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Original article

Design, synthesis and cytotoxic evaluation of 4-methylidenepyrazolidin-3-ones

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ABSTRACT

Three series of new 4-methylidenepyrazolidin-3-ones with various substitution patterns were synthesized and tested for the cytotoxic activity against two human leukemia cell lines NALM-6 and HL-60 as well as MCF-7 breast cancer cell line. Several obtained methylidenepyrazolidinones exhibited high cytotoxic activity with IC_{50} values below 10 μM, mainly against HL-60 leukemia cell line and two of them, **18d**,**e**, displayed $IC_{50} \leq 5$ μM, against all tested cell lines. Structure–activity relationship studies revealed that the presence of phenyl substituents on both ring nitrogen atoms and vinyl or phenyl substituents in position 5 are crucial for high activity. Selected methylidenepyrazolidinones were also tested on normal human umbilical vein endothelial cells (HUVEC) and pyrazolidinone **18a** was found to be 5-fold more toxic against HL-60 than normal cells.

1. Introduction

α-Alkylidene-γ-lactone or γ-lactam scaffold constitutes the basic skeleton in many natural and synthetic compounds with diverse biological properties [1,2]. In particular, many α-alkylidene-γ-lactones **1** or γ-lactams **2** exhibit strong anticancer activities due to their ability to act as the Michael acceptors towards various bionucleophiles possessing mercapto groups, such as enzymes, other proteins or free intracellular glutathione [3–6]. Such alkylation of cellular tiols can result in the disruption of many major processes in the cells. Not surprisingly, great progress in the development of new methodologies for the synthesis of these classes of compounds can be noticed, especially from the beginning of this century. Consequently, many natural as well as synthetic α-alkylidenelactones and lactams were synthesized and their cytotoxicity was tested [7]. Also in our laboratory we have developed synthesis of several classes of new α-alkylidenelactones and lactams and many of the compounds obtained turned out to be highly potent against several cancer cell lines [7–11]. Recently, we designed a series of 4-methylideneisoxazolidin-5-ones **3** containing additional nitrogen atom in the γ-lactone ring in hope of getting compounds with enhanced biological activity. Gratifyingly, certain isoxazolidinones **3** proved to be very potent against several cancer cell lines such as human leukemia HL-60 and NALM-6 cells or breast cancer, MCF-7 and MDA-MB-231 cells [12]. Furthermore, the most active compounds have been subjected to extended biological studies which have shed light on their mode of action at the molecular level. In particular, Caspase-3 activity assay revealed that isoxazolidinones **3** were able to induce apoptosis process in time- and concentration–dependent manner. In addition, cytotoxicity data obtained for drug-sensitive and drug-resistant HL-60 ADR cells revealed that the investigated compounds were poor substrates for transport by MRP1 efflux pump, suggesting that they might be useful for treating drug-resistant tumors [13]. Also, comparative studies of 4-methylideneisoxazolidin-5-one **3a** ($R^1 = i$-Pr, $R^2 = Me$) and Parthenolide **4** – the major sesquiterpene lactone present in feverfew (Tanacetum *parthenium*) were performed [14,15]. These studies showed, for example, that both compounds dose-dependently inhibited incorporation of [^{3}H] thymidine, up-regulated Bax and down regulated Bc1-2 mRNA and the effect produced by **3a** was much stronger compared with Parthenolide. These results show that simple analogs of α-alkylidene-γ-lactones **1** containing additional nitrogen atom in the ring can be good substitutes for more complex structures isolated from plants.

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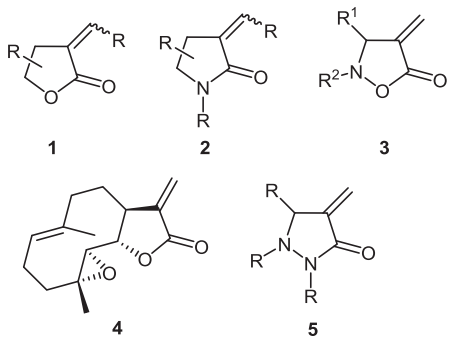


Inspired by these findings and aiming to develop novel, effective anticancer agents, we designed 4-methylidenepyrazolidin-3-ones **5** containing additional nitrogen atom in the γ-lactam ring. α-Methylidene-γ-lactams are considered as particularly promising anticancer agents because it is believed that the γ-lactam moiety can help to mitigate the biological toxicity often observed for γ-lactones [16,17]. On the other hand, we expected that the presence of an additional nitrogen atom might enhance the activity because γ-lactams usually display lower cytotoxicity than corresponding α-alkylidene-γ-lactones [8–10].

To verify these assumptions we synthesized three series of variously substituted 4-methylidenepyrazolidin-3-ones **9a**–**d**, **14a**–**f** and **18a**–**e** using methodologies recently developed in our laboratory [18] and tested the obtained compounds for the cytotoxic activity against several cancer cell lines.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of 2-aryl-1-methyl-4-methylidenepyrazolidin-3-ones *9a–d*

Synthesis of 1-methyl-4-methylidenepyrazolidin-3-ones **9a**–**d** substituted with various aryl groups in position 2 is shown in Scheme 1. Starting 1-aryl-4-diethoxyphosphoryl-1H-pyrazol-5-ols **6a**–**d**, prepared according to the literature procedure described for the corresponding 4-dimethoxyphosphorylpyrazol-5-ols [19], were N-methylated with dimethyl sulfate to give 2-aryl-1-methyl-4-diethoxyphosphorylpyrazol-3-ones **7a**–**d**. Reduction of the double bond in pyrazolones **7** using L-selectride as a reducing agent gave pyrazolidinones **8a**–**d** which were next used in Horner–Wadsworth–Emmons olefination of formaldehyde yielding the targeted 4-methylidenepyrazolidin-3-ones **9a**–**d**.

2.1.2. Synthesis of 5-alkyl or 5-aryl-1-methyl-2-phenyl-4-methylidenepyrazolidin-3-ones *14a–f*

1-Methyl-2-phenyl-4-methylidenepyrazolidin-3-ones **14a**–**f** containing various alkyl or aryl substituents in position 5 were synthesized according to Scheme 2. Reaction of ethyl 2-alkanoyl-2-diethoxyphosphorylacetates **10a**–**c** with phenylhydrazine hydrochloride (procedure a) or ethyl 2-acyl-2-diethoxyphosphorylacetates **10d**–**f** with phenylhydrazine (procedure b) furnished pyrazolols **11a**–**f** in good yields. *N*-Methylation of these compounds using methyl triflate followed by reduction of 2-aryl-1-methylpyrazol-3-ones **12a**–**f** with L-Selectride gave Horner–Wadsworth–Emmons reagents **13a**–**f**, which were obtained as single *trans* isomers or mixtures of *trans*- and *cis*-diastereoisomers in 95:5 to 85:15 ratio. In view of the planned transformation of pyrazolidinones **13** into methylidenepyrazolidinones **14a**–**f** no efforts were undertaken to separate the diastereoisomers. In the last step, pyrazolidinones **13a**–**f** were used for the olefination with formaldehyde, to provide final 5-substituted pyrazolidinones **14a**–**f** in good yields.

2.1.3. Synthesis of 5-alkyl or 5-aryl-1,2-diphenyl-4-methylidenepyrazolidin-3-ones *18a–e*

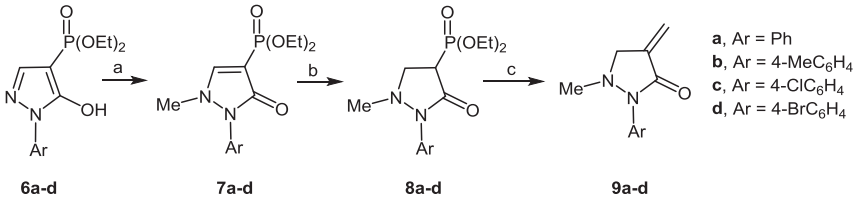
1,2-Diphenyl-4-methylidenepyrazolidin-3-ones **18a**–**e** containing alkyl or aryl substituent in position 5 were synthesized starting from 3-methoxy-2-diethoxyphosphorylacrylate **15** [20] and 1,2-diphenylhydrazine (Scheme 3). Heating the substrates in boiling toluene gave expected 4-diethoxyphosphoryl-1,2-diphenyl-1,2-dihydro-3*H*-pyrazol-3-one (**16**). Addition of Grignard reagents to pyrazolone **16** in boiling THF yielded the expected 5-substituted 4-diethoxyphosphoryl-1,2-diphenylpyrazolidin-3-ones **17a**–**e** in reasonable yields as pure *trans* or a mixtures of *trans*- and *cis*-isomers in 95:5 to 85:15 ratio. Phosphorylated pyrazolidinones **17a**–**e** were next used as Horner–Wadsworth–Emmons reagents for the olefination with formaldehyde to furnish the targeted 4-methylidene-1,2-diphenylpyrazolidin-3-ones **18a**–**e** in excellent yields.

The structures and purity of final compounds **9a**–**d**, **14a**–**f** and **18a**–**e** as well as all intermediates were confirmed by IR, ^{1}H NMR, ^{13}C NMR, ESI MS and elemental analyses.

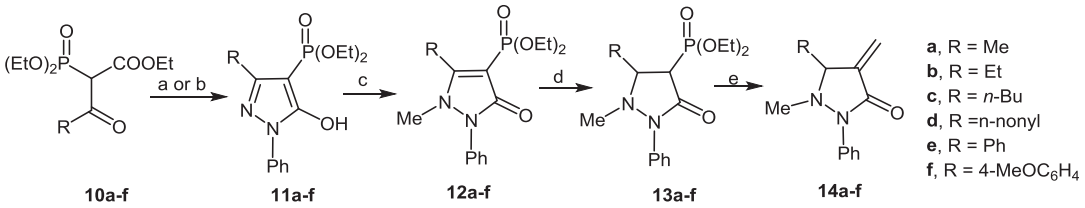
2.2. Cytotoxicity

All obtained methylidenepyrazolidin-3-ones **9a**–**d**, **14a**–**f** and **18a**–**e** were tested *in vitro* against three human cancer cell lines: leukemia NALM-6 and HL-60 as well as MCF-7 breast cancer and results are shown in Table 1. Additionally, cytotoxicities of selected 3-methylidenepyrolidin-2-ones **19** and 4-methylideneisoxazolidin-5-ones **20**, recently prepared in our laboratory, are given for comparison. Carboplatin was used as a reference compound [21].

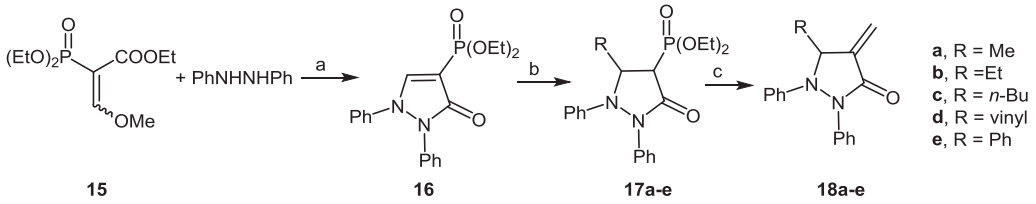
The IC_{50} values of methylidenepyrazolidin-3-ones vary dramatically and depend on the nature of substituents in the pyrazolidinone ring. The least active are pyrazolidinones **14a**–**c** with IC_{50} values over 100 μM against all three cell lines. These compounds have methyl and phenyl group attached to N-1 and N-2 nitrogen atom, respectively and short alkyl substituent (methyl, ethyl or butyl) in position 5. Majority of the remaining pyrazolidinones have moderate activity with IC_{50} values falling in the range between 91.1 and 24.4 μM. These pyrazolidinones also have



Scheme 1. *Reagents and conditions*: (a) Me_2SO_4 (1.2 equiv), DCE, 80 °C, 18 h. (b) L-Selectride (1.25 equiv), THF, −78 °C, 1 h, then r.t., 18 h. (c) $(CH_2O)_n$ (5 equiv), NaH (1.2 equiv), THF, r.t., 2 h.



Scheme 2. *Reagents and conditions*: (a) 1. $H_2NNHPh \times HCl$, H_2O, reflux, 2 h. 2. K_2CO_3 (2 equiv), 2 h, reflux, then 18 h, r.t. (b) H_2NNHPh, AcOH (2 equiv), H_2O, reflux, 3 h. (c) CF_3SO_3Me (2 equiv), DCE, 80 °C, 2 h. (d) L-Selectride (1.25 equiv), THF, −78 °C, 1 h, then r.t., 18 h. (e) $(CH_2O)_n$ (5 equiv), NaH (1.2 equiv), THF, 2 h, r.t.



Scheme 3. *Reagents and conditions*: (a) Toluene, reflux, 80 h. (b) RMgX (1.2 equiv), THF, reflux, 2 h. (c) NaH (1.2 equiv), $(CH_2O)_n$ (5 equiv), THF, r.t., 2 h.

methyl and aryl group attached to nitrogen atoms but have *n*-nonyl (**14d**), phenyl (**14e**) or no substituent (**9a**–**e**) in position 5. No clear structure activity relationship within this group can be found. However, comparison between pyrazolidinones with low (**14a**–**c**) and moderate (**9a**–**e**, **14d**,**e**) activity shows that lack of the substituent in position 5 or presence of phenyl or n-nonyl group in this position increases the activity approximately ten times against HL-60 and NALM-6 cell lines and two to three times against MCF-7 cell line. Pyrazolidinones **18a**–**e** with phenyl substituent attached to each nitrogen atom displayed the highest activity. IC_{50} values in this group vary from 29.1 μM (**18c**, against NALM-6 cells) to 0.74 μM (**18d**, against NALM-6 cells). Obviously, the presence of phenyl substituent on each nitrogen atom enhances activity significantly. Furthermore, additional unsaturated substituent in position 5 (vinyl in **18d** or phenyl in **18e**) further enhances the activity. Clearly, pyrazolidinones **18d**,**e** are the most potent compounds against all three tested cell lines with IC_{50} values ranging from 4.5 to 0.74 μM. Notably, when compared to carboplatin, these pyrazolidinones exhibited superior or comparable activity against all three cell lines tested.

Excellent anticancer activity of methylidenepyrazolidinones **18a**–**e** and in particular **18d**,**e** and even moderate activity of **9a**–**d** contrasts dramatically with low cytotoxicity usually displayed by 3-methylidenepyrolidin-2-ones. For the comparison, cytotoxicities of three methylidenepyrolidin-2-ones **19a**–**c**, tested previously in our laboratory against HL-60 and NALM-6 cell lines are given in Table 1. Clearly, introduction of the additional nitrogen atom to the lactam ring is extremely beneficial for the activity. Another important factor enhancing activity is the presence of phenyl substituents attached to both nitrogen atoms. It is also worth to mention that activity of methylidenepyrazolidinones **18d**–**e** is comparable to the activity of 4-methylideneisoxazolidin-5-ones – highly active analogs of α-methylidene-γ-lactones containing additional nitrogen atom in the lactone ring, which have been synthesized recently in our laboratory. Cytotoxicity data for selected methylideneisoxazolidin-5-ones **20a**–**c** are given in Table 1.

Finally, 4-methylidene-1,2-diphenylpyrazolidin-3-ones **18a**–**e** which showed the highest activity against all three cancer cell lines were tested on human umbilical vein endothelial cells (HUVEC), to evaluate their toxicity against normal cells (Table 1). In most cases toxicity of these compounds against normal cells was similar to the toxicity against cancer cells. However, pyrazolidinones **18a** and **18d** were 4-fold less toxic against HUVEC than against NALM-6 cancer cells and pyrazolidinone **18a** was also 5-fold less toxic against HUVEC than against HL-60 cancer cells.

3. Conclusions

Three series of 4-methylidenepyrazolidin-3-ones **9**, **14** and **18**, with different substitution patterns, were synthesized to verify the assumption that additional nitrogen atom in the γ-lactam ring might enhance, usually very low, cytotoxic activity of α-methylidene-γ-lactams. Prepared compounds were tested for the cytotoxic activity against NALM-6 and HL-60 leukemia cell lines as well as against MCF-7 breast cancer cell line. Many of them turned out to be moderate or highly active, with IC_{50} values less than 50 μM, proving that additional nitrogen atom in the ring might be crucial for high activity. Structure-activity studies revealed that the presence of phenyl group on both nitrogen atoms of the pyrazolidinone ring highly increases activity. Further enhancement in the cytotoxic activity was achieved by introducing vinyl or phenyl group in position 5. Tests on HUVEC cells showed that compounds **18a**,**d** have moderate therapeutic indexes (IC_{50}HUVEC/IC_{50}NALM-6 or IC_{50}HL-60 ~ 4–5). Currently, the most active 4-methylidenepyrazolidin-3-ones are subjected to more advanced biological screenings, to establish their mode of action. We believe that 4-methylidenepyrazolidin-3-ones are a very promising group of new anticancer agents and careful manipulations of their substitution pattern might further improve both, anticancer activity and therapeutic index.

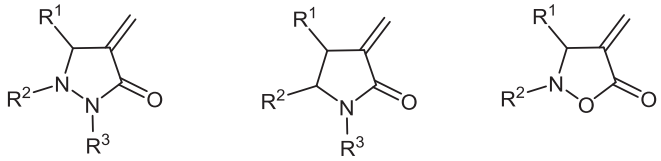
4. Materials and methods

4.1. Chemistry

4.1.1. General

NMR spectra were recorded on a Bruker DPX 250 or Bruker Avance II instrument at 250.13 MHz or 700 MHz for ^1H, 62.9 MHz or 176 MHz for ^{13}C, and 101.3 MHz for ^{31}P NMR using tetramethylsilane as internal and 85% H_3PO_4 as external standard. ^{31}P NMR spectra were recorded using broadband proton decoupling. IR spectra were recorded on a Bruker Alpha ATR spectrophotometer. Melting points were determined in open capillaries and are uncorrected. Column chromatography was performed on Aldrich® silica gel 60 (230–400 mesh). Thin-layer chromatography was performed with precoated TLC sheets of silica gel 60 F_{254} (Aldrich®).

Table 1
In vitro cytotoxic activity of pyrazolidinones **9a**–**d**, **14a**–**f** and **18a**–**e** tested on three cancer cell lines and on normal HUVEC cells.



9a-d,14a-f or **18a-e** **19a-c** **20a-c**

Compd	R^1	R^2	R^3	IC_{50}[a] (μM)			
				HL-60	NALM-6	MCF-7	HUVEC
9a	H	Me	Ph	45.7 ± 3.8	56.0 ± 8.9	56.0 ± 6.3	–[b]
9b	H	Me	4-MeC_6H_4	65.7 ± 3.2	90.1 ± 8.8	59.1 ± 6.9	–[b]
9c	H	Me	4-ClC_6H_4	38.1 ± 6.2	51.9 ± 7.8	45.2 ± 4.1	–[b]
9d	H	Me	4-BrC_6H_4	51.8 ± 6.0	62.0 ± 9.4	43.8 ± 7.5	–[b]
14a	Me	Me	Ph	531 ± 14	412 ± 22	153 ± 18	–[b]
14b	Et	Me	Ph	750 ± 31	576 ± 27	185 ± 12	–[b]
14c	*n*-Bu	Me	Ph	460 ± 18	432 ± 15	235 ± 26	–[b]
14d	*n*-nonyl	Me	Ph	49.9 ± 5.8	57.5 ± 3.9	91.1 ± 8.7	–[b]
14e	Ph	Me	Ph	40.9 ± 6.1	24.4 ± 3.8	84.4 ± 9.2	–[b]
14f	4-$MeOC_6H_4$	Me	Ph	37.3 ± 6.0	49.3 ± 2.0	75.0 ± 6.7	–[b]
18a	Me	Ph	Ph	5.85 ± 0.44	6.98 ± 0.19	12.5 ± 2.4	29.9 ± 3.6
18b	Et	Ph	Ph	8.89 ± 0.52	14.9 ± 2.9	20.0 ± 0.9	23.9 ± 4.5
18c	*n*-Bu	Ph	Ph	8.92 ± 0.50	29.1 ± 4.5	25.2 ± 3.4	27.0 ± 3.3
18d	vinyl	Ph	Ph	1.32 ± 0.21	0.74 ± 0.03	5.1 ± 0.7	2.73 ± 0.38
18e	Ph	Ph	Ph	1.61 ± 0.19	3.82 ± 0.43	4.5 ± 0.40	4.46 ± 0.49
19a[c]	H	Ph	Me	989 ± 19	552 ± 50	–[b]	–[b]
19b[c]	H	4-MeC_6H_4	Me	611 ± 18	522 ± 21	–[b]	–[b]
19c[d]	4-BrC_6H_4	Me	H	515 ± 47	439 ± 41	–[b]	–[b]
20a[e]	2-pentyl	Me	–	4.7 ± 0.8	0.34 ± 0.04	–[b]	–[b]
20b[e]	Ph	Me	–	34.8 ± 3.6	4.96 ± 0.31	–[b]	–[b]
20c[e]	4-BrC_6H_4	Me	–	5.1 ± 0.5	4.6 ± 0.5	–[b]	–[b]
Carboplatin	–	–	–	2.9 ± 0.1	0.7 ± 0.3	3.8 ± 0.45	–[b]

[a] Compound concentration required to inhibit tumor cell proliferation by 50%. Data are expressed as the mean ± SD from the concentration–response curves of at least three experiments.
[b] Not determined.
[c] Data taken from Ref. [9].
[d] Data taken from Ref. [22].
[e] Data taken from Ref. [12].

The purity of tested compounds was determined by combustion elemental analyses (CHN, elemental analyzer EuroVector 3018, Elementar Analysensysteme GmbH). Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values. MS spectra were performed on combined Waters 2695-Waters ZQ 2000 LC/MS apparatus. Reagents and starting materials were purchased from commercial vendors and used without further purification. All organic solvents were dried over appropriate drying agents and distilled prior to use. Standard syringe techniques were used for transferring dry solvents.

4.1.2. Chemical synthesis

*4.1.2.1. General procedure for the synthesis of 2-aryl-1-methyl-4-diethoxyphosphorylpyrazol-3-ones **7a**–**d**.* A solution of corresponding pyrazolol **6a**–**d** (5 mmol) and dimethyl sulfate (0.57 mL, 6 mmol) in 1,2-dichloroethane (50 mL) was heated in reaction vessel at 80 °C for 18 h. The solvent was evaporated and the crude product was purified by column chromatography (eluent: EtOAc – MeOH, 9:1).

*4.1.2.1.1. Diethyl (1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**7a**).* Yellow oil. Yield: 54%; **IR** (film): 2980, 1661, 1544, 1486, 1255, 1148, 1017, 969, 738, 546; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.29 (t, J = 7.0, 6H, ($CH_3CH_2O)_2P(O)$), 3.36 (s, 3H, CH_3), 4.10–4.17 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.26–7.30 (m, 2H, *H*–Ar), 7.38–7.40 (m, 1H, *H*–Ar), 7.44–7.49 (m, 2H, *H*–Ar), 7.93 (d, 1H, J = 4.5 Hz, *H*-5); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 16.1 (d, J = 6.9, ($CH_3CH_2O)_2P(O)$), 37.2 (s, CH_3), 62.2 (d, J = 5.5, ($CH_3CH_2O)_2P(O)$), 94.2 (d, J = 222.5, *C*-4), 126.1 (s, 2× *C*–Ar), 128.3 (s, *C*–Ar) 129.3 (s, 2× *C*–Ar), 132.7 (s, *C*–Ar), 147.8 (d, J = 18.5, *C*-5), 163.0 (d, J = 13.9, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 13.64. Anal. $C_{14}H_{19}N_2O_4P$ (C, H, N).

*4.1.2.1.2. Diethyl (1-methyl-3-oxo-2-(p-tolyl)-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**7b**).* Yellow oil. Yield: 67%; **IR** (film): 3035, 1655, 1509, 1258, 1029, 758, 542; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1, 6H, ($CH_3CH_2O)_2P(O)$), 2.28 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 4.06–4.14 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.09 (d, J = 8.2, 2H, *H*–Ar), 7.18 (d, J = 8.2, 2H, *H*–Ar), 7.84 (d, J = 4.4, 1H, *H*-5); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 16.0 (d, J = 6.9, ($CH_3CH_2O)_2P(O)$), 20.8 (s, CH_3), 36.9 (s, CH_3), 62.0 (d, J = 5.6, ($CH_3CH_2O)_2P(O)$), 93.8 (d, J = 222.2, *C*-4), 126.3 (s, 2× *C*–Ar), 129.8 (s, 2× *C*–Ar), 130.0 (s, *C*–Ar), 138.6 (s, *C*–Ar), 147.1 (d, J = 18.8, *C*-5), 162.9 (d, J = 14.0 Hz, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 12.51. Anal. $C_{15}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.1.3. Diethyl (2-(4-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**7c**).* Yellow oil. Yield: 46%; **IR** (film): 3016, 1642, 1491, 1254, 1011, 739, 551; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.33 (t, J = 7.0, 6H, ($CH_3CH_2O)_2P(O)$), 3.32 (s, 3H, CH_3), 4.12–4.25 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.23–7.27 (m, 2H, *H*–Ar), 7.41–7.50 (m, 2H, *H*–Ar), 7.93 (d, J = 4.5, 1H, *H*-5); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 16.0 (d, J = 6.8, ($CH_3CH_2O)_2P(O)$), 37.1 (s, CH_3), 62.1 (d, J = 5.6, ($CH_3CH_2O)_2P(O)$), 94.4 (d, J = 222.6, *C*-4), 126.9 (s,

2× *C*–Ar), 129.3 (s, 2× *C*–Ar), 131.3 (s, *C*–Ar), 133.8 (s, *C*–Ar), 148.8 (d, J = 18.7, *C*-5), 162.9 (d, J = 14.3, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 12.07. Anal. $C_{14}H_{18}ClN_2O_4P$ (C, H, N).

*4.1.2.1.4. Diethyl (2-(4-bromophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**7d**).* Yellow oil. Yield: 63%; **IR** (film): 2983, 1647, 1487, 1223, 1013, 742, 556; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.38 (t, J = 7.1, 6H, ($CH_3CH_2O)_2P(O)$), 3.40 (s, 3H, CH_3), 4.18–4.30 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.23–7.32 (m, 2H, *H*–Ar), 7.64–7.68 (m, 2H, *H*–Ar), 7.97 (d, J = 4.6, 1H, *H*-5); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 16.0 (d, J = 6.8, ($CH_3CH_2O)_2P(O)$), 37.2 (s, CH_3), 62.1 (d, J = 5.7, ($CH_3CH_2O)_2P(O)$), 94.6 (d, J = 222.4, *C*-4), 121.8 (s, *C*–Ar), 127.1 (s, 2× *C*–Ar), 131, 8 (s, 2× *C*–Ar), 132.3 (s, *C*–Ar), 149.0 (d, J = 18.6, *C*-5), 162.9 (d, J = 14.2, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 11.97. Anal. $C_{14}H_{18}BrN_2O_4P$ (C, H, N).

*4.1.2.2. General procedure for the synthesis of 2-aryl-4-diethoxyphosphoryl-1-methylpyrazolidin-3-ones **8a**–**d**, **13a**–**f**.* To a cooled (−78 °C) solution of the corresponding pyrazolone **7a**–**d**, **13a**–**f** (2 mmol) in THF (25 mL) was added dropwise a 1 M THF solution of L-Selectride (2.5 mmol, 2.5 mL) under argon atmosphere and the mixture was stirred at this temperature for 1 h. Then, the mixture was allowed to slowly warm to room temperature and was stirred at room temperature overnight. The reaction mixture was concentrated to a half of starting volume and quenched with 10% aq NH_4Cl. After extraction with CH_2Cl_2 (3 × 15 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (eluent: EtOAc − MeOH, 9:1).

*4.1.2.2.1. Diethyl (1-methyl-3-oxo-2-phenylpyrazolidin-4-yl) phosphonate (**8a**).* Yellow oil. Yield: 86%; **IR** (film): 2982, 1691, 1594, 1491, 1355, 1248, 1019, 963; **^{1}H NMR** (250 MHz, DMSO-d6, 100 °C): δ 1.15 (t, J = 7.2, 3H, ($CH_3CH_2O)P(O)$), 1.18 (t, J = 7.0, 3H, (CH_3CH_2O) P(O)), 2.51 (s, 3H, CH_3), 3.45–3.63 (m, 2H, 2× *H*-5), 3.72–3.85 (m, 1H, *H*-4), 4.00–4.12 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.00–7.07 (m, 1H, *H*–Ar), 7.23–7.29 (m, 2H, *H*–Ar), 7.54–7.58 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, DMSO-d6, 100 °C): δ 14.7 (d, J = 5.4, ($CH_3CH_2O)_2P(O)$), 39.6 (d, J = 146.9, *C*-4), 42.1 (s, CH_3), 50.9 (d, J = 1.6, *C*-5), 60.7 (d, J = 6.6, ($CH_3CH_2O)P(O)$), 61.1 (d, J = 6.4, ($CH_3CH_2O)P(O)$), 118.6 (s, 2× *C*–Ar), 123.4 (s, *C*–Ar) 127.4 (s, 2× *C*–Ar), 135.8 (s, *C*–Ar), 164.4 (d, J = 2.3, *C*-3); **^{31}P NMR** (101 MHz, DMSO-d6, 100 °C): δ 23.01. Anal. $C_{14}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.2.2. Diethyl (1-methyl-3-oxo-2-(p-tolyl)pyrazolidin-4-yl) phosphonate (**8b**).* Yellow oil. Yield: 82%; **IR** (film): 2982, 1689, 1614, 1508, 1354, 1248, 1018, 963; **^{1}H NMR** (250 MHz, DMSO-d6, 100 °C): δ 1.24 (t, J = 7.0, 3H, ($CH_3CH_2O)P(O)$), 1.27 (t, J = 7.0, 3H, ($CH_3CH_2O)P(O)$), 2.25 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.56 (dd, J = 14.5, 9.2, 2H, 2× *H*-5), 3.84 (dt, J = 21.5, 9.2, 1H, *H*-4), 4.05–4.20 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.13–7.20 (m, 2H, *H*–Ar), 7.48–7.55 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, DMSO-d6, 100 °C): δ 15.5 (d, J = 5.6, ($CH_3CH_2O)_2P(O)$), 19.8 (s, CH_3), 40.4 (d, J = 146.9, *C*-4), 42.9 (s, CH_3), 51.7 (d, J = 1.8, *C*-5), 61.5 (d, J = 6.7, ($CH_3CH_2O)P(O)$), 61.9 (d, J = 6.4, ($CH_3CH_2O)P(O)$), 119.7 (s, 2× *C*–Ar), 128.7 (s, 2× *C*–Ar), 133.7 (s, *C*–Ar), 134.1 (s, *C*–Ar), 164.9 (d, J = 2.3, *C*-3); **^{31}P NMR** (101 MHz, DMSO-d6, 100 °C): δ 23.13. Anal. $C_{15}H_{23}N_2O_4P$ (C, H, N).

*4.1.2.2.3. Diethyl (2-(4-chlorophenyl)-1-methyl-3-oxopyrazolidin-4-yl)phosphonate (**8c**).* Yellow oil. Yield: 80%; **IR** (film): 2981, 1694, 1587, 1485, 1348, 1249, 1018, 963; **^{1}H NMR** (250 MHz, DMSO-d6, 100 °C): δ 1.23 (t, J = 7.0, 3H, ($CH_3CH_2O)P(O)$), 1.25 (t, J = 7.0 Hz, 3H, ($CH_3CH_2O)P(O)$), 2.60 (s, 3H, CH_3), 3.57 (dd, J = 13.4, 9.2, 2H, 2× *H*-5), 3.92 (dt, J = 21.9, 9.2 Hz, 1H, *H*-4), 4.04–4.18 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.49–7.62 (m, 4H, *H*–Ar); **^{13}C NMR** (62.9 MHz, DMSO-d6, 100 °C): δ 15.4 (d, J = 5.6, ($CH_3CH_2O)_2P(O)$), 40.3 (d, J = 147.1, *C*-4), 42.8 (s, CH_3), 51.6 (d, J = 1.7, *C*-5), 61.3 (d, J = 6.7 Hz, ($CH_3CH_2O)P(O)$), 61.8 (d, J = 6.5, (CH_3CH_2O) P(O)), 115.9 (s, *C*–Ar), 120.8 (s, 2× *C*–Ar), 131.1 (s, 2× *C*–Ar), 135.8 (s, *C*–Ar), 165.5 (d, J = 2.4, *C*-3); **^{31}P NMR** (101 MHz, DMSO-d6, 100 °C): δ 22.65. Anal. $C_{14}H_{20}ClN_2O_4P$ (C, H, N).

*4.1.2.2.4. Diethyl (2-(4-bromophenyl)-1-methyl-3-oxopyrazolidin-4-yl)phosphonate (**8d**).* Yellow oil. Yield: 79%; **IR** (film): 2970, 1694, 1593, 1487, 1347, 1266, 1008, 966; **^{1}H NMR** (250 MHz, DMSO-d6, 100 °C): δ 1.23 (t, J = 7.0, 3H, ($CH_3CH_2O)P(O)$), 1.25 (t, J = 7.0, 3H, ($CH_3CH_2O)P(O)$), 2.59 (s, 3H, CH_3), 3.50–3.65 (m, 2H, 2× *H*-5), 3.82–4.03 (m, 1H, *H*-4), 4.05–4.20 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.34–7.42 (m, 2H, *H*–Ar), 7.62–7.73 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, DMSO-d6, 100 °C): δ 15.5 (d, J = 5.5, ($CH_3CH_2O)_2P(O)$), 40.4 (d, J = 146.9, *C*-4), 42.9 (s, CH_3), 51.6 (d, J = 1.9, *C*-5), 61.6 (d, J = 6.5, ($CH_3CH_2O)P(O)$), 62.0 (d, J = 6.5, ($CH_3CH_2O)P(O)$), 120.6 (s, 2× *C*–Ar), 128.1 (s, 2× *C*–Ar), 128.3 (s, *C*–Ar), 135.4 (s, *C*–Ar), 165.5 (d, J = 2.5, *C*-3); **^{31}P NMR** (101 MHz, DMSO-d6, 100 °C): δ 22.72. Anal. $C_{14}H_{20}BrN_2O_4P$ (C, H, N).

*4.1.2.2.5. Diethyl (1,5-dimethyl-3-oxo-2-phenylpyrazolidin-4-yl) phosphonate (**13a**).* Yellow oil. Yield: 75%; **IR** (film): 3209, 2981, 1693, 1356, 1225, 1195, 1018, 966, 753; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 1.36 (m, 9H, CH_3, ($CH_3CH_2O)_2P(O)$), 2.66 (s, 3H, N–CH_3), 2.91 (bd, J = 22.2 Hz, 1H, *H*-4), 3.45–3.83 (m, 1H, *H*-5), 4.14–4.38 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.09–7.18 (m, 1H, *H*–Ar), 7.28–7.38 (m, 2H, *H*–Ar), 7.65–7.78 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, DMSO-d_6, 100 °C): δ 15.5 (d, J = 5.5 Hz, ($CH_3CH_2O)_2P(O)$), 19.6 (t, J = 9.1 Hz, CH_3), 41.3 (s, N–CH_3), 48.1 (d, J = 141.9 Hz, *C*-4), 58.0 (s, *C*-5), 61.6 (d, J = 6.7 Hz, $CH_3CH_2OP(O)$), 62.1 (d, J = 6.7 Hz, $CH_3CH_2OP(O)$), 120.3 (s, 2× *C*–Ar), 124.5 (s, *C*–Ar), 128.2 (s, 2× *C*–Ar), 136.8 (s, *C*–Ar), 164.6 (d, J = 3.4 Hz, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 21.28 (15%), 21.79 (85%). Anal. $C_{15}H_{23}N_2O_4P$ (C, H, N).

*4.1.2.2.6. Diethyl (5-ethyl-1-methyl-3-oxo-2-phenylpyrazolidin-4-yl)phosphonate (**13b**).* Yellow oil. Yield: 75%; **IR** (film): 3220, 2966, 1691, 1492, 1354, 1247, 1019, 967, 753; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 1.05 (t, J = 7.3 Hz, 3H, CH_3CH_2), 1.40 (t, J = 7.1 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 1.50–1.77 (m, 2H, CH_3CH_2), 2.78 (s, 3H, N–CH_3), 2.91 (dd, J = 3.2 Hz, 24.6 Hz, 1H, *H*-4), 3.36–3.52 (m, 1H, *H*-5), 4.16–4.40 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.11–7.20 (m, 1H, *H*–Ar), 7.32–7.42 (m, 2H, *H*–Ar), 7.71–7.79 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$, trans isomer): δ 9.6 (s, CH_3CH_2), 16.3 (d, J = 5.1 Hz, $CH_3CH_2OP(O)$), 16.3 (d, J = 5.1 Hz, $CH_3CH_2OP(O)$), 29.7 (bs, CH_3CH_2), 44.5 (bs, N–CH_3), 48.7 (d, J = 137.3 Hz, *C*-4), 62.4 (d, J = 7.6 Hz, $CH_3CH_2OP(O)$), 63.4 (d, J = 6.4 Hz, $CH_3CH_2OP(O)$) 63.7 (s, *C*-5), 120.5 (s, 2× *C*–Ar), 125.0 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 137.0 (s, *C*–Ar), 164.4 (s, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 21.04 (5%), 22.04 (95%). Anal. $C_{15}H_{25}N_2O_4P$ (C, H, N).

*4.1.2.2.7. Diethyl (5-butyl-1-methyl-3-oxo-2-phenylpyrazolidin-4-yl)phosphonate (**13c**).* Yellow oil. Yield: 88%; **IR** (film): 3223, 2959, 2931, 1692, 1491, 1354, 1248, 1020, 967, 753; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 0.93 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CH_2$), 1.32–1.44 (m, 8H, $CH_3CH_2CH_2CH_2$, ($CH_3CH_2O)_2P(O)$), 1.45–1.58 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.62–1.78 (m, 2H, $CH_3CH_2CH_2CH_2$), 2.78 (s, 3H, N–CH_3), 2.91 (dd, J = 3.1 Hz, 24.6 Hz, 1H, *H*-4), 3.43–3.58 (m, 1H, *H*-5), 4.17–4.37 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.11–7.21 (m, 1H, *H*–Ar), 7.32–7.42 (m, 2H, *H*–Ar), 7.71–7.78 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$, trans isomer): δ 13.9 (s, $CH_3CH_2CH_2CH_2$), 16.3 (d, J = 5.1 Hz, $CH_3CH_2OP(O)$), 16.3 (d, J = 6.4 Hz, $CH_3CH_2OP(O)$), 22.3 (s, $CH_3CH_2CH_2CH_2$), 27.3 (s, $CH_3CH_2CH_2CH_2$), 36.6 (bs, $CH_3CH_2CH_2CH_2$), 44.4 (bs, N–CH_3), 49.0 (d, J = 139.9 Hz, *C*-4), 62.4 (s, *C*-5), 63.5 (d, J = 6.4 Hz, ($CH_3CH_2O)_2P(O)$), 120.5 (s, 2× *C*–Ar), 125.0 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 137.0 (s, *C*–Ar), 164.5 (s, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 20.19 (5%), 20.90 (95%). Anal. $C_{18}H_{29}N_2O_4P$ (C, H, N).

*4.1.2.2.8. Diethyl (1-methyl-5-nonyl-3-oxo-2-phenylpyrazolidin-4-yl)phosphonate (**13d**).* Yellow oil. Yield: 80%; **IR** (film): 3236, 2925, 2854, 1694, 1492, 1354, 1251, 1021, 965, 753, 692; **^{1}H NMR**

(250 MHz, $CDCl_3$, trans isomer): δ 0.88 (t, J = 6.9 Hz, 3H, CH_3(CH_2)$_8$), 1.17–1.77 (m, 22H, CH_3(CH_2)$_8$, (C$H_3$$CH_2O$)$_2$P(O)), 2.77 (s, 3H, N–C$H_3$), 2.90 (dd, J = 3.0 Hz, 24.7 Hz, 1H, *H*-4), 3.42–3.58 (m, 1H, *H*-5), 4.18–4.39 (m, 4H, (CH_3CH_2O)$_2$P(O)), 7.10–7.20 (m, 1H, *H*–Ar), 7.30–7.41 (m, 2H, *H*–Ar), 7.70–7.77 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$, trans isomer): δ 14.0 (s, CH_3(CH_2)$_8$), 16.3 (d, J = 6.1 Hz, ($CH_3$$CH_2O$)$_2$P(O)), 22.6 (s, C$H_2$), 25.2 (s, C$H_2$), 29.2 (s, 2× C$H_2$), 29.4 (s, 2× C$H_2$), 31.8 (s, C$H_2$), 36.7 (bs, C$H_2$), 44.4 (bs, N–C$H_3$), 49.0 (d, J = 138.3 Hz, *C*-4), 62.4 (s, *C*-5), 63.5 (d, J = 6.7 Hz, (CH_3CH_2O)$_2$P(O)), 120.5 (s, 2× *C*–Ar), 125.0 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 137.0 (s, *C*–Ar), 164.5 (d, J = 2.7 Hz, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 21.14 (5%), 21.84 (95%). Anal. $C_{23}H_{39}N_2O_4P$ (C, H, N).

*4.1.2.2.9. Diethyl (1-methyl-3-oxo-2,5-diphenylpyrazolidin-4-yl) phosphonate (**13e**).* Yellow oil. Yield: 84%; **IR** (film): 3217, 2967, 2931, 1698, 1328, 1024, 965, 726, 665; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.31–1.44 (m, 6H, (C$H_3$$CH_2OP$)$_2$(O)), 2.83 (s, 3H, N–C$H_3$), 3.28 (dd, J = 5.3 Hz, 23.4 Hz, 1H, *H*-4), 4.09–4.44 (m, 4H, (CH_3CH_2O)$_2$P(O)), 4.63 (dd, J = 5.1 Hz, 18.4 Hz, *H*-5), 7.17–7.53 (m, 8H, *H*–Ar), 7.78–7.87 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 16.2 (d, J = 6.4 Hz, C$H_3$$CH_2OP$(O)), 16.3 (d, J = 6.4 Hz, C$H_3$$CH_2OP$(O)), 44.0 (bs, N–C$H_3$), 51.5 (d, J = 139.9 Hz, *C*-4), 62.6 (d, J = 6.4 Hz, CH_3CH_2OP(O)), 63.9 (d, J = 6.4 Hz, CH_3CH_2OP(O)), 65.5 (s, *C*-5), 120.9 (s, 2× *C*–Ar), 125.5 (s, *C*–Ar), 126.0 (s, 2× *C*–Ar), 127.9 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 136.5 (s, *C*–Ar), 141.5 (bs, *C*–Ar), 163.6 (d, J = 2.5 Hz, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 21.21. Anal. $C_{20}H_{25}N_2O_4P$ (C, H, N).

*4.1.2.2.10. Diethyl [5-(4-methoxyphenyl)-1-methyl-3-oxo-2-phenylpyrazolidin-4-yl]phosphonate (**13f**).* Yellow oil. Yield: 51%; **IR** (film): 3201, 2969, 1693, 1404, 1195, 1024, 965, 735, 647; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.34 (t, J = 7.1 Hz, 3H, C$H_3$$CH_2OP$(O)), 1.38 (t, J = 7.1 Hz, 3H, C$H_3$$CH_2OP$(O)), 2.78 (s, 3H, N–C$H_3$), 3.28 (dd, J = 5.5 Hz, 23.9 Hz, 1H, *H*-4), 3.80 (s, 3H, CH_3O), 4.14–4.24 (m, 2H, CH_3CH_2OP(O)), 4.28–4.40 (m, 2H, CH_3CH_2OP(O)), 4.57 (dd, J = 5.7 Hz, 17.8 Hz, *H*-5), 6.86–6.93 (m, 2H, *H*–Ar), 7.16–7.25 (m, 1H, *H*–Ar), 7.31–7.46 (m, 4H, *H*–Ar), 7.75–7.82 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 16.2 (d, J = 6.4 Hz, C$H_3$$CH_2OP$(O)), 16.3 (d, J = 6.4 Hz, C$H_3$$CH_2OP$(O)), 43.8 (bs, N–C$H_3$), 51.3 (d, J = 125.9 Hz, *C*-4), 55.3 (s, CH_3O), 62.6 (d, J = 6.4 Hz, CH_3CH_2OP(O)), 63.8 (d, J = 6.4 Hz, CH_3CH_2OP(O)), 65.3 (s, *C*-5), 114.1 (s, 2× *C*–Ar), 121.1 (s, 2× *C*–Ar), 125.6 (s, *C*–Ar), 127.4 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 131.5 (s, *C*–Ar), 136.6 (s, *C*–Ar), 159.3 (s, *C*–Ar), 163.8 (d, J = 5.1 Hz, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 21.29. Anal. $C_{21}H_{27}N_2O_5P$ (C, H, N).

*4.1.2.3. General procedure for the synthesis of 4-diethoxyphosphoryl-1-phenylpyrazol-5-ols **11a**–**11c**.* To a suspension of 2-alkanoyl-2-diethoxyphosphorylacetates **10a**–**c** (5 mmol) in water (20 mL) phenylhydrazine hydrochloride (795 mg, 5.5 mmol) was added and the resulting mixture was refluxed for 2 h. The reaction was cooled and K_2CO_3 (1.38 g, 10 mmol) was added. Then the mixture was refluxed for 2 h, cooled to room temperature and stirred overnight at r.t. The resulting mixture was washed with Et_2O, acidified to pH = 2 with 0.5 N HCl and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent was evaporated. The resulting pyrazolols were used in next step without further purification.

*4.1.2.3.1. Diethyl (5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) phosphonate (**11a**).* Red oil. Yield: 86%; **IR** (film): 2983, 1725, 1593, 1536, 1241, 1014, 975, 758, 576; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.36 (t, J = 7.1 Hz, 6H, (C$H_3$$CH_2O$)$_2$P(O)), 2.28 (d, J = 0.8 Hz, 3H, CH_3) 3.96–4.24 (m, 4H, (CH_3CH_2O)$_2$P(O)), 7.24–7.32 (m, 1H, *H*–Ar), 7.38–7.48 (m, 2H, *H*–Ar), 7.73–7.81 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 13.6 (s, CH_3), 16.0 (d, J = 7.0 Hz, (C$H_3$$CH_2O$)$_2$P(O)), 62.3 (d, J = 4.6 Hz, CH_3CH_2O)$_2$P(O)), 83.7 (d, J = 218.4 Hz, *C*-4), 121.1 (s, 2× *C*–Ar), 126.4 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.5 (s, *C*–Ar), 149.3 (d, J = 10.4 Hz, *C*-3), 159.1 (d, J = 23.2 Hz, *C*-5); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 18.85. Anal. $C_{14}H_{19}N_2O_4P$ (C, H, N).

*4.1.2.3.2. Diethyl (3-ethyl-5-hydroxy-1-phenyl-1H-pyrazol-4-yl) phosphonate (**11b**).* Red oil. Yield: 64%; **IR** (film): 2980, 1721, 1536, 1456, 1151, 1016, 967, 758, 573; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.30 (t, J = 7.5 Hz, 3H, C$H_3$$CH_2$) 1.36 (t, J = 7.1 Hz, 6H, (C$H_3$$CH_2O$)$_2$P(O)), 2.64 (q, J = 7.5 Hz, 2H, CH_3CH_2) 4.00–4.22 (m, 4H, (CH_3CH_2O)$_2$P(O)), 7.24–7.32 (m, 1H, *H*–Ar), 7.39–7.48 (m, 2H, *H*–Ar), 7.75–7.82 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 12.5 (s, C$H_3$$CH_2$), 15.9 (d, J = 7.0 Hz, (C$H_3$$CH_2O$)$_2$P(O)), 21.8 (s, CH_3CH_2), 62.2 (d, J = 4.6 Hz, CH_3CH_2O)$_2$P(O)), 82.7 (d, J = 218.7 Hz, *C*-4), 121.2 (s, 2× *C*–Ar), 126.3 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 137.6 (s, *C*–Ar), 154.6 (d, J = 10.7 Hz, *C*-3), 159.1 (d, J = 23.2 Hz, *C*-5); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 18.71. Anal. $C_{15}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.3.3. Diethyl (3-butyl-5-hydroxy-1-phenyl-1H-pyrazol-4-yl) phosphonate (**11c**).* Brown oil. Yield: 72%; **IR** (film): 2959, 1718, 1537, 1455, 1151, 1017, 970, 758, 589; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 0.87 (t, J = 7.3 Hz, 3H, C$H_3$$CH_2CH_2CH_2$), 1.15–1.42 (m, 8H, CH_3C$H_2CH_2CH_2$, (C$H_3$$CH_2O$)$_2$P(O)), 1.50–1.70 (m, 2H, CH_3CH_2CH_2CH_2), 2.53 (t, J = 8.1 Hz, 2H, $CH_3CH_2CH_2$CH_2)) 3.93–4.17 (m, 4H, (CH_3CH_2O)$_2$P(O)), 7.15–7.24 (m, 1H, *H*–Ar), 7.31–7.40 (m, 2H, *H*–Ar), 7.66–7.73 (m, 2H, *H*–Ar), 8.50 (bs, 1H, –OH); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 13.7 (s, $CH_3CH_2CH_2CH_2$), 16.1 (d, J = 7.0 Hz, (CH_3CH_2O)$_2$P(O)), 22.5 (s, $CH_3CH_2CH_2CH_2$), 28.3 (s, $CH_3CH_2CH_2CH_2$), 30.4 (s, $CH_3CH_2CH_2CH_2$), 62.4 (d, J = 4.9 Hz, CH_3CH_2O)$_2$P(O)), 83.0 (d, J = 219.3 Hz, *C*-4), 121.5 (s, 2× *C*–Ar), 126.5 (s, *C*–Ar), 128.9 (s, 2× *C*–Ar), 137.6 (s, *C*–Ar), 153.8 (d, J = 10.7 Hz, *C*-3), 159.1 (d, J = 23.2 Hz, *C*-5); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 18.32. Anal. $C_{17}H_{25}N_2O_4P$ (C, H, N).

*4.1.2.4. General procedure for the synthesis of 4-diethoxyphosphoryl-1-phenylpyrazol-5-ols **11d**–**11f**.* A mixture of ethyl 2-acyl-2-diethoxyphosphorylacetate **10d**–**f** (10 mmol), phenylhydrazine (11 mmol), and AcOH (0.6 g, 20 mmol) was refluxed in H_2O (50 mL) for 3 h. The reaction mixture was cooled and extracted with EtOAc (2 × 30 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (eluent: EtOAc–hexane, 1:1).

*4.1.2.4.1. Diethyl (5-hydroxy-3-nonyl-1-phenyl-1H-pyrazol-4-yl) phosphonate (**11d**).* Orange oil. Yield: 72%; **IR** (film): 2922, 2851, 1624, 1500, 1455, 1179, 1018, 964, 757, 602; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 0.87 (t, J = 6.9 Hz, 3H, CH_3(CH_2)$_8$, 1.15–1.45 (m, 18H, CH_3(CH_2)$_6$$CH_2CH_2$, (C$H_3$$CH_2O$)$_2$P(O)), 1.62–1.77 (m, 2H, CH_3(CH_2)$_6$C$H_2$$CH_2$), 2.56 (t, J = 8.1 Hz, 2H, CH_3(CH_2)$_6$$CH_2CH_2$)), 3.93–4.18 (m, 4H, ($CH_3CH_2O$)$_2$P(O)), 7.12–7.21 (m, 1H, *H*–Ar), 7.26–7.36 (m, 2H, *H*–Ar), 7.65–7.77 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 14.0 (s, CH_3(CH_2)$_8$), 16.0 (d, J = 6.7 Hz, (C$H_3$$CH_2O$)$_2$P(O)), 22.6 (s, C$H_2$), 28.5 (s, C$H_2$), 28.8 (s, C$H_2$), 29.2 (s, C$H_2$), 29.4 (s, C$H_2$), 29.45 (s, C$H_2$), 29.5 (s, C$H_2$), 31.8 (s, C$H_2$), 62.1 (d, J = 3.4 Hz, CH_3CH_2O)$_2$P(O)), 82.2 (d, J = 220.8 Hz, *C*-4), 121.4 (s, 2× *C*–Ar), 125.8 (s, *C*–Ar), 128.6 (s, 2× *C*–Ar), 138.2 (s, *C*–Ar), 153.8 (d, J = 11.9 Hz, *C*-3), 160.8 (d, J = 21.6 Hz, *C*-5); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 19.33. Anal. $C_{22}H_{35}N_2O_4P$ (C, H, N).

*4.1.2.4.2. Diethyl (5-hydroxy-1,3-diphenyl-1H-pyrazol-4-yl)phosphonate (**11e**).* Orange oil. Yield: 75%; **IR** (film): 3270, 3052, 2985, 1736, 1600, 1481, 1249, 1023, 749, 689; **^{1}H NMR** (62.9 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 6H, (C$H_3$$CH_2O$)$_2$P(O)), 3.93–4.17 (m, 4H, (CH_3CH_2O)$_2$P(O)), 7.24–7.32 (m, 1H, *H*–Ar), 7.36–7.48 (m, 5H, *H*–Ar), 7.85–7.94 (m, 4H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 16.0 (d, J = 7.0 Hz, (C$H_3$$CH_2O$)$_2$P(O)), 62.6 (d, J = 4.3 Hz, CH_3CH_2O)$_2$P(O)), 81.5 (d, J = 216.2 Hz, *C*-4), 121.6 (s, 2× *C*–Ar), 126.5 (s, *C*–Ar), 127.4 (s, 2× *C*–Ar), 128.2 (s, 2× *C*–Ar), 128.6 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 132.6 (s, *C*–Ar), 138.0 (s, *C*–Ar), 151.2 (d, J = 10.1 Hz, *C*-3), 161.1 (d,

J = 30.5 Hz, *C*-5); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 19.41. Anal. $C_{19}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.4.3. Diethyl [5-hydroxy-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]phosphonate (**11f**).* Red oil. Yield: 72%; **IR** (film): 3262, 2983, 1637, 1600, 1496, 1248, 1014, 972, 754, 692; ^{1}**H NMR** (62.9 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 3.84 (s, 3H, CH_3O) 3.92–4.18 (m, 4H, ($CH_3CH_2O)_2P(O)$), 6.93–6.98 (m, 3H, *H*–Ar), 7.27–7.47 (m, 3H, *H*–Ar), 7.84–7.92 (m, 3H, *H*–Ar); ^{13}**C NMR** (62.9 MHz, $CDCl_3$): δ 15.8 (d, J = 7.3 Hz, ($CH_3CH_2O)_2P(O)$), 55.1 (s, CH_3O), 62.5 (d, J = 3.7 Hz, $CH_3CH_2O)_2P(O)$), 80.9 (d, J = 215.6 Hz, *C*-4), 113.5 (s, 2× *C*–Ar), 121.4 (s, 2× *C*–Ar), 125.2 (s, *C*–Ar), 126.3 (s, *C*–Ar), 128.6 (s, 2× *C*–Ar), 128.7 (s, 2× *C*–Ar), 138.0 (s, *C*–Ar), 150.9 (d, J = 9.8 Hz, *C*-3), 159.9 (s, *C*–Ar), 161.1 (d, J = 23.2 Hz, *C*-5); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 19.62. Anal. $C_{20}H_{23}N_2O_5P$ (C, H, N).

*4.1.2.5. General procedure for the synthesis of 4-diethoxyphosphoryl-1-methyl-2-phenylpyrazol-3-ones **12a–f**.* A solution of corresponding pyrazolol **11a–f** (5 mmol) and methyl triflate (1.10 mL, 10 mmol) in 1,2-dichloroethane (20 mL) was heated in reaction vessel at 80 °C for 2 h. The solvent was evaporated and the crude product was purified by column chromatography (eluent: EtOAc – MeOH, 9:1).

*4.1.2.5.1. Diethyl (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**12a**).* Yellow oil. Yield: 61%; **IR** (film): 2979, 1665, 1537, 1486, 1232, 1024, 939, 760, 569; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 1.28 (t, J = 7.0 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 2.53 (d, J = 1.6 Hz, 3H, CH_3), 3.21 (s, 3H, N–CH_3), 4.05–4.20 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.21–7.33 (m, 3H, *H*–Ar), 7.36–7.46 (m, 2H, *H*–Ar); ^{13}**C NMR** (62.9 MHz, $CDCl_3$): δ 12.2 (s, CH_3), 16.0 (d, J = 7.0 Hz, ($CH_3CH_2O)_2P(O)$), 34.0 (s, N–CH_3), 62.9 (d, J = 5.2 Hz, ($CH_3CH_2O)_2P(O)$), 90.8 (d, J = 224.8, *C*-4), 127.4 (s, 2× *C*–Ar), 129.7 (s, 2× *C*–Ar), 129.8 (s, *C*–Ar), 131.9 (s, *C*–Ar), 155.5 (d, J = 18.9 Hz, *C*-5), 162.9 (d, J = 13.1 Hz, *C*-3); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 13.41. Anal. $C_{15}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.5.2. Diethyl (5-ethyl-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**12b**).* Yellow oil. Yield: 60%; **IR** (film): 2980, 1661, 1522, 1488, 1235, 1018, 957, 562; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 1.13–1.32 (m, 9H, ($CH_3CH_2O)_2P(O)$, CH_3CH_2), 2.55 (q, J = 7.5 Hz, 2H, CH_3CH_2), 3.23 (s, 3H, N–CH_3), 3.97–4.17 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.15–7.33 (m, 2H, *H*–Ar), 7.33–7.45 (m, 3H, *H*–Ar); ^{13}**C NMR** (62.9 MHz, $CDCl_3$): δ 13.0 (s, CH_3CH_2), 16.2 (d, J = 6.7 Hz, ($CH_3CH_2O)_2P(O)$), 19.3 (s, CH_3CH_2), 34.0 (s, N–CH_3), 62.0 (d, J = 5.5 Hz, ($CH_3CH_2O)_2P(O)$), 92.1 (d, J = 220.2, *C*-4), 125.6 (s, 2× *C*–Ar), 127.7 (s, *C*–Ar), 129.2 (s, 2× *C*–Ar), 133.9 (s, *C*–Ar), 164.0 (d, J = 13.7 Hz, *C*-3), 164.4 (d, J = 21.9 Hz, *C*-5); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 13.33. Anal. $C_{16}H_{23}N_2O_4P$ (C, H, N).

*4.1.2.5.3. Diethyl (5-butyl-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**12c**).* Yellow oil. Yield: 57%; **IR** (film): 2929, 1659, 1523, 1490, 1233, 1018, 960, 799, 576; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CH_2$), 1.27 (t, J = 7.1 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 1.35–1.52 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.54–1.69 (m, 2H, $CH_3CH_2CH_2CH_2$), 2.94 (t, J = 7.9 Hz, 2H, $CH_3CH_2CH_2CH_2$), 3.21 (s, 3H, N–CH_3), 4.04–4.18 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.19–7.32 (m, 2H, *H*–Ar), 7.36–7.45 (m, 3H, *H*–Ar); ^{13}**C NMR** (62.9 MHz, $CDCl_3$): δ 13.6 (s, $CH_3CH_2CH_2CH_2$), 16.1 (d, J = 6.7 Hz, ($CH_3CH_2O)_2P(O)$), 22.4 (s, $CH_3CH_2CH_2CH_2$), 25.6 (s, $CH_3CH_2CH_2CH_2$), 30.8, (s, $CH_3CH_2CH_2CH_2$), 34.1 (s, N–CH_3), 61.9 (d, J = 5.5 Hz, $CH_3CH_2O)_2P(O)$), 92.4 (d, J = 221.1 Hz, *C*-4), 125.6 (s, 2× *C*–Ar), 127.7 (s, *C*–Ar), 129.2 (s, 2× *C*–Ar), 133.9 (s, *C*–Ar), 163.4 (d, J = 21.9 Hz, *C*-5), 164.1 (d, J = 14.3 Hz, *C*-3); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 13.47. Anal. $C_{18}H_{27}N_2O_4P$ (C, H, N).

*4.1.2.5.4. Diethyl (1-methyl-5-nonyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**12d**).* Yellow oil. Yield: 59%; **IR** (film): 2923, 2853, 1665, 1520, 1490, 1278, 1235, 1021, 961, 573; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 0.81 (t, J = 6.5 Hz, 3H, $CH_3(CH_2)_8$, 1.10–1.45 (m, 18H, $CH_3(CH_2)_6CH_2CH_2$, ($CH_3CH_2O)_2P(O)$), 1.55–1.70 (m, 2H, $CH_3(CH_2)_6CH_2CH_2$), 2.93 (t, J = 8.3 Hz, 2H, $CH_3(CH_2)_6CH_2CH_2$)), 3.21 (s, 3H, N–CH_3), 4.03–4.25 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.18–7.32 (m, 3H, *H*–Ar), 7.36–7.45 (m, 2H, *H*–Ar); ^{13}**C NMR** (176 MHz, $CDCl_3$): δ 13.8 (s, $CH_3(CH_2)_8$), 16.1 (d, J = 7.6 Hz, ($CH_3CH_2O)_2P(O)$), 22.4 (s, CH_2), 25.8 (s, CH_2), 28.8 (s, CH_2), 29.0 (s, CH_2), 29.1 (s, CH_2), 29.2 (s, CH_2), 29.3 (s, CH_2), 31.6 (s, CH_2), 34.2 (s, N–CH_3), 61.8 (d, J = 6.4 Hz, $CH_3CH_2O)_2P(O)$), 92.5 (d, J = 221.3 Hz, *C*-4), 125.5 (s, 2× *C*–Ar), 127.6 (s, *C*–Ar), 129.1 (s, 2× *C*–Ar), 134.0 (s, *C*–Ar), 163.6 (d, J = 22.9 Hz, *C*-5), 164.0 (d, J = 14.0 Hz, *C*-3); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 13.29. Anal. $C_{23}H_{37}N_2O_4P$ (C, H, N).

*4.1.2.5.5. Diethyl (1-methyl-3-oxo-2,5-diphenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**12e**).* Yellow oil. Yield: 65%; **IR** (film): 2981, 1659, 1486, 1221, 1016, 947, 750, 583; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 1.17 (t, J = 6.9 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 3.46 (s, 3H, N–CH_3), 4.00–4.18 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.54–7.64 (m, 6H, *H*–Ar), 7.67–7.78 (m, 4H, *H*–Ar); ^{13}**C NMR** (176 MHz, $CDCl_3$): δ 15.7 (d, J = 7.6 Hz, ($CH_3CH_2O)_2P(O)$), 35.5 (s, N–CH_3), 63.6 (s, $CH_3CH_2O)_2P(O)$), 91.0 (d, J = 225.1 Hz, *C*-4), 125.6 (s, *C*–Ar), 128.2 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 129.5 (s, 2× *C*–Ar), 130.0 (s, 2× *C*–Ar), 130.2 (s, *C*–Ar), 131.2 (s, *C*–Ar), 131.5 (s, *C*–Ar), 154.1 (d, J = 12.7 Hz, *C*-3), 161.5 (d, J = 20.3 Hz, *C*-5); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 12.05. Anal. $C_{20}H_{23}N_2O_4P$ (C, H, N).

*4.1.2.5.6. Diethyl [5-(4-methoxyphenyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]phosphonate (**12f**).* Yellow oil. Yield: 61%; **IR** (film): 2964, 1658, 1604, 1492, 1255, 1014, 792, 577; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 1.14 (t, J = 7.1 Hz, 6H, ($CH_3CH_2O)_2P(O)$), 3.00 (s, 3H, N–CH_3), 3.80 (s, 3H, CH_3O) 3.96–4.12 (m, 4H, ($CH_3CH_2O)_2P(O)$), 6.92–7.02 (m, 2H, *H*–Ar), 7.22–7.32 (m, 1H, *H*–Ar), 7.32–7.56 (m, 6H, *H*–Ar); ^{13}**C NMR** (62.9 MHz, $CDCl_3$): δ 15.2 (d, J = 7.0 Hz, ($CH_3CH_2O)_2P(O)$), 36.8 (s, N–CH_3), 54.4 (s, CH_3O), 61.2 (d, J = 5.8 Hz, $CH_3CH_2O)_2P(O)$), 95.3 (d, J = 221.7 Hz, *C*-4), 113.0 (s, 2× *C*–Ar), 119.2 (s, *C*–Ar), 123.8 (s, 2× *C*–Ar), 126.4 (s, *C*–Ar), 128.3 (s, 2× *C*–Ar), 130.5 (s, 2× *C*–Ar), 133.3 (s, *C*–Ar), 160.7 (s, *C*–Ar), 161.9 (d, J = 18.3 Hz, *C*-5), 162.6 (d, J = 14.9 Hz, *C*-3); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 12.15. Anal. $C_{21}H_{25}N_2O_5P$ (C, H, N).

*4.1.2.6. Preparation of diethyl (3-oxo-1,2-diphenyl-2,3-dihydro-1H-pyrazol-4-yl)phosphonate (**16**).* A solution of 3-methoxy-2-diethoxyphosphorylacrylate (**15**) (2.66 g, 10 mmol) and 1,2-diphenylhydrazine (1.84 g, 10 mmol) in toluene (100 mL) was heated in reaction vessel at 110 °C for 80 h. Next, the mixture was cooled and the solvent was evaporated. A crude product was purified by crystallization from Et_2O – hexane, 1:1 to give **16** (83%) as orange solid; mp 111–113 °C; **IR** (film): 2976, 1670, 1548, 1492, 1248, 1022, 971; ^{1}**H NMR** (250 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2, 6H, ($CH_3CH_2O)_2P(O)$), 4.10–4.25 (m, 4H, ($CH_3CH_2O)_2P(O)$), 7.06–7.30 (m, 10H, *H*–Ar), 8.10 (d, 1H, J = 4.6, *H*-5); ^{13}**C NMR**^{13}**C NMR** (176.0 MHz, $CDCl_3$): δ 16.0 (d, J = 6.8, ($CH_3CH_2O)_2P(O)$), 62.2 (d, J = 5.6, ($CH_3CH_2O)_2P(O)$), 97.2 (d, J = 220.4, *C*-4), 121.2 (s, 2× *C*–Ar), 123.9 (s, 2× *C*–Ar), 126.8 (s, *C*–Ar), 127.4 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 129.6 (s, 2× *C*–Ar), 134.3 (s, *C*–Ar), 136.9 (s, *C*–Ar), 148.8 (d, J = 18.9, *C*-5), 163.6 (d, J = 13.4, *C*-3); ^{31}**P NMR** (101 MHz, $CDCl_3$): δ 11.75. Anal. $C_{19}H_{21}N_2O_4P$ (C, H, N).

*4.1.2.7. General procedure for the synthesis of 4-diethoxyphosphoryl-1,2-diphenylpyrazolidin-3-ones **17a–e**.* To a solution of the 4-diethoxyphosphoryl-1,2-diphenylpyrazol-3-one **16** (745 mg, 2 mmol) in THF (15 mL) a solution of corresponding Grignard reagent (2.4 mmol) was added dropwise, under an argon atmosphere at r.t., and the resulting mixture was refluxed for 2 h. After this time the reaction mixture was quenched with H_2O (5 mL), acidified to pH ca. 3 with 10% aq HCl solution and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the

solvent was evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$ – MeOH, 98:2).

*4.1.2.7.1. Diethyl (5-methyl-3-oxo-1,2-diphenylpyrazolidin-4-yl) phosphonate (**17a**).* Yellow oil. Yield: 52%; **IR** (film): 2982, 1698, 1595, 1488, 1384, 1248, 1017, 946; **^{1}H NMR** (250 MHz, $CDCl_3$, trans and cis isomers): δ 1.09 (t, *J* = 7.1, 3H, (CH_3CH_2O)P(O)), 1.36 (t, *J* = 7.1, 3H, (CH_3CH_2O)P(O)), 1.66 (d, *J* = 6.7, 3H, CH_3, 85%), 1.76 (d, *J* = 5.7, 3H, CH_3, 15%), 2.94 (dd, *J* = 23.3, 2.8, 1H, *H*-4), 3.62–3.73 (m, 1H, (CH_3CHO)P(O)), 3.90–3.96 (m, 1H, (CH_3CHO)P(O)), 4.11–4.38 (m, 2H, (CH_3CH_2O)P(O)), 4.49–4.60 (m, 1H, *H*-5), 6.93–7.03 (m, 2H, *H*–Ar), 7.11–7.40 (m, 6H, *H*–Ar), 7.78–7.86 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$, trans isomer): δ 15.9 (d, *J* = 5.3, (CH_3CH_2O)P(O)), 16.1 (d, *J* = 6.1, (CH_3CH_2O)P(O)), 23.3 (d, *J* = 13.4, CH_3), 50.0 (d, *J* = 138.3, *C*-4), 61.6 (d, *J* = 1.8, *C*-5), 62.5 (d, *J* = 7.0, (CH_3CH_2O)P(O)), 62.9 (d, *J* = 6.7, (CH_3CH_2O)P(O)), 117.3 (s, 2× *C*–Ar), 119.0 (s, 2× *C*–Ar), 122.7 (s, *C*–Ar), 124.9 (s, *C*–Ar), 128.6 (s, 2× *C*–Ar), 128.7 (s, 2× *C*–Ar), 138.3 (s, *C*–Ar), 148.9 (s, *C*–Ar), 165.5 (d, *J* = 5.6, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 19.64 (15%), 19.73 (85%). Anal. $C_{20}H_{25}N_2O_4P$ (C, H, N).

*4.1.2.7.2. Diethyl (5-ethyl-3-oxo-1,2-diphenylpyrazolidin-4-yl) phosphonate (**17b**).* Yellow oil. Yield: 42%; **IR** (film): 2971, 1701, 1592, 1493, 1389, 1244, 1018, 955; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 0.92 (t, *J* = 7.1, 3H, CH_3CH_2), 1.18 (t, *J* = 7.2, 3H, (CH_3CH_2O) P(O)), 1.23 (t, *J* = 7.1, 3H, (CH_3CH_2O)P(O)), 1.65–1.92 (m, 2H, CH_3CH_2), 2.84 (dd, *J* = 23.8, 1.8, 1H, *H*-4), 3.39–3.49 (m, 1H, (CH_3CHO)P(O)), 3.70–3.81 (m, 1H, (CH_3CHO)P(O)), 3.98–4.13 (m, 2H, (CH_3CH_2O)P(O)), 4.16–4.29 (m, 1H, *H*-5), 6.79–6.92 (m, 2H, *H*–Ar), 7.02–7.28 (m, 6H, *H*–Ar), 7.67–7.69 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$, trans isomer): δ 10.3 (s, CH_3), 15.8 (d, *J* = 5.1, (CH_3CH_2O)P(O)), 16.1 (d, *J* = 6.0, (CH_3CH_2O)P(O)), 30.1 (d, *J* = 13.7, CH_2), 48.9 (d, *J* = 137.2, *C*-4), 62.4 (d, *J* = 7.0, (CH_3CH_2O)P(O)), 62.9 (d, *J* = 6.5, (CH_3CH_2O)P(O)), 67.2 (d, *J* = 2.0, *C*-5), 116.8 (s, 2× *C*–Ar), 118.8 (s, 2× *C*–Ar), 122.2 (s, *C*–Ar), 124.8 (s, *C*–Ar), 128.5 (s, 2× *C*–Ar), 129.2 (s, 2× *C*–Ar), 138.4 (s, *C*–Ar), 149.5 (s, *C*–Ar), 165.8 (d, *J* = 5.8, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 19.63 (10%), 19.76 (90%).Anal. $C_{21}H_{27}N_2O_4P$ (C, H, N).

*4.1.2.7.3. Diethyl (5-butyl-3-oxo-1,2-diphenylpyrazolidin-4-yl) phosphonate (**17c**).* Yellow oil, Yield: 56%; **IR** (film): 2959, 1700, 1593, 1486, 1388, 1246, 1014, 955; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 0.96 (t, *J* = 7.3, 3H, CH_3CH_2), 0.98 (t, *J* = 7.0, 3H, (CH_3CH_2O)P(O)), 1.24 (t, *J* = 7.0, 3H, (CH_3CH_2O)P(O)), 1.32–1.99 (m, 6H, $CH_3(CH_2)_3$), 2.92 (dd, *J* = 23.8, 1.7, 1H, *H*-4), 3.44–3.61 (m, 1H, (CH_3CHO)P(O)), 3.76–3.93 (m, 1H, (CH_3CHO)P(O)), 4.00–4.22 (m, 2H, (CH_3CH_2O)P(O)), 4.25–4.39 (m, 1H, *H*-5), 6.84–6.94 (m, 3H, *H*–Ar), 7.07–7.21 (m, 3H, *H*–Ar), 7.25–7.34 (m, 2H, *H*–Ar), 7.71–7.75 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$, trans isomer): δ 13.9 (s, CH_3), 15.9 (d, *J* = 5.3, (CH_3CH_2O)P(O)), 16.1 (d, *J* = 6.1, (CH_3CH_2O)P(O)), 22.3 (s, CH_2), 27.9 (s, CH_2), 36.9 (d, *J* = 13.4, CH_2), 49.2 (d, *J* = 136.9, *C*-4), 62.4 (d, *J* = 7.0, (CH_3CH_2O)P(O)), 62.9 (d, *J* = 6.4, (CH_3CH_2O)P(O)), 66.1 (d, *J* = 2.0, *C*-5), 116.8 (s, 2× *C*–Ar), 118.8 (s, 2× *C*–Ar), 122.2 (s, *C*–Ar), 124.8 (s, *C*–Ar), 128.6 (s, 2× *C*–Ar), 128.8 (s, 2× *C*–Ar), 138.5 (s, *C*–Ar), 149.4 (s, *C*–Ar), 165.9 (d, *J* = 5.8, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 19.96 (5%), 20.05 (95%).Anal. $C_{23}H_{31}N_2O_4P$ (C, H, N).

*4.1.2.7.4. Diethyl (3-oxo-1,2-diphenyl-5-vinylpyrazolidin-4-yl) phosphonate (**17d**).* Yellow oil, Yield: 83%; **IR** (film): 2960, 1698, 1591, 1492, 1388, 1244, 1012, 950; **^{1}H NMR** (250 MHz, $CDCl_3$, trans isomer): δ 1.05 (t, *J* = 7.1, 3H, (CH_3CH_2O)P(O)), 1.29 (t, *J* = 7.0, 3H, (CH_3CH_2O)P(O)), 3.07 (dd, *J* = 23.1, 2.8, 1H, *H*-4), 3.59–3.78 (m, 1H, (CH_3CHO)P(O)), 3.84–4.01 (m, 1H, (CH_3CHO)P(O)), 4.05–4.29 (m, 2H, (CH_3CH_2O)P(O)), 4.80–4.90 (m, 1H, *H*-5), 5.31 (d, *J* = 10.6, 1H, *H*–CH=CH), 5.66 (d, *J* = 16.9, 1H, *H*–CH=CH), 6.02 (ddd, *J* = 16.9, 10.6, 5.2, 1H, CH_2=C*H*), 6.87–6.99 (m, 3H, *H*–Ar), 7.07–7.23 (m, 3H, *H*–Ar), 7.27–7.34 (m, 2H, *H*–Ar), 7.74–7.79 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$, trans isomer): δ 16.2 (d, *J* = 5.0, (CH_3CH_2O)P(O)), 16.3 (d, *J* = 6.0, (CH_3CH_2O)P(O)), 41.3 (d, *J* = 152.7, *C*-4), 55.9 (d, *J* = 2.3, *C*-5), 62.6 (d, *J* = 6.4, (CH_3CH_2O)P(O)), 63.2 (d, *J* = 6.6, (CH_3CH_2O)P(O)), 118.3 (s, 2× *C*–Ar), 118.5 (s, 2× *C*–Ar), 123.9 (s, *C*–Ar), 124.7 (s, *C*–Ar), 128.7 (d, *J* = 7.1, *C*H=CH_2), 128.8 (s, 2× *C*–Ar), 129.1 (s, 2× *C*–Ar), 129.3 (s, CH_2), 137.8 (s, *C*–Ar), 149.0 (s, *C*–Ar), 166.6 (d, *J* = 1.2, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 18.55 (10%), 19.47 (90%).Anal. $C_{21}H_{25}N_2O_4P$ (C, H, N).

*4.1.2.7.5. Diethyl (3-oxo-1,2,5-triphenylpyrazolidin-4-yl)phosphonate (**17e**).* Yellow oil, Yield: 35%; **IR** (film): 2981, 1703, 1593, 1489, 1391, 1250, 1014, 964; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.1, 3H, (CH_3CH_2O)P(O)), 1.30 (t, *J* = 7.0, 3H, (CH_3CH_2O)P(O)), 3.30 (dd, *J* = 23.4, 3.0, 1H, *H*-4), 3.67–3.84 (m, 1H, (CH_3CHO)P(O)), 3.91–4.04 (m, 1H, (CH_3CHO)P(O)), 4.08–4.22 (m, 2H, (CH_3CH_2O) P(O)), 5.39 (dd, *J* = 19.1, 2.9, 1H, *H*-5), 6.81–6.98 (m, 4H, *H*–Ar), 7.10–7.24 (m, 4H, *H*–Ar), 7.31–7.43 (m, 5H, *H*–Ar), 7.50–7.53 (m, 2H, 2*H*–Ar), 7.83–7.87 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 15.9 (d, *J* = 5.4, (CH_3CH_2O)P(O)), 16.1 (d, *J* = 6.1, (CH_3CH_2O)P(O)), 46.7 (d, *J* = 137.2, *C*-4), 62.9 (d, *J* = 6.9, (CH_3CH_2O)P(O)), 63.3 (d, *J* = 6.6, (CH_3CH_2O)P(O)), 68.6 (d, *J* = 0.9, *C*-5), 115.3 (s, *C*–Ar), 117.4 (s, 2× *C*–Ar), 118.9 (s, 2× *C*–Ar), 119.4 (s, *C*–Ar), 123.1 (s, *C*–Ar), 125.0 (s, *C*–Ar), 125.2 (s, 2× 2× *C*–Ar), 128.1 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 129.1 (s, 2× *C*–Ar), 129.2 (s, *C*–Ar), 137.7 (s, *C*–Ar), 142.1 (d, *J* = 12.1, *C*–Ar), 149.4 (s, *C*–Ar), 156.8 (s, *C*–Ar), 164.6 (d, *J* = 5.7, *C*-3); **^{31}P NMR** (101 MHz, $CDCl_3$): δ 19.60, Anal. $C_{25}H_{27}N_2O_4P$ (C, H, N).

*4.1.2.8. General procedure for the synthesis of 4-methylidenepyrazolidin-3-ones **9a**–**d**, **14a**–**f**, **18a**–**e**.* To a solution of the corresponding pyrazolidinone **8a**–**d**, **13a**–**f**, **17a**–**e** (1 mmol) in THF (10 mL), NaH (28 mg, 1.2 mmol) was added and the resulting mixture was stirred at r.t. for 30 min. Then, paraformaldehyde (150 mg, 5 mmol) was added in one portion. After 2 h the reaction mixture was quenched with brine (5 mL), THF was evaporated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (eluent: CH_2Cl_2).

*4.1.2.8.1. 1-Methyl-4-methylene-2-phenylpyrazolidin-3-one (**9a**).* Yellow oil. Yield: 91%; **IR** (film): 2961, 2853, 1689, 1661, 1488, 1352, 754; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3), 3.52–3.87 (m, 1H, *H*-5), 4.07–4.39 (m, 1H, *H*-5), 5.53–5.55 (m, 1H, *H*–CH=), 6.18–6.21 (m, 1H, *H*–CH=), 7.12–7.20 (m, 1H, 1× *H*–Ar), 7.34–7.42 (m, 2H, *H*–Ar), 7.86–7.91 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 45.7 (s, CH_3), 56.3 (s, *C*-5), 117.5 (s, CH_2=), 119.5 (s, 2× *C*–Ar), 124.9 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.2 (s, *C*–Ar), 139.0 (s, *C*-4), 163.5 (s, *C*-3), **ESI-MS**: *m/z* 189.3 (M+1). $C_{11}H_{12}N_2O$ (188.23). Anal. $C_{11}H_{12}N_2O$ (C, H, N).

*4.1.2.8.2. 1-Methyl-4-methylene-2-(p-tolyl)pyrazolidin-3-one (**9b**).* Yellow oil. Yield: 68%; **IR** (film): 2960, 2858, 1693, 1662, 1492, 1348, 822; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.54–3.83 (m, 1H, 1× *H*-5), 4.10–4.37 (m, 1H, 1× *H*-5), 5.51–5.53 (m, 1H, *H*–CH=), 6.16–6.19 (m, 1H, *H*–CH=), 7.17–7.21 (m, 2H, *H*–Ar), 7.73–7.77 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 20.9 (s, CH_3), 45.6 (s, CH_3), 56.2 (s, *C*-5), 117.2 (s, CH_2=), 119.7 (s, 2× *C*–Ar), 129.4 (s, 2× 2× *C*–Ar), 134.6 (s, *C*–Ar), 134.7 (s, *C*–Ar), 139.0 (s, *C*-4), 163.2 (s, *C*-3). **ESI-MS**: *m/z* 203.3 (M+1), 225.3 (M+Na). $C_{12}H_{14}N_2O$ (202.25). Anal. $C_{12}H_{14}N_2O$ (C, H, N).

*4.1.2.8.3. 2-(4-Chlorophenyl)-1-methyl-4-methylenepyrazolidin-3-one (**9c**).* Yellow oil. Yield: 84%; **IR** (film): 2962, 2851, 1692, 1663, 1485, 1344, 827; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.53–3.79 (m, 1H, *H*-5), 4.12–4.38 (m, 1H, *H*-5), 5.55–5.57 (m, 1H, *H*–CH=), 6.19–6.21 (m, 1H, *H*–CH=), 7.32–7.36 (m, 2H, *H*–Ar), 7.84–7.89 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 45.1 (s, CH_3), 55.7 (s, *C*-5), 117.6 (s, CH_2=), 120.0 (s, 2× *C*–Ar), 128.4 (s, 2× *C*–Ar), 129.1 (s, *C*–Ar), 135.5 (s, *C*–Ar), 138.3 (s, *C*-4), 163.1 (s, *C*-

3). **ESI-MS**: *m/z* 223.2 (M+1). $C_{12}H_{14}ClN_2O$ (222.67). Anal. $C_{11}H_{11}ClN_2O$ (C, H, N).

*4.1.2.8.4. 2-(4-Bromophenyl)-1-methyl-4-methylenepyrazolidin-3-one (**9d**).* Yellow oil. Yield: 61%; **IR** (film): 2960, 2855, 1689, 1661, 1506, 1349, 816; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.59 (s, 3H, C*H*$_3$), 3.45–3.86 (m, 1H, *H*-5), 4.07–4.42 (m, 1H, *H*-5), 5.56–5.57 (m, 1H, *H*–CH=), 6.20–6.22 (m, 1H, *H*–CH=), 7.47–7.51 (m, 2H, *H*–Ar), 7.79–7.83 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 45.4 (s, *C*H$_3$), 55.9 (s, *C*-5), 117.2 (s, *C*H$_2$=), 117.9 (s, *C*–Ar), 120.5 (s, 2× *C*–Ar), 131.5 (s, 2× *C*–Ar), 136.1 (s, *C*–Ar), 138.4 (s, *C*-4), 163.4 (s, *C*-3). **ESI-MS**: *m/z* 267.2 (M+1). $C_{11}H_{11}BrN_2O$ (267.12). Anal. $C_{11}H_{11}BrN_2O$ (C, H, N).

*4.1.2.8.5. 1,5-Dimethyl-4-methylidene-2-phenylpyrazolidin-3-one (**14a**).* Yellow oil. Yield: 72%; **IR** (film): 2970, 2865, 1691, 1661, 1492, 1354, 754; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.35 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 2.57 (s, 3H, N–C*H*$_3$), 3.73 (m, 1H, *H*-5), 5.48 (d, *J* = 1.8 Hz, 1H, *H*–CH=), 6.19 (d, *J* = 2.1 Hz, 1H, *H*–CH=), 7.12–7.20 (m, 1H, *H*–Ar), 7.34–7.43 (m, 2H, *H*–Ar), 7.84–7.91 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 21.7 (s, *C*H$_3$), 45.1 (s, N–*C*H$_3$), 62.0 (s, *C*-5), 117.5 (s, *C*H$_2$=), 119.8 (s, 2× *C*–Ar), 124.9 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.6 (s, *C*–Ar), 144.5 (s, *C*-4), 163.1 (s, *C*-3). **ESI-MS**: *m/z* 203.3 (M+1). $C_{12}H_{14}N_2O$ (202.11). Anal. $C_{12}H_{14}N_2O$ (C, H, N).

*4.1.2.8.6. 5-Ethyl-1-methyl-4-methylidene-2-phenylpyrazolidin-3-one (**14b**).* Yellow oil. Yield: 61%; **IR** (film): 2961, 2872, 1691, 1660, 1492, 1355, 753, 692; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.02 (d, *J* = 7.3 Hz, 3H C*H*$_3$CH$_2$), 1.48–1.75 (m, 2H, CH$_3$C*H*$_2$), 2.60 (s, 3H, N–C*H*$_3$), 3.51 (bt, *J* = 6.5 Hz, 1H, *H*-5), 5.49 (d, *J* = 1.6 Hz, 1H, *H*–CH=), 6.22 (d, *J* = 1.9 Hz, 1H, *H*–CH=), 7.12–7.20 (m, 1H, *H*–Ar), 7.35–7.43 (m, 2H, *H*–Ar), 7.88–7.94 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 9.7 (s, *C*H$_3$CH$_2$), 29.3 (s, CH$_3$*C*H$_2$), 45.8 (s, N–*C*H$_3$), 67.8 (s, *C*-5), 118.3 (s, *C*H$_2$=), 119.5 (s, 2× *C*–Ar), 124.7 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.7 (s, *C*–Ar), 143.2 (s, *C*-4), 163.4 (s, *C*-3). **ESI-MS**: *m/z* 217.2 (M+1). $C_{13}H_{16}N_2O$ (216.13). Anal. $C_{13}H_{16}N_2O$ (C, H, N).

*4.1.2.8.7. 5-Butyl-1-methyl-4-methylidene-2-phenylpyrazolidin-3-one (**14c**).* Yellow oil. Yield: 58%; **IR** (film): 2927, 2857, 1693, 1492, 1355, 753, 692; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 0.91 (d, *J* = 7.2 Hz, 3H, C*H*$_3$(CH$_2$)$_3$, 1.24–1.73 (m, 6H, C*H*$_3$(C*H*$_2$)$_3$), 2.59 (s, 3H, N–C*H*$_3$), 3.50–3.61 (m, 1H, *H*-5), 5.49 (d, *J* = 1.6 Hz, 1H, *H*–CH=), 6.21 (d, *J* = 1.9 Hz, 1H, *H*–CH=), 7.11–7.20 (m, 1H, *H*–Ar), 7.34–7.44 (m, 2H, *H*–Ar), 7.88–7.94 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 14.0 (s, *C*H$_3$(CH$_2$)$_3$), 22.5 (s, *C*H$_2$), 27.5 (s, *C*H$_2$), 36.0 (s, *C*H$_2$), 45.8 (s, N–*C*H$_3$), 66.6 (s, *C*-5), 118.2 (s, *C*H$_2$=), 119.5 (s, 2× *C*–Ar), 124.8 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.8 (s, *C*–Ar), 143.6 (s, *C*-4), 163.5 (s, *C*-3). **ESI-MS**: *m/z* 245.2 (M+1). $C_{15}H_{20}N_2O$ (244.16). Anal. $C_{15}H_{20}N_2O$ (C, H, N).

*4.1.2.8.8. 1-Methyl-4-methylidene-5-nonyl-2-phenylpyrazolidin-3-one (**14d**).* Yellow oil. Yield: 75%; **IR** (film): 2923, 2853, 1694, 1492, 1354, 754, 691; **^{1}H NMR** (700 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, C*H*$_3$), 1.23–1.36 (m, 12H, CH$_3$(C*H*$_2$)$_6$CH$_2$CH$_2$), 1.42–1.55 (m, 3H, CH$_3$(CH$_2$)$_6$C*H*$_2$C*H*$_2$)), 1.64–1.71 (m, 1H, CH$_3$(CH$_2$)$_6$CH$_2$C*H*$_2$)), 2.60 (s, 3H, N–C*H*$_3$), 3.58 (m, 1H, *H*-5), 5.49 (d, *J* = 1.8 Hz, 1H, *H*–CH=), 6.19 (d, *J* = 1.8 Hz, 1H, *H*–CH=), 7.14–7.18 (m, 1H, *H*–Ar), 7.37–7.41 (m, 2H, *H*–Ar), 7.90–7.93 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 14.0 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 25.2 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.3 (s, *C*H$_2$), 29.4 (s, *C*H$_2$), 29.43(s, *C*H$_2$), 31.8 (s, *C*H$_2$), 36.2 (s, *C*H$_2$), 45.7 (s, N–*C*H$_3$), 66.5 (s, *C*-5), 118.1 (s, *C*H$_2$=), 119.4 (s, 2× *C*–Ar), 124.7 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 137.7 (s, *C*–Ar), 143.5 (s, *C*-4), 163.4 (s, *C*-3). **ESI-MS**: *m/z* 315.3 (M+1). $C_{20}H_{30}N_2O$ (314.24). Anal. $C_{20}H_{30}N_2O$ (C, H, N).

*4.1.2.8.9. 1-Methyl-4-methylidene-2,5-diphenylpyrazolidin-3-one (**14e**).* Yellow oil. Yield: 63%; **IR** (film): 3063, 2863, 1690, 1660, 1593, 1489, 1355, 753, 692; **^{1}H NMR** (700 MHz, $CDCl_3$): δ 2.74 (s, 3H, N–C*H*$_3$), 4.69 (bs, 1H, *H*-5), 5.53 (d, *J* = 2.2 Hz, 1H, *H*–CH=), 6.31 (d, *J* = 2.4 Hz, 1H, *H*–CH=), 7.19–7.22 (m, 1H, *H*–Ar), 7.30–7.33 (m, 1H, *H*–Ar), 7.35–7.38 (m, 2H, *H*–Ar), 7.39–7.44 (m, 4H, *H*–Ar), 7.89–7.92 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 45.0 (s, N–*C*H$_3$), 69.6 (s, *C*-5), 119.4 (s, *C*H$_2$=), 120.2 (s, 2× *C*–Ar), 124.3 (s, *C*–Ar), 125.3 (s, 2× *C*–Ar), 126.8 (s, *C*–Ar), 128.0 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 137.2 (s, *C*–Ar), 142.7 (s, *C*-4), 162.6 (s, *C*-3). **ESI-MS**: *m/z* 265.3 (M+1). $C_{17}H_{16}N_2O$ (264.13). Anal. $C_{17}H_{16}N_2O$ (C, H, N).

*4.1.2.8.10. 5-(4-Methoxyphenyl)-1-methyl-4-methylidene-2-phenylpyrazolidin-3-one (**14f**).* Yellow oil. Yield: 85%; **IR** (film): 2960, 2836, 1690, 1593, 1490, 1354, 1247, 1173, 1031, 756; **^{1}H NMR** (700 MHz, $CDCl_3$): δ 2.71 (s, 3H, N–C*H*$_3$), 3.81 (s, 3H, C*H*$_3$O), 4.63 (m, 1H, *H*-5), 5.49 (d, *J* = 2.2 Hz, 1H, *H*–CH=), 6.30 (d, *J* = 2.4 Hz, 1H, *H*–CH=), 6.88–6.91 (m, 2H, *H*–Ar), 7.18–7.22 (m, 1H, *H*–Ar), 7.30–7.34 (m, 2H, *H*–Ar), 7.40–7.43 (m, 2H, *H*–Ar), 7.86–7.89 (m, 2H, *H*–Ar); **^{13}C NMR** (176 MHz, $CDCl_3$): δ 44.9 (s, N–*C*H$_3$), 55.3 (s, *C*H$_3$O), 69.3 (s, *C*-5), 114.1 (s, 2× *C*–Ar), 119.2 (s, *C*H$_2$=), 120.3 (s, 2× *C*–Ar), 125.3 (s, 2× *C*–Ar), 128.1 (s, 2× *C*–Ar), 128.9 (s, 2× *C*–Ar), 137.2 (s, *C*–Ar), 142.9 (s, *C*-4), 159.4 (s, *C*–Ar), 162.8 (s, *C*-3). **ESI-MS**: *m/z* 295.2 (M+1). $C_{18}H_{18}N_2O_2$ (294.14). Anal. $C_{18}H_{18}N_2O_2$ (C, H, N).

*4.1.2.8.11. 5-Methyl-4-methylene-1,2-diphenylpyrazolidin-3-one (**18a**).* Yellow oil. Yield: 87%; **IR** (film): 2970, 2852, 1697, 1663, 1488, 1346, 747; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.9, C*H*$_3$), 4.41 (qdd, *J* = 6.9, 1.9, 1.2 Hz, 1H, *H*-5), 5.46 (d, *J* = 1.2, 1H, *H*–CH=), 6.22 (d, *J* = 1.9, 1H, *H*–CH=), 7.01–7.15 (m, 4H, *H*–Ar), 7.29–7.40 (m, 4H, *H*–Ar), 7.92–7.96 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 23.4 (s, *C*H$_3$), 66.1 (s, *C*-5), 118.0 (s, *C*H$_2$=), 118.7 (s, 2× *C*–Ar), 118.8 (s, 2× *C*–Ar), 124.2 (s, *C*–Ar), 124.8 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 129.2 (s, 2× *C*–Ar), 138.7 (s, *C*-4), 143.5 (s, *C*–Ar), 150.7 (s, *C*–Ar), 164.1 (s, *C*-3). **ESI-MS**: *m/z* 265.3 (M+1), 287.3 (M+Na). $C_{17}H_{16}N_2O$ (264.32). Anal. $C_{17}H_{16}N_2O$ (C, H, N).

*4.1.2.8.12. 5-Ethyl-4-methylene-1,2-diphenylpyrazolidin-3-one (**18b**).* Yellow oil. Yield: 92%; **IR** (film): 2972, 2849, 1696, 1663, 1486, 1349, 747; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.49 (t, *J* = 7.3, 3H, C*H*$_3$CH$_2$), 1.95–2.24 (m, 2H, CH$_3$C*H*$_2$), 4.40–4.47 (m, 1H, *H*-5), 5.69 (d, *J* = 1.4, 1H, *H*–CH=), 6.47 (d, *J* = 1.7, 1H, *H*–CH=), 7.23–7.40 (m, 4H, *H*–Ar), 7.42–7.62 (m, 4H, *H*–Ar), 8.16–8.20 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 10.2 (s, *C*H$_3$), 30.1 (s, *C*H$_2$), 72.0 (s, *C*-5), 118.2 (s, *C*H$_2$=), 118.4 (s, 2× *C*–Ar), 118.5 (s, 2× *C*–Ar), 123.9 (s, *C*–Ar), 124.6 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 129.2 (s, 2× *C*–Ar), 138.6 (s, *C*-4), 142.2 (s, *C*–Ar), 150.9 (s, *C*–Ar), 164.6 (s, *C*-3). **ESI-MS**: *m/z* 279.3 (M+1). $C_{18}H_{18}N_2O$ (278.35). Anal. $C_{18}H_{18}N_2O$ (C, H, N).

*4.1.2.8.13. 5-Butyl-4-methylene-1,2-diphenylpyrazolidin-3-one (**18c**).* Yellow oil. Yield: 92%; **IR** (film): 2977, 2847, 1689, 1660, 1488, 1343, 745; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2, 3H, C*H*$_3$CH$_2$), 1.41–2.02 (m, 6H, CH$_3$(C*H*$_2$)$_3$), 4.23–4.29 (m, 1H, *H*-5), 5.45 (d, *J* = 1.4, 1H, *H*–CH=), 6.22 (d, *J* = 1.7 Hz, 1H, *H*–CH=), 6.99–7.18 (m, 4H, *H*–Ar), 7.26–7.40 (m, 4H, *H*–Ar), 7.93–7.97 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 13.9 (s, *C*H$_3$), 22.4 (s, *C*H$_2$), 27.8 (s, *C*H$_2$), 36.6 (s, *C*H$_2$), 70.8 (s, *C*-5), 118.3 (s, *C*H$_2$=), 118.4 (s, 2× *C*–Ar), 118.5 (s, 2× *C*–Ar), 123.9 (s, *C*–Ar), 124.6 (s, *C*–Ar), 128.7 (s, 2× *C*–Ar), 129.2 (s, 2× *C*–Ar), 138.6 (s, *C*-4), 142.4 (s, *C*–Ar), 150.8 (s, *C*–Ar), 164.6 (s, *C*-3). **ESI-MS**: *m/z* 307.4 (M+1). $C_{20}H_{22}N_2O$ (306.40). Anal. $C_{20}H_{22}N_2O$ (C, H, N).

4.1.2.8.14. 4-Methylene-1,2-diphenyl-5-vinylpyrazolidin-3-one (18d). Yellow oil. Yield: 85%; **IR** (film): 2978, 2846, 1692, 1664, 1493, 1340, 749; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 4.70 (ddd, *J* = 5.2, 1.7, 1.4, 1H, *H*-5), 5.21 (ddd, *J* = 10.1,1.7,1.2, 1H, *H*–CH=CH), 5.40 (d, *J* = 1.4, 1H, *H*–CH=), 5.46 (ddd, *J* = 16.9, 1.4, 1.2, 1H, *H*–CH=CH), 5.93 (ddd, *J* = 16.9, 10.1, 5.2, 1H, CH$_2$=C*H*), 6.20 (d, *J* = 1.7, 1H, *H*–CH=), 6.91–7.05 (m, 4H, *H*–Ar), 7.14–7.27 (m, 4H, *H*–Ar), 7.81–7.84 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 59.5 (s, *C*-5), 117.7 (s, *C*H$_2$), 118.4 (s, *C*H$_2$), 118.5 (s, 2× *C*–Ar), 118.8 (s, 2× *C*–Ar), 124.0 (s, *C*–Ar), 124.6 (s, *C*–Ar), 128.8 (s, 2× *C*–Ar), 129.2 (s, 2× *C*–Ar), 137.9 (s, *C*H=CH$_2$), 138.3 (s, *C*-4), 151.0 (s, 2× *C*–Ar), 164.6 (s, *C*-3). **ESI-MS**: *m/z* 277.3 (M+1). $C_{18}H_{16}N_2O$ (276.33). Anal. $C_{18}H_{16}N_2O$ (C, H, N).

4.1.2.8.15. 4-Methylene-1,2,5-triphenylpyrazolidin-3-one (18e). Yellow oil. Yield: 89%; **IR** (film): 3029, 2917, 1696, 1660, 1487, 1352, 750; **^{1}H NMR** (250 MHz, $CDCl_3$): δ 5.29 (dd, J = 2.0, 1.7, 1H, *H*-5), 5.55 (d, J = 1.7, 1H, *H*–CH=), 6.31 (d, J = 2.0, 1H, *H*–CH=), 7.01–7.14 (m, 4H, *H*–Ar), 7.22–7.43 (m, 7H, *H*–Ar), 7.48–7.52 (m, 2H, *H*–Ar), 7.92–7.96 (m, 2H, *H*–Ar); **^{13}C NMR** (62.9 MHz, $CDCl_3$): δ 72.7 (s, *C*-5), 118.5 (s, *C*H_2=), 118.7 (s, 2× *C*–Ar), 118.8 (s, 2× *C*–Ar), 120.1 (s, *C*–Ar), 124.4 (s, *C*–Ar), 124.9 (s, *C*–Ar), 126.1 (s, 2× *C*–Ar), 128.1 (s, *C*–Ar), 128.9 (s, 2× *C*–Ar), 129.0 (s, *C*–Ar), 129.3 (s, 2× *C*–Ar), 138.2 (s, *C*-4), 140.4 (s, *C*–Ar), 141.6 (s, *C*–Ar), 150.5 (s, *C*–Ar), 163.7 (s, *C*-3). **ESI-MS**: *m/z* 327.3 (M+1). $C_{22}H_{18}N_2O$ (326.39). Anal. $C_{22}H_{18}N_2O$ (C, H, N).

4.2. Cytotoxicity assay by MTT

Cytotoxicity of the compounds was assessed by the mitochondrial reduction assay on two leukemia cell lines, promyelocytic HL-60 and lymphoblastic NALM-6 and on one solid tumor-derived cell line, breast cancer MCF-7 adenocarcinoma. Cells were purchased from the European Collection of Cell Cultures (ECACC). Leukemia cells were cultured in RPMI 1640 medium, while MCF-7 cells in DMEM (Dulbecco's Modified Eagle Medium), both supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen, Paisley, UK) and antibiotics (100 μg/mL streptomycin and 100 U/ml penicillin). Normal human umbilical vein endothelial cells (HUVECs) and all reagents for cell culture were purchased from Cascade Biologics (Portland, Oregon, USA). The HUVECs were cultured according to the manufacturer's instructions and the cells underwent 3–8 passages. Cells were grown in 37 °C in a humidified atmosphere of 5% CO_2 in air. Exponentially growing cells were seeded at 8×10^3/well on 96-well plates (Nunc, Roskilde, Denmark). After 24 h, the tested compounds (freshly prepared in DMSO and diluted with complete culture medium to obtain the concentration range from 10^{-7} to 10^{-3} M) were added and the plates were incubated for 48 h. Afterwards, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg/mL in PBS) was added and incubation was continued for 2 h. The metabolically active cells reduced MTT to blue formazan crystals. Then, the MTT-containing medium was carefully aspirated and 100 μL DMSO was added to dissolve the crystals. After shaking 10 min in the dark absorbance was read at 560 nm on an ELISA–plate reader (ELX 800, Bio-Tek, USA) and compared with control (untreated cells). The IC_{50} values were calculated from concentration–response curves.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.01.029.

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