45	1
7	Δ	1:1:1.5	15% Zn(OTf) ₂	MeCN	100	3	43	47	10
8	Δ	1:1:1.5	15% Zn(OTf) ₂	PhMe	100	3	32	52	16
9	Δ	1:1:1.5	15% Zn(OTf) ₂	—	100	3	27	59	14
10	MW	1:1:1.5	15% Zn(OTf) ₂	—	100	2	28	66	6
11	MW	1:1:1.5	—	—	100	2	55	33	12
12	MW	1:1:1.5	15% Zn(OTf) ₂	—	100	4	24	71	5
13	MW	1:1:2	15% Zn(OTf) ₂	—	100	2	23	73	4
14	MW	1:1:2.5	15% Zn(OTf) ₂	—	100	2	21	74	5
15	MW	1:1.2:2	15% Zn(OTf) ₂	—	100	2	7	84	9
16	MW	1:1.5:2	15% Zn(OTf) ₂	—	100	2	0	89 ^b	11

^a Based on ³¹P NMR. ^b An isolated yield of 75% was obtained.

Scheme 3. Proposed mechanism of the formation of compound **12a**.

As a structure proving synthesis, 5-diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**11a**) was reacted with 2 equivalents of benzaldehyde in acetonitrile at 82 °C for 24 h in the presence of 10 mol% of Zn(OTf)₂ (Scheme 4). The 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-one (**12a**) could be isolated from the reaction mixture, and it was characterized by ³¹P, ¹H and ¹³C NMR spectroscopy, as well as HRMS. The analytical data were identical to the observed signals of the by-product during the Biginelli reactions.

Scheme 4. Structure proving synthesis of by-product **12a**.

Next, the MW-assisted Biginelli reaction was extended to various β -ketophosphonates (diethyl and dimethyl (2-oxopropyl)phosphonate) and to a series of aromatic aldehydes (benzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, 2-fluoro-4-iodobenzaldehyde, 3-methylbenzaldehyde, 4-hydroxybenzaldehyde, 4-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde) (Scheme 5). The solvent-free condensations were performed applying the optimized parameters (15 mol% $\text{Zn}(\text{OTf})_2$, 100 °C, 2 h) under MW conditions. Overall, 20 dihydropyrimidin-2(1*H*)-one phosphonate derivatives (**11a–j** and **13a–j**) were synthesized in yields of 56–81% after column chromatography, from which 14 derivatives (**11b**, **11c**, **11e–h**, **11j**, **13b**, **13c**, **13e–h** and **13j**) are new compounds. Although the yields of the Biginelli reaction were slightly influenced by the reactivity of the different aromatic aldehydes, the outcome was almost independent from the starting β -ketophosphonate.

Scheme 5. Biginelli reaction of diethyl or dimethyl (2-oxopropyl)phosphonate, substituted benzaldehydes and urea.

The Biginelli reaction of β -ketophosphonates (diethyl and dimethyl (2-oxopropyl) phosphonate) was also investigated with benzaldehyde and *N*-methylurea (Scheme 6). Applying the optimal conditions, the new *N*-Me-dihydropyrimidin-2(1*H*)-one-phosphonates (**14a** and **14b**) could be synthesized in yields of 56% and 53%, respectively.

^a Isolated yield.

Scheme 6. Biginelli reaction of β -ketophosphonates, benzaldehyde and *N*-methylurea.

According to literature reports, aliphatic aldehydes are not suitable substrates in the Biginelli reaction starting from β -ketophosphonates [27,28]. However, one of our aims was to accomplish the condensation with aliphatic aldehydes as well (Scheme 7). At first, the reaction of diethyl (2-oxopropyl)phosphonate, 1.5 equivalents of butyraldehyde and 2 equivalents of urea was carried out in the absence of any solvent applying the optimized conditions (15 mol% $\text{Zn}(\text{OTf})_2$, 100 °C, 2 h) under MW irradiation. The 4-propyl-dihydropyrimidin-2(1*H*)-one phosphonate (**15a**) could be synthesized in a yield of 41% (Scheme 6). Then, the condensation was extended to dimethyl (2-oxopropyl)phosphonate and isovaleraldehyde as well. Utilizing the MW-assisted synthesis developed, four novel 4-alkyl-dihydropyrimidin-2(1*H*)-one phosphonates (**15a,b** and **16a,b**) were prepared in yields of 41–43%.

^a Isolated yield.

Scheme 7. Biginelli reaction of diethyl or dimethyl (2-oxopropyl)phosphonate, aliphatic aldehydes and urea.

The MW-assisted approach developed is an efficient and simple methodology for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates by the Biginelli reaction of β -ketophosphonates, which apply milder, faster, and greener reaction conditions compared to the previous reports [18,27,28]. Besides a comprehensive optimization, we have provided

exact product compositions, including the by-product containing a styryl group at the position of six (**12a**).

3. Materials and Methods

3.1. General

All chemicals were acquired from Fluorochem Ltd., Hadfield, UK and used without further purification, e.g., diethyl (2-oxopropyl)phosphonate (95% purity), dimethyl (2-oxopropyl)phosphonate (97% purity), urea (>99% purity), benzaldehyde (>98% purity), zinc triflate (anhydrous, 98% purity).

The reactions under conventional heating were carried out in an oil bath. The microwave-assisted experiments were performed in a 300 W CEM[®] Discover[®] focused microwave reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller using 5–20 W irradiation under isothermal conditions.

HPLC-MS measurements were performed with an Agilent 1200 liquid chromatography system coupled with a 6130 quadrupole mass spectrometer equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). Analysis was performed at 40 °C on a Gemini C18 column (150 mm × 4.6 mm, 3 µm; Phenomenex, Torrance, CA, USA) with a mobile phase flow rate of 0.6 mL/min. Composition of eluent A was 0.1% (NH₄)(HCOO) in water; eluent B was 0.1% (NH₄)(HCOO) and 8% water in acetonitrile. 0–3 min. 5% B, 3–13 min. gradient, 13–20 min. 100% B. The injection volume was 5 µL. The chromatographic profile was registered at 222 nm. The MSD operating parameters were as follows: positive ionization mode, scan spectra from m/z 120 to 1200, drying gas temperature 300 °C, nitrogen flow rate 10 L/min, nebulizer pressure 60 psi, capillary voltage 4000 V.

High resolution mass spectrometric measurements were performed using a Sciex 5600+ Q-TOF mass spectrometer (AB Sciex UK Limited, Warrington, UK) in positive electrospray mode.

The ³¹P, ¹H, ¹³C, NMR spectra (see in Supplementary Materials) were taken in DMSO-D₆ solution on a Bruker AV-300 spectrometer (Bruker Scientific LLC, Billerica, MA, USA) operating at 121.5, 300 and 75.5 MHz, respectively. Chemical shifts are downfield relative to 85% H₃PO₄ and TMS. Non-equivalence effects were observed in the ¹H and ¹³C{¹H} NMR spectra. Corresponding pairs of resonances were marked with (I) and (II), respectively.

3.2. General Procedure for the Synthesis of 5-Diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11a**) under Thermal Heating

A mixture of 1.0 mmol (0.19 mL) diethyl (2-oxopropyl)phosphonate, 1.0 mmol (0.10 mL) benzaldehyde, 1.5 mmol (0.09 g) urea and catalyst [*p*-toluenesulfonic acid (0.50 mmol, 0.10 g) or zinc triflate (0.10 mmol, 0.04 g or 0.15 mmol, 0.05 g or 0.20 mmol, 0.07 g) or scandium triflate (0.15 mmol, 0.07 g) or ytterbium triflate (0.15 mmol, 0.09 g)] in 2 mL of acetonitrile, toluene or without any solvent was heated at 82–110 °C for 2–4 h in a tube in an oil bath. The volatile components were removed in vacuum, and the residue was analysed by ³¹P NMR and HPLC-MS.

3.3. General Procedure for the Synthesis of 5-Diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11a**) in a Microwave Reactor

A mixture of 1.0 mmol (0.19 mL) diethyl (2-oxopropyl)phosphonate, 1.0 mmol (0.10 mL), 1.5 mmol (0.15 mL) or 2.0 mmol (0.21 mL) benzaldehyde, 1.5 mmol (0.09 g), 2 mmol (0.12 g) or 2.5 mmol (0.15 g) urea and 0.15 mmol (0.05 g) zinc triflate was irradiated in a sealed tube at 100 °C for 2–4 h in a CEM Microwave reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller. The volatile components were removed in vacuum, and the residue was analyzed by ³¹P NMR and HPLC-MS.

3.4. General Procedure for the Synthesis of 5-Phosphonato-3,4-dihydropyrimidin-2(1H)-one (**11**, **13–16**) Derivatives

A mixture of 1.0 mmol β-ketophosphonate (diethyl (2-oxopropyl)phosphonate (0.19 mL) or 0.14 mL dimethyl (2-oxopropyl)phosphonate), 1.5 mmol aldehyde (0.15 mL benzalde-

hyde, 0.17 mL 2-chlorobenzaldehyde, 0.17 mL 3-chlorobenzaldehyde, 0.17 mL 4-chlorobenzaldehyde, 0.16 mL 4-fluorobenzaldehyde, 0.38 g 2-fluoro-4-iodobenzaldehyde, 0.18 mL 3-methylbenzaldehyde, 0.18 g 4-hydroxybenzaldehyde, 0.23 g 4-nitrobenzaldehyde, 0.29 g 3,4,5-trimethoxybenzaldehyde, 0.14 mL butyraldehyde or 0.16 mL isovaleraldehyde), 2.0 mmol urea derivative (0.12 g urea or 0.14 g *N*-methylurea) and 0.15 mmol (0.05 g) zinc triflate was irradiated in a sealed tube at 100 °C for 2 h in a CEM Microwave reactor equipped with a pressure controller. The volatile components were removed in vacuum, and the residue was analyzed by ^{31}P NMR and HPLC-MS. The 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones (**4**, **6–8**) were obtained by column chromatography using silica gel as the absorbent and dichloromethane:methanol (9:1) as the eluent, or by reversed-phase column chromatography using C18-reversed phase silica gel and the composition of eluent A was 0.1% (NH₄)(HCOO) in water; eluent B was 0.1% (NH₄)(HCOO) and 8% water in acetonitrile. The following products were thus prepared:

5-Diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (11a): Yield: 75% (0.24 g), white solid; Mp: 168–169 °C; Mp [27]: 169–170 °C; ^{31}P (DMSO-*d*₆) δ 19.8; ^{31}P (DMSO-*d*₆) δ [27] 19.1; $[\text{M} + \text{H}]^+$ _{found} = 325.1314, $[\text{M} + \text{H}]^+$ _{calculated} = 325.1317.

5-Diethoxyphosphoryl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (11b): Yield: 66% (0.24 g), white solid; Mp: 230–231 °C; ^{31}P (DMSO-*d*₆) δ 19.0; ^{13}C NMR (DMSO-*d*₆) δ 16.1 (d, $^3J_{\text{CP}}$ = 7.0, CH₃CH₂O^I), 16.6 (d, $^3J_{\text{CP}}$ = 6.4, CH₃CH₂O^{II}), 17.7 (d, $^3J_{\text{CP}}$ = 3.4, CCH₃), 52.3 (d, $^2J_{\text{CP}}$ = 15.1, CHNH), 60.8 (d, $^2J_{\text{CP}}$ = 5.0, CH₃CH₂O^I), 61.1 (d, $^2J_{\text{CP}}$ = 5.2, CH₃CH₂O^{II}), 93.1 (d, $^1J_{\text{CP}}$ = 207.0, PC=C), 128.1 (C₆), 129.5 (C₄), 129.7 (C₅), 129.8 (C₃), 132.1 (C₂), 141.6 (C₁), 149.8 (d, $^2J_{\text{CP}}$ = 21.8, PC=C), 152.4 (C=O); ^1H NMR (DMSO-*d*₆) δ 0.85 (t, J_{HH} = 7.0, 3H, CH₃CH₂O^I), 1.18 (t, J_{HH} = 7.1, 3H, CH₃CH₂O^{II}), 2.20 (d, J_{HP} = 2.0, 3H, CCH₃), 3.36–3.47 (m, 1H, CH_A, CH₃CH₂O^I), 3.59–3.76 (m, 1H, CH_B, CH₃CH₂O^I), 3.76–3.92 (m, 2H, CH₃CH₂O^{II}), 5.36 (dd, $^3J_{\text{HP}}$ = 8.5, J_{HH} = 3.3, 1H, CHNH), 7.20–7.49 (m, 4H, ArH), 7.64 (br s, 1H, NH), 9.18 (d, J_{HH} = 4.6, 1H, NH); $[\text{M} + \text{H}]^+$ _{found} = 359.0924, $[\text{M} + \text{H}]^+$ _{calculated} = 359.0927.

5-Diethoxyphosphoryl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (11c): Yield: 75% (0.27 g), light yellow solid; Mp: 170–171 °C, Mp [28]: 171–172 °C; ^{31}P (DMSO-*d*₆) δ 19.5; ^{13}C NMR (DMSO-*d*₆) δ 16.3 (d, $^3J_{\text{CP}}$ = 6.7, CH₃CH₂O^I), 16.5 (d, $^3J_{\text{CP}}$ = 6.4, CH₃CH₂O^{II}), 17.9 (d, $^3J_{\text{CP}}$ = 3.4, CCH₃), 55.1 (d, $^2J_{\text{CP}}$ = 15.2, CHNH), 61.1 (d, $^2J_{\text{CP}}$ = 5.1, CH₃CH₂O^I), 61.2 (d, $^2J_{\text{CP}}$ = 5.2, CH₃CH₂O^{II}), 93.8 (d, $^1J_{\text{CP}}$ = 206.3, PC=C), 125.6 (C₆), 126.9 (C₂), 127.9 (C₄), 130.9 (C₅), 133.4 (C₃), 147.4 (C₁), 149.3 (d, $^2J_{\text{CP}}$ = 20.7, PC=C), 152.9 (C=O); ^1H NMR (DMSO-*d*₆) δ 1.00 (t, J_{HH} = 6.3, 3H, CH₃CH₂O^I), 1.14 (t, J_{HH} = 7.0, 3H, CH₃CH₂O^{II}), 2.11 (d, J_{HP} = 2.2, 3H, CCH₃), 3.55–3.68 (m, 1H, CH_A, CH₃CH₂O^I), 3.72–3.87 (m, 3H, CH_B, CH₃CH₂O^I, CH₃CH₂O^{II}), 4.88 (dd, $^3J_{\text{HP}}$ = 8.8, J_{HH} = 3.6, 1H, CHNH), 7.15–7.45 (m, 4H, ArH), 7.70 (br s, 1H, NH), 9.19 (d, J_{HH} = 4.6, 1H, NH); ^1H NMR (CDCl₃ + DMSO-*d*₆) δ [28] 1.10 (t, J_{HH} = 6.9, 3H, CH₃CH₂O^I), 1.22 (t, J_{HH} = 6.9, 3H, CH₃CH₂O^{II}), 2.17 (s, 3H, CCH₃), 3.80–3.91 (m, 4H, CH₃CH₂O), 4.96–4.99 (m, 1H, CHNH), 7.24–7.34 (m, 3H, ArH), 7.63 (s, 1H, ArH), 8.01 (s, 1H, NH), 9.12 (s, 1H, NH); $[\text{M} + \text{H}]^+$ _{found} = 359.0916, $[\text{M} + \text{H}]^+$ _{calculated} = 359.0927.

5-Diethoxyphosphoryl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (11d): Yield: 69% (0.25 g), white solid; Mp: 120–121 °C; Mp [27]: 120–122 °C; ^{31}P (DMSO-*d*₆) δ 19.6; ^{31}P (DMSO-*d*₆) δ [27] 19.8; $[\text{M} + \text{H}]^+$ _{found} = 359.0923, $[\text{M} + \text{H}]^+$ _{calculated} = 359.0927.

5-Diethoxyphosphoryl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (11e): Yield: 79% (0.27 g), white solid; Mp: 109–110 °C; Mp [28]: 110–112 °C; ^{31}P NMR (DMSO-*d*₆) δ 19.7; ^{13}C NMR (DMSO-*d*₆) δ 16.3 (d, $^3J_{\text{CP}}$ = 6.7, CH₃CH₂O^I), 16.5 (d, $^3J_{\text{CP}}$ = 6.2, CH₃CH₂O^{II}), 17.8 (d, $^3J_{\text{CP}}$ = 3.4, CCH₃), 54.9 (d, $^2J_{\text{CP}}$ = 15.0, CHNH), 61.0 (d, $^2J_{\text{CP}}$ = 5.0, CH₃CH₂O^I), 61.1 (d, $^2J_{\text{CP}}$ = 5.1, CH₃CH₂O^{II}), 94.2 (d, $^1J_{\text{CP}}$ = 205.5, PC=C), 115.5 (d, $^2J_{\text{CF}}$ = 21.4, C₃), 129.0 (d, $^3J_{\text{CF}}$ = 8.3, C₂), 141.3 (d, J_{CF} = 2.5, C₁), 148.8 (d, $^2J_{\text{CP}}$ = 20.7, PC=C), 152.9 (C=O), 161.9 (d, $^1J_{\text{CF}}$ = 243.0, C₄); ^1H NMR (DMSO-*d*₆) δ 0.98 (t, J_{HH} = 7.0, 3H, CH₃CH₂O^I), 1.13 (t, J_{HH} = 7.0, 3H, CH₃CH₂O^{II}), 2.10 (d, J_{HP} = 2.5, 3H, CCH₃), 3.49–3.65 (m, 1H, CH_A, CH₃CH₂O^I), 3.68–3.85 (m, 3H, CH_B, CH₃CH₂O^I, CH₃CH₂O^{II}), 4.86 (dd, $^3J_{\text{HP}}$ = 8.6, J_{HH} = 3.5, 1H, CHNH),

7.10–7.22 (m, 2H, ArH), 7.24–7.37 (m, 2H, ArH), 7.65 (br s, 1H, NH), 9.15 (d, $J_{\text{HH}} = 4.7$, 1H, NH); ^1H NMR ($\text{CDCl}_3 + \text{DMSO-d}_6$) δ [28] 1.04 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.19 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.13 (s, 3H, CCH₃), 3.70–3.85 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$), 4.92 (dd, $^3J_{\text{HP}} = 8.5$, $J_{\text{HH}} = 3.2$, 1H, CHNH), 7.04–7.34 (m, 4H, ArH), 7.60 (s, 1H, NH), 9.12 (d, $J_{\text{HH}} = 3.6$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 343.1221$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 343.1222$.

5-Diethoxyphosphoryl-6-methyl-4-(2-fluoro-4-iodophenyl)-3,4-dihydropyrimidin-2(1H)-one (11f): Yield: 61% (0.29 g), white solid; Mp: 103–104 °C; ^{31}P (DMSO- d_6) δ 25.9; ^{13}C NMR (DMSO- d_6) δ 20.1 (d, $^3J_{\text{CP}} = 7.0$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 20.5 (d, $^3J_{\text{CP}} = 6.2$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 21.8 (d, $^3J_{\text{CP}} = 3.5$, CCH₃), 53.3 (dd, $^2J_{\text{CP}} = 24.4$, $^3J_{\text{CF}} = 2.6$, CHNH), 64.9 (d, $^2J_{\text{CP}} = 5.1$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 65.1 (d, $^2J_{\text{CP}} = 5.2$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 96.0 (d, $^1J_{\text{CP}} = 207.0$, PC=C), 97.8 (d, $^3J_{\text{CF}} = 8.7$, C₆), 128.7 (d, $^2J_{\text{CF}} = 24.8$, C₃), 135.3 (d, $^3J_{\text{CF}} = 4.0$, C₅), 135.7 (d, $^2J_{\text{CF}} = 13.8$, C₁), 138.0 (d, $^3J_{\text{CF}} = 3.4$, C₄), 153.6 (d, $^2J_{\text{CP}} = 21.4$, PC=C), 156.3 (C=O), 163.5 (d, $^1J_{\text{CF}} = 252.0$, C₂); ^1H NMR (DMSO- d_6) δ 0.93 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.14 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.13 (d, $J_{\text{HP}} = 2.4$, 3H, CCH₃), 3.43–3.58 (m, 1H, CH_A, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.64–3.88, (m, 3H, CH_B, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 5.14 (dd, $^3J_{\text{HP}} = 8.0$, $J_{\text{HH}} = 3.2$, 1H, CHNH), 7.07 (t, $J_{\text{HH}} = 8.0$, 1H, ArH), 7.47–7.78 (m, 3H, ArH, NH), 9.16 (d, $J_{\text{HH}} = 3.0$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 469.0184$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 469.0189$.

5-Diethoxyphosphoryl-6-methyl-4-(3-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (11g): Yield: 72% (0.24 g), white solid; Mp: 192–193 °C; ^{31}P (DMSO- d_6) δ 19.9; ^{13}C NMR (DMSO- d_6) δ 16.2 (d, $^3J_{\text{CP}} = 6.8$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.5 (d, $^3J_{\text{CP}} = 6.3$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 17.9 (d, $^3J_{\text{CP}} = 3.5$, CCH₃), 21.6 (s, C₃CH₃), 55.5 (d, $^2J_{\text{CP}} = 15.1$, CHNH), 60.9 (d, $^2J_{\text{CP}} = 4.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 61.0 (d, $^2J_{\text{CP}} = 5.1$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 94.2 (d, $^1J_{\text{CP}} = 205.3$, PC=C), 124.1 (C₆), 127.6 (C₂), 128.4 (C₄), 128.7 (C₅), 137.7 (C₃), 144.9 (C₁), 148.7 (d, $^2J_{\text{CP}} = 20.7$, PC=C), 153.0 (C=O); ^1H NMR (DMSO- d_6) δ 0.98 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.14 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.11 (d, $J_{\text{HP}} = 2.3$, 3H, CCH₃), 2.28 (s, 3H, C₃CH₃), 3.51–3.60 (m, 1H, CH_A, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.72–3.82 (m, 3H, CH_B, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 4.82 (dd, $^3J_{\text{HP}} = 8.7$, $J_{\text{HH}} = 3.4$, 1H, CHNH), 7.07–7.13 (m, 3H, ArH), 7.19–7.25 (m, 1H, ArH), 7.60 (br s, 1H, NH), 9.11 (d, $J_{\text{HH}} = 3.1$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 339.1473$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 339.1473$.

5-Diethoxyphosphoryl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (11h): Yield: 62% (0.21 g), yellow solid; Mp: 186–188 °C; ^{31}P (DMSO- d_6) δ 20.1; ^{13}C NMR (DMSO- d_6) δ 16.3 (d, $^3J_{\text{CP}} = 7.0$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.6 (d, $^3J_{\text{CP}} = 6.3$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 17.8 (d, $^3J_{\text{CP}} = 3.7$, CCH₃), 55.0 (d, $^2J_{\text{CP}} = 14.8$, CHNH), 60.9 (d, $^2J_{\text{CP}} = 4.5$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 61.0 (d, $^2J_{\text{CP}} = 4.7$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 94.7 (d, $^1J_{\text{CP}} = 204.6$, PC=C), 115.4 (C₃), 127.7 (C₂), 135.6 (C₁), 148.2 (d, $^2J_{\text{CP}} = 21.0$, PC=C), 153.1 (C=O), 157.1 (C₄); ^1H NMR (DMSO- d_6) δ 0.92 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.07 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.03 (d, $J_{\text{HP}} = 2.1$, 3H, CCH₃), 3.41–3.52 (m, 1H, CH_A, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.61–3.77 (m, 3H, CH_B, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 4.67 (dd, $^3J_{\text{HP}} = 9.1$, $J_{\text{HH}} = 3.3$, 1H, CHNH), 6.53–6.72 (m, 2H, ArH), 6.93–7.09 (m, 2H, ArH), 7.45 (br s, 1H, NH), 8.98 (br s, 1H, NH), 9.28 (s, 1H, OH); $[\text{M} + \text{H}]^+_{\text{found}} = 341.1262$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 341.1266$.

5-Diethoxyphosphoryl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (11i): Yield: 73% (0.27 g), yellow solid; Mp: 218–219 °C; Mp [27]: 218–220 °C; ^{31}P (DMSO- d_6) δ 19.1; ^{31}P (DMSO- d_6) δ [27] 19.2; $[\text{M} + \text{H}]^+_{\text{found}} = 370.1166$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 370.1167$.

5-Diethoxyphosphoryl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (11j): Yield: 60% (0.25 g), white solid; Mp: 175–177 °C; ^{31}P (DMSO- d_6) δ 20.0; ^{13}C NMR (DMSO- d_6) δ 16.3 (d, $^3J_{\text{CP}} = 6.6$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.6 (d, $^3J_{\text{CP}} = 6.3$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 17.9 (d, $^3J_{\text{CP}} = 3.5$, CCH₃), 55.3 (d, $^2J_{\text{CP}} = 15.3$, CHNH), 56.3 (C₃OCH₃), 60.5 (C₄OCH₃), 61.10 (d, $^2J_{\text{CP}} = 5.2$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 61.13 (d, $^2J_{\text{CP}} = 5.6$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 94.0 (d, $^1J_{\text{CP}} = 206.7$, PC=C), 104.4 (C₂), 137.4 (C₃), 140.4 (C₄), 149.0 (d, $^2J_{\text{CP}} = 20.7$, PC=C), 152.7 (C=O), 153.2 (C₁); ^1H NMR (DMSO- d_6) δ 1.03 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.16 (t, $J_{\text{HH}} = 7.1$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 2.11 (d, $J_{\text{HP}} = 2.5$, 3H, CCH₃), 3.57–3.90 [3.63 (s, C₄OCH₃), 3.73 (s, C₃OCH₃) overlapped by the multiplet of $\text{CH}_3\text{CH}_2\text{O}$ total int. 13 H], 4.83 (dd, $^3J_{\text{HP}} = 8.9$, $J_{\text{HH}} = 3.5$, 1H, CHNH), 6.61 (s, 2H, ArH),

7.62 (br s, 1H, NH), 9.11 (d, $J_{\text{HH}} = 3.0$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 415.1631$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 415.1634$.

5-Dimethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (13a): Yield: 80% (0.24 g), white solid; Mp: 197–199 °C; Mp [27]: 198–200 °C; ^{31}P (DMSO- d_6) δ 23.0; ^{31}P (DMSO- d_6) δ [27] 22.8; $[\text{M} + \text{H}]^+_{\text{found}} = 297.1001$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 297.1004$.

5-Dimethoxyphosphoryl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (13b) Yield: 62% (0.20 g), white solid; Mp: 230–231 °C; ^{31}P (DMSO- d_6) δ 22.1; ^{13}C NMR (DMSO- d_6) δ 17.8 (d, $^3J_{\text{CP}} = 3.4$, CCH₃), 51.7 (d, $^2J_{\text{CP}} = 5.1$, CH₃O^I), 52.0 (d, $^2J_{\text{CP}} = 5.4$, CH₃O^{II}), 52.3 (d, $^2J_{\text{CP}} = 15.0$, CHNH), 91.9 (d, $^1J_{\text{CP}} = 207.4$, PC=C), 128.1 (C₆), 129.5 (C₄), 129.7 (C₅), 129.9 (C₃), 132.0 (C₂), 141.5 (C₁), 150.4 (d, $^2J_{\text{CP}} = 21.7$, PC=C), 152.3 (C=O); ^1H NMR (DMSO- d_6) δ 2.18 (s, 3H, CCH₃), 3.18 (d, $^3J_{\text{HP}} = 11.1$, 3H, CH₃O^I), 3.48 (d, $^3J_{\text{HP}} = 11.2$, 3H, CH₃O^{II}), 5.34 (dd, $^3J_{\text{HP}} = 8.4$, $J_{\text{HH}} = 3.4$, 1H, CHNH), 7.21–7.50 (m, 4H, ArH), 7.68 (br s, 1H, NH), 9.24 (d, $J_{\text{HH}} = 6.1$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 331.0612$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 331.0614$.

5-Dimethoxyphosphoryl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (13c): Yield: 75% (0.25 g), white solid; Mp: 126–127 °C; ^{31}P (DMSO- d_6) δ 22.6; ^{13}C NMR (DMSO- d_6) δ 17.9 (d, $^3J_{\text{CP}} = 3.6$, CCH₃), 51.9 (d, $^2J_{\text{CP}} = 5.0$, CH₃O^I), 52.1 (d, $^2J_{\text{CP}} = 5.3$, CH₃O^{II}), 55.0 (d, $^2J_{\text{CP}} = 15.2$, CHNH), 92.5 (d, $^1J_{\text{CP}} = 206.7$, PC=C), 125.6 (C₆), 126.9 (C₂), 127.9 (C₄), 131.0 (C₅), 133.4 (C₃), 147.3 (C₁), 149.9 (d, $^2J_{\text{CP}} = 20.5$, PC=C), 152.8 (C=O); ^1H NMR (DMSO- d_6) δ 2.09 (d, $J_{\text{HP}} = 2.4$, 3H, CCH₃), 3.36 (d, $^3J_{\text{HP}} = 11.4$, 3H, CH₃O^I), 3.44 (d, $^3J_{\text{HP}} = 11.3$, 3H, CH₃O^{II}), 4.87 (dd, $^3J_{\text{HP}} = 8.6$, $J_{\text{HH}} = 3.5$, 1H, CHNH), 7.23–7.31 (m, 2H, ArH), 7.32–7.42 (m, 2H, ArH), 7.74 (d, $J_{\text{HH}} = 2.0$, 1H, NH), 9.27 (d, $J_{\text{HH}} = 2.7$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 331.0617$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 331.0614$.

5-Dimethoxyphosphoryl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (13d): Yield: 67% (0.22 g), white solid; Mp: 226–227 °C; Mp [27]: 226–227 °C; ^{31}P (DMSO- d_6) δ 22.8; ^{31}P (DMSO- d_6) δ [27] 22.6; $[\text{M} + \text{H}]^+_{\text{found}} = 331.0613$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 331.0614$.

5-Dimethoxyphosphoryl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (13e): Yield: 81% (0.25 g), white solid; Mp: 234–235 °C; Mp [28]: 232–233 °C; ^{31}P (DMSO- d_6) δ 22.7; ^{13}C NMR (DMSO- d_6) δ 17.8 (d, $^3J_{\text{CP}} = 3.6$, CCH₃), 51.9 (d, $^2J_{\text{CP}} = 5.0$, CH₃O^I), 52.0 (d, $^2J_{\text{CP}} = 5.3$, CH₃O^{II}), 54.8 (d, $^2J_{\text{CP}} = 15.3$, CHNH), 93.0 (d, $^1J_{\text{CP}} = 206.2$, PC=C), 115.6 (d, $^2J_{\text{CF}} = 21.3$, C₃), 129.0 (d, $^3J_{\text{CF}} = 8.0$, C₂), 141.3 (d, $J_{\text{CF}} = 3.0$, C₁), 149.4 (d, $^2J_{\text{CP}} = 20.6$, PC=C), 152.8 (C=O), 161.9 (d, $^1J_{\text{CF}} = 243.2$, C₄); ^1H NMR (DMSO- d_6) δ 2.09 (d, $J_{\text{HP}} = 2.4$, 3H, CCH₃), 3.32 (d, $^3J_{\text{HP}} = 11.4$, 3H, CH₃O^I), 3.42 (d, $^3J_{\text{HP}} = 11.4$, 3H, CH₃O^{II}), 4.85 (dd, $^3J_{\text{HP}} = 8.6$, $J_{\text{HH}} = 3.4$, 1H, CHNH), 7.12–7.20 (m, 2H, ArH), 7.27–7.33 (m, 2H, ArH), 7.68 (br s, 1H, NH), 9.21 (d, $J_{\text{HH}} = 2.7$, 1H, NH); ^1H NMR (CDCl₃ + DMSO- d_6) δ [28] 2.11 (s, 3H, CCH₃), 3.34 (d, $^3J_{\text{HP}} = 11.2$, 3H, CH₃O^I), 3.39 (d, $^3J_{\text{HP}} = 11.3$, 3H, CH₃O^{II}), 4.90 (dd, $^3J_{\text{HP}} = 8.5$, $J_{\text{HH}} = 3.2$, 1H, CHNH), 7.02–7.09 (m, 2H, ArH), 7.31–7.35 (m, 2H, ArH), 7.63 (s, 1H, NH), 9.17 (d, $J_{\text{HH}} = 3.4$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 315.0910$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 315.0909$.

5-Dimethoxyphosphoryl-6-methyl-4-(2-fluoro-4-iodophenyl)-3,4-dihydropyrimidin-2(1H)-one (13f): Yield: 63% (0.28 g), white solid; Mp: 250–251 °C; ^{31}P (DMSO- d_6) δ 22.2; ^{13}C NMR (DMSO- d_6) δ 17.8 (d, $^3J_{\text{CP}} = 3.5$, CCH₃), 49.5 (dd, $^2J_{\text{CP}} = 14.9$, $^3J_{\text{CF}} = 2.9$, CHNH), 51.8 (d, $^2J_{\text{CP}} = 5.1$, CH₃O^I), 52.0 (d, $^2J_{\text{CP}} = 5.3$, CH₃O^{II}), 90.7 (d, $^1J_{\text{CP}} = 207.5$, PC=C), 94.0 (d, $^3J_{\text{CF}} = 8.2$, C₆), 124.7 (d, $^2J_{\text{CF}} = 24.7$, C₃), 131.1 (d, $^3J_{\text{CF}} = 4.1$, C₅), 131.6 (d, $^2J_{\text{CF}} = 13.9$, C₁), 134.0 (d, $^3J_{\text{CF}} = 3.1$, C₄), 150.2 (d, $^2J_{\text{CP}} = 21.1$, PC=C), 152.3 (C=O), 159.4 (d, $^1J_{\text{CF}} = 252.6$, C₂); ^1H NMR (DMSO- d_6) δ 2.11 (d, $J_{\text{HP}} = 2.4$, 3H, CCH₃), 3.27 (d, $^3J_{\text{HP}} = 11.2$, 3H, CH₃O^I), 3.44 (d, $^3J_{\text{HP}} = 11.3$, 3H, CH₃O^{II}), 5.11 (dd, $^3J_{\text{HP}} = 8.0$, $J_{\text{HH}} = 3.2$, 1H, CHNH), 7.03 (t, $J_{\text{HH}} = 8.0$, 1H, ArH), 7.48–7.77 [7.67 (br s, NH) overlapped by the multiplet of ArH total int. 3H], 9.26 (d, $J_{\text{HH}} = 2.8$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 440.9870$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 440.9876$.

5-Dimethoxyphosphoryl-6-methyl-4-(3-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (13g) Yield: 76% (0.24 g), white solid; Mp: 205–206 °C; ^{31}P (DMSO- d_6) δ 22.9; ^{13}C NMR (DMSO- d_6) δ 17.9 (d, $^3J_{\text{CP}} = 3.5$, CCH₃), 21.7 (C₃CH₃), 51.8 (d, $^2J_{\text{CP}} = 5.0$, CH₃O^I), 52.0 (d, $^2J_{\text{CP}} = 5.3$, CH₃O^{II}), 55.4 (d, $^2J_{\text{CP}} = 15.1$, CHNH), 93.0 (d, $^1J_{\text{CP}} = 205.8$, PC=C), 124.1 (C₆), 127.6 (C₂),

128.6 (C₄), 128.8 (C₅), 137.9 (C₃), 144.9 (C₁), 149.3 (d, $^2J_{CP}$ = 20.8, PC=C), 153.0 (C=O); 1H NMR (DMSO-*d*₆) δ 2.09 (d, J_{HP} = 2.5, 3H, CCH₃), 2.29 (s, 3H, C₃CH₃), 3.30 (d, $^3J_{HP}$ = 11.2, 3H, CH₃O^I), 3.42 (d, $^3J_{HP}$ = 11.5, 3H, CH₃O^{II}), 4.80 (dd, $^3J_{HP}$ = 8.8, J_{HH} = 3.5, 1H, CHNH), 7.04–7.11 (m, 3H, ArH), 7.18–7.25 (m, 1H, ArH), 7.64 (d, 1H, J_{HH} = 2.2, NH), 9.16 (d, J_{HH} = 2.7, 1H, NH); $[M + H]^+$ _{found} = 311.1160, $[M + H]^+$ _{calculated} = 311.1160.

5-Dimethoxyphosphoryl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (13h): Yield: 60% (0.19 g), white solid; Mp: 230–231 °C; ^{31}P (DMSO-*d*₆) δ 23.2; ^{13}C NMR (DMSO-*d*₆) δ 17.8 (d, $^3J_{CP}$ = 3.6, CCH₃), 51.8 (d, $^2J_{CP}$ = 5.0, CH₃O^I), 51.9 (d, $^2J_{CP}$ = 5.2, CH₃O^{II}), 54.9 (d, $^2J_{CP}$ = 15.3, CHNH), 93.5 (d, $^1J_{CP}$ = 205.3, PC=C), 115.5 (C₃), 128.2 (C₂), 135.6 (C₁), 148.8 (d, $^2J_{CP}$ = 20.8, PC=C), 153.0 (C=O), 157.2 (C₄); 1H NMR (DMSO-*d*₆) δ 2.08 (d, J_{HP} = 2.5, 3H, CCH₃), 3.28 (d, $^3J_{HP}$ = 11.2, 3H, CH₃O^I), 3.40 (d, $^3J_{HP}$ = 11.3, 3H, CH₃O^{II}), 4.72 (dd, $^3J_{HP}$ = 8.7, J_{HH} = 3.4, 1H, CHNH), 6.61–6.81 (m, 2H, ArH), 6.99–7.12 (m, 2H, ArH), 7.54 (br s, 1H, NH), 9.10 (d, J_{HH} = 2.9, 1H, NH), 9.34 (s, 1H, OH); $[M + H]^+$ _{found} = 313.0956, $[M + H]^+$ _{calculated} = 313.0953.

5-Dimethoxyphosphoryl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (13i): Yield: 68% (0.23 g), yellow solid; Mp: 235–236 °C; Mp [27]: 235–237 °C; ^{31}P (DMSO-*d*₆) δ 22.3; ^{31}P (DMSO-*d*₆) δ [27] 22.3; $[M + H]^+$ _{found} = 342.0856, $[M + H]^+$ _{calculated} = 342.0854.

5-Dimethoxyphosphoryl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (13j): Yield: 56% (0.22 g), white solid; Mp: 219–220 °C; ^{31}P (DMSO-*d*₆) δ 23.0; ^{13}C NMR (DMSO-*d*₆) δ 17.8 (d, $^3J_{CP}$ = 3.6, CCH₃), 52.0 (d, $^2J_{CP}$ = 4.7, CH₃O^I), 52.1 (d, $^2J_{CP}$ = 5.5, CH₃O^{II}), 55.1 (d, $^2J_{CP}$ = 15.1, CHNH), 56.3 (C₃OCH₃), 60.5 (C₄OCH₃), 96.8 (d, $^1J_{CP}$ = 206.6, PC=C), 104.4 (C₂), 137.4 (C₃), 140.3 (C₄), 149.6 (d, $^2J_{CP}$ = 20.6, PC=C), 153.0 (C=O), 153.2 (C₁); 1H NMR (DMSO-*d*₆) δ 2.06 (d, J_{HP} = 2.4, 3H, CCH₃), 3.37 (d, $^3J_{HP}$ = 11.2, 3H, CH₃O^I), 3.46 (d, $^3J_{HP}$ = 11.3, 3H, CH₃O^{II}), 3.61 (s, 3H, C₄OCH₃), 3.71 (s, 6H, C₃OCH₃), 4.80 (dd, $^3J_{HP}$ = 9.0, J_{HH} = 3.4, 1H, CHNH), 6.58 (s, 2H, ArH), 7.64 (br s, 1H, NH), 9.16 (d, J_{HH} = 5.5, 1H, NH); $[M + H]^+$ _{found} = 387.1322, $[M + H]^+$ _{calculated} = 387.1321.

5-Diethoxyphosphoryl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (14a): Yield: 56% (0.19 g), light yellow oil; ^{31}P (DMSO-*d*₆) δ 19.9, 20.9; ^{13}C NMR (DMSO-*d*₆) δ 16.3 (d, $^3J_{CP}$ = 6.8, CH₃CH₂O^I), 16.5 (d, $^3J_{CP}$ = 6.5, CH₃CH₂O^{II}), 17.6 (d, $^3J_{CP}$ = 3.7, CCH₃), 29.2 (NCH₃), 53.7 (d, $^2J_{CP}$ = 14.1, CHNH), 61.16 (d, $^3J_{CP}$ = 4.1, CH₃CH₂O^I), 61.23 (d, $^3J_{CP}$ = 4.9, CH₃CH₂O^{II}), 97.3 (d, $^1J_{CP}$ = 203.4, PC=C), 126.9 (C₃), 127.9 (C₄), 128.8 (C₂), 144.2 (d, $^3J_{CP}$ = 1.5, C₁), 151.1 (d, $^2J_{CP}$ = 21.5, PC=C), 153.9 (d, J_{CP} = 1.5, C=O); 1H NMR (DMSO-*d*₆) δ 1.00 (t, J_{HH} = 7.1, 3H, CH₃CH₂O^I), 1.15 (t, J_{HH} = 7.0, 3H, CH₃CH₂O^{II}), 2.32 (d, J_{HP} = 2.5, 3H, CCH₃), 3.08 (s, 3H, NCH₃), 3.51–3.68 (m, 1H, CH_A, CH₃CH₂O^I), 3.71–3.91 (m, 3H, CH_B, CH₃CH₂O^I, CH₃CH₂O^{II}), 4.84 (dd, $^3J_{HP}$ = 10.1, J_{HH} = 3.9, 1H, CHNH), 7.17–7.42 (m, 5H, ArH) 7.85 (br s, 1H, NH); $[M + H]^+$ _{found} = 339.1473, $[M + H]^+$ _{calculated} = 339.1474.

5-Dimethoxyphosphoryl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (14b): Yield: 53% (0.16 g), white solid; Mp: 127–128 °C; ^{31}P (DMSO-*d*₆) δ 23.1, 23.9; ^{13}C NMR (DMSO-*d*₆) δ 17.6 (d, $^3J_{CP}$ = 3.7, CCH₃), 30.0 (NCH₃), 52.0 (d, $^2J_{CP}$ = 5.0, CH₃O^I), 52.2 (d, $^2J_{CP}$ = 5.4, CH₃O^{II}), 53.6 (d, $^2J_{CP}$ = 14.3, CHNH), 96.0 (d, $^1J_{CP}$ = 204.4, PC=C), 126.9 (C₃), 127.9 (C₄), 128.89 (C₂), 144.2 (d, $^3J_{CP}$ = 1.4, C₁), 151.7 (d, $^2J_{CP}$ = 21.4, PC=C), 153.9 (d, J_{CP} = 1.5, C=O); 1H NMR (DMSO-*d*₆) δ 2.31 (d, J_{HP} = 2.6, 3H, CCH₃), 3.08 (s, 3H, NCH₃), 3.36 (d, $^3J_{HP}$ = 11.2, 3H, CH₃O^I), 3.46 (d, $^3J_{HP}$ = 11.4, 3H, CH₃O^{II}), 4.82 (dd, $^3J_{HP}$ = 10.1, J_{HH} = 3.9, 1H, CHNH), 7.21–7.41 (m, 5H, ArH) 7.89 (t, J_{HH} = 3.9, 1H, NH); $[M + H]^+$ _{found} = 311.1159, $[M + H]^+$ _{calculated} = 311.1161.

5-Diethoxyphosphoryl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one (15a): Yield: 41% (0.12 g), yellow oil; ^{31}P (DMSO-*d*₆) δ 20.5; ^{13}C NMR (DMSO-*d*₆) δ 14.2 (CH₂CH₂CH₃), 16.60 (d, $^3J_{CP}$ = 6.6, CH₃CH₂O^I), 16.61 (d, $^3J_{CP}$ = 6.6, CH₃CH₂O^{II}), 17.3 (CH₂CH₂CH₃), 17.7 (d, $^3J_{CP}$ = 3.7, CCH₃), 39.7 (CH₂CH₂CH₃), 51.4 (d, $^2J_{CP}$ = 16.4, CHNH), 61.0 (d, $^2J_{CP}$ = 5.3, CH₃CH₂O^I), 61.1 (d, $^2J_{CP}$ = 5.3, CH₃CH₂O^{II}), 94.3 (d, $^1J_{CP}$ = 204.2, PC=C), 148.5 (d, $^2J_{CP}$ = 21.2, PC=C), 153.6 (d, J_{CP} = 1.3, C=O); 1H NMR (DMSO-*d*₆) δ 0.86 (t, J_{HH} = 6.7, 3H, CH₂CH₂CH₃), 1.12–1.53 [1.22 (t, J_{HH} = 7.0, CH₃CH₂O) overlapped by the multiplet of

$\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$ total int. 10H], 2.00 (d, $J_{\text{HP}} = 2.6$, 3H, CCH_3), 3.71–3.82 (m, 1H, CH_A , $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.84–4.00 (m, 4H, CH_B , $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$, CHNH), 7.25 (br s, 1H, NH), 8.85 (d, $J_{\text{HH}} = 3.2$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 291.1472$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 291.1473$.

5-Dimethoxyphosphoryl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one (15b): Yield: 43% (0.11 g), yellow oil; ^{31}P (DMSO- d_6) δ 23.6; ^{13}C NMR (DMSO- d_6) δ 14.2 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 17.3 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 17.7 (d, $^3J_{\text{CP}} = 3.7$, CCH_3), 39.7 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 51.4 (d, $^2J_{\text{CP}} = 14.7$, CHNH), 52.0 (d, $^2J_{\text{CP}} = 5.2$, $\text{CH}_3\text{O}^{\text{I}}$), 52.1 (d, $^2J_{\text{CP}} = 5.4$, $\text{CH}_3\text{O}^{\text{II}}$), 93.0 (d, $^1J_{\text{CP}} = 204.6$, $\text{PC}=\text{C}$), 149.2 (d, $^2J_{\text{CP}} = 21.2$, $\text{PC}=\text{C}$), 153.6 (d, $J_{\text{CP}} = 1.3$, $\text{C}=\text{O}$); ^1H NMR (DMSO- d_6) δ 0.85 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.16–1.26 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$, CH_A), 1.30–1.46 (m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$, CH_B , $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.00 (d, $J_{\text{HP}} = 2.4$, 3H, CCH_3), 3.71–3.82 (m, 1H, CH_A , $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.57 (d, $^3J_{\text{HP}} = 11.3$, 3H, $\text{CH}_3\text{O}^{\text{I}}$), 3.57 (d, $^3J_{\text{HP}} = 11.2$, 3H, $\text{CH}_3\text{O}^{\text{II}}$), 43.71–3.79 (m, 1H, CHNH), 7.26–7.30 (m, 1H, NH), 8.92 (d, $J_{\text{HH}} = 2.8$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 263.1156$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 263.1160$.

5-Diethoxyphosphoryl-6-methyl-4-isobutyl-3,4-dihydropyrimidin-2(1H)-one (16a): Yield: 43% (0.13 g), yellow oil; ^{31}P (DMSO- d_6) δ 20.2; ^{13}C NMR (DMSO- d_6) δ 16.2 (d, $^3J_{\text{CP}} = 6.4$, $\text{CH}_3\text{CH}_2\text{O}$), 17.3 (d, $^3J_{\text{CP}} = 3.5$, CCH_3), 21.1 ($\text{CH}_2\text{CHCH}_3^{\text{I}}$), 22.7 ($\text{CH}_2\text{CHCH}_3^{\text{II}}$), 23.9 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 45.6 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 49.1 (d, $^2J_{\text{CP}} = 14.1$, CHNH), 60.5 (d, $^2J_{\text{CP}} = 5.3$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 60.7 (d, $^2J_{\text{CP}} = 5.4$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 95.0 (d, $^1J_{\text{CP}} = 204.5$, $\text{PC}=\text{C}$), 147.9 (d, $^2J_{\text{CP}} = 21.7$, $\text{PC}=\text{C}$), 153.2 ($\text{C}=\text{O}$); ^1H NMR (DMSO- d_6) δ 0.84 (d, $J_{\text{HH}} = 6.5$, 3H, $(\text{CH}_2\text{CHCH}_3^{\text{I}})$), 0.86 (d, $J_{\text{HH}} = 6.7$, 3H, $(\text{CH}_2\text{CHCH}_3^{\text{II}})$), 1.08–1.15 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, CH_A), 1.22 (t, $J_{\text{HH}} = 7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 1.39–1.46 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, CH_B), 1.68–1.77 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.01 (d, $J_{\text{HP}} = 2.4$, 3H, CCH_3), 3.72–3.80 (m, 1H, CHNH), 3.87–3.98 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$), 7.37–7.41 (m, 1H, NH), 8.88 (d, $J_{\text{HH}} = 4.8$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 305.1632$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 305.1630$.

5-Dimethoxyphosphoryl-6-methyl-4-isobutyl-3,4-dihydropyrimidin-2(1H)-one (16b): Yield: 42% (0.12 g), yellow oil; ^{31}P (DMSO- d_6) δ 20.2; ^{13}C NMR (DMSO- d_6) δ 17.3 (d, $^3J_{\text{CP}} = 3.6$, CCH_3), 21.6 ($\text{CH}_2\text{CHCH}_3^{\text{I}}$), 23.2 ($\text{CH}_2\text{CHCH}_3^{\text{II}}$), 24.3 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 46.2 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 49.5 (d, $^2J_{\text{CP}} = 14.3$, CHNH), 52.0 (d, $^2J_{\text{CP}} = 10.2$, $\text{CH}_3\text{O}^{\text{I}}$), 52.1 (d, $^2J_{\text{CP}} = 10.1$, $\text{CH}_3\text{O}^{\text{II}}$), 94.2 (d, $^1J_{\text{CP}} = 204.8$, $\text{PC}=\text{C}$), 149.0 (d, $^2J_{\text{CP}} = 21.6$, $\text{PC}=\text{C}$), 153.5 (d, $J_{\text{CP}} = 1.2$, $\text{C}=\text{O}$); ^1H NMR (DMSO- d_6) δ 0.83 (d, $J_{\text{HH}} = 6.5$, 3H, $(\text{CH}_2\text{CHCH}_3^{\text{I}})$), 0.86 (d, $J_{\text{HH}} = 6.8$, 3H, $(\text{CH}_2\text{CHCH}_3^{\text{II}})$), 1.02–1.18 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, CH_A), 1.37–1.49 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, CH_B), 1.64–1.80 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.00 (d, $J_{\text{HP}} = 2.6$, 3H, CCH_3), 3.57 (d, $^3J_{\text{HP}} = 11.3$, 3H, $\text{CH}_3\text{O}^{\text{I}}$), 3.57 (d, $^3J_{\text{HP}} = 11.2$, 3H, $\text{CH}_3\text{O}^{\text{II}}$), 3.68–3.80 (m, 1H, CHNH), 7.33–7.45 (m, 1H, NH), 8.93 (d, $J_{\text{HH}} = 3.4$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 277.1317$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 277.1317$.

3.5. General Procedure for the Synthesis of 5-Diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-One (12a)

A mixture of 1.0 mmol (0.32 g) 5-diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11a**), 2.0 mmol (0.21 mL) benzaldehyde and 0.10 mmol (0.036 g) zinc triflate was heated in acetonitrile at 82 °C for 24 h in an oil bath. The volatile components were removed in vacuum, and the residue was purified by column chromatography using silica gel as the absorbent and dichloromethane:methanol (97:3) as the eluent. The following product was prepared:

5-Diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-one (12a): Yield: 25% (0.10 g), white solid; Mp: 194–195 °C; ^{31}P (DMSO- d_6) δ 18.4; ^{13}C NMR (DMSO- d_6) δ 16.2 (d, $^3J_{\text{CP}} = 6.7$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 16.6 (d, $^3J_{\text{CP}} = 6.1$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 55.6 (d, $^2J_{\text{CP}} = 13.4$, CHNH), 61.4 (d, $^2J_{\text{CP}} = 4.9$, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 61.5 (d, $^2J_{\text{CP}} = 5.0$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 98.7 (d, $^1J_{\text{CP}} = 200.8$, $\text{PC}=\text{C}$), 119.9 (d, $^3J_{\text{CP}} = 5.0$, $\text{CH}=\text{CHPh}$), 127.1 (C_3), 127.4 ($\text{C}_{3'}$), 128.1 (C_4), 129.0 (C_2), 129.49 ($\text{C}_{4'}$), 129.52 ($\text{C}_{2'}$), 133.8 (C_1), 136.4 ($\text{C}_{1'}$), 144.4 (d, $J_{\text{CP}} = 1.5$, $\text{CH}=\text{CHPh}$), 145.9 (d, $^2J_{\text{CP}} = 20.1$, $\text{PC}=\text{C}$), 153.3 ($\text{C}=\text{O}$); ^1H NMR (DMSO- d_6) δ 0.93 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 1.16 (t, $J_{\text{HH}} = 7.0$, 3H, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 3.46–3.62 (m, 1H, CH_A , $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$), 3.72–3.92 (m, 3H, CH_B , $\text{CH}_3\text{CH}_2\text{O}^{\text{I}}$, $\text{CH}_3\text{CH}_2\text{O}^{\text{II}}$), 4.97 (dd, $^3J_{\text{HP}} = 9.6$, $J_{\text{HH}} = 3.5$, 1H, CHNH), 7.20–7.55 (m, 11H,

ArH, CH=CH), 7.56–7.69 (m, 1H, CH=CH), 7.79 (br s, 1H, NH), 9.23 (d, $J_{\text{HH}} = 3.5$, 1H, NH); $[\text{M} + \text{H}]^+_{\text{found}} = 413.1631$, $[\text{M} + \text{H}]^+_{\text{calculated}} = 413.1630$.

4. Conclusions

In this paper, the synthesis of novel 3,4-dihydropyrimidin-2(1H)-one-phosphonates was elaborated by the solvent-free MW-assisted three-component condensation of β -ketophosphonates, aromatic or aliphatic aldehydes and urea derivatives. The Biginelli reaction was optimized in respect of the heating method, the type of the catalyst and solvent, the temperature, the reaction time, and the molar ratio of the starting materials. The optimized conditions were found to be 1.5 equivalents of benzaldehyde and 2 equivalents of urea in the presence of 15 mol% of $\text{Zn}(\text{OTf})_2$ at 100 °C for 2 h under solvent-free MW irradiation. The MW-assisted method developed was then extended to a range of aromatic aldehydes, β -ketophosphonates and urea derivatives to prove the wide scope and functional group tolerance of the process. The 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1H)-one, as a new by-product of the condensation, was isolated and characterized. Our MW-assisted approach made also possible the Biginelli reaction of aliphatic aldehydes, diethyl (2-oxopropyl)phosphonate and urea, which transformation was previously reported as impossible in the literature. Altogether 26 3,4-dihydropyrimidin-2(1H)-one-phosphonates of which 20 derivatives are new, were synthesized in yields of 41–81%.

Supplementary Materials: Supplementary data associated with this article are available online at <https://www.mdpi.com/2073-4344/11/1/45/s1>. Copies of ^{31}P , ^1H , and ^{13}C NMR spectra for all compounds synthesized are presented.

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