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Synthesis and cytotoxic activity of γ-aryl substituted α-alkylidene-γ-lactones and α-alkylidene-γ-lactams

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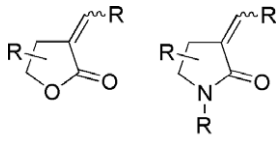
Abstract—A series of 5-aryl-3-alkylidenedihydrofuran-2(3*H*)-ones **6a**–**g**″ and **11a**,**b** as well as 5-aryl-3-methylidenepyrrolidin-2-ones **10a**–**c** and **12** were synthesized starting from 4-aryl-2-diethoxyphosphoryl-4-oxobutanoates **3a**–**g**. Reaction sequence includes reduction or reductive amination of the carbonyl group, lactonization or lactamization step and finally the Horner–Wadsworth–Emmons olefination of aldehydes using thus obtained 5-aryl-3-diethoxyphosphoryl-3,4-dihydrofuran-2(5*H*)-ones **5a**–**g**″ or 5-aryl-3-diethoxyphosphorylpyrrolidin-2-ones **9a**–**c**. Furanones **6** and **11**, as well as pyrrolidinones **10** and **12**, were evaluated in vitro against mouse leukemia cell line L-1210 and two human leukemia cell lines HL-60 and NALM-6. Several of the obtained furanones proved to be very potent against all three cell lines with IC_{50} values lower than 6 μM. Structure–activity relationships of these compounds, as well as 5-alkyl or 5-arylmethyl-3-methylidenedihydrofuran-2(3*H*)-ones **13a**–**e**, previously obtained in our laboratory, are discussed.

1. Introduction

α-Alkylidene-γ-lactone skeleton **1** is the active constituent of many natural and synthetic compounds exhibiting pronounced biological properties, such as antimicrobial, cardiovascular, antifungal, anti-inflammatory and, in particular, cytotoxic activity.[1–5] It was demonstrated, that compounds containing this moiety can act as the Michael-type acceptors in the reaction with mercapto groups of bionucleophiles, especially those present in the cysteine residue.[1,6] More recently it was shown that α-methylidene-γ-lactones **1** have an interesting photoreactivity potential and can form intramolecular photoadducts with psoralens[7] and intra or intermolecular photoadducts with thymine.[8–10] The biological activity of these compounds is not restricted to the highly functionalized sesquiterpene lactones. Many simple natural or synthetic lactones of this structure, including tulipaline A, were found to have significant pharmacological activities.[1,11,12] Also, the α-alkylidene-γ-lactam moiety **2** is present in natural[13,14] and synthetic compounds which exhibit moderate cytotoxic activity.[15,16]



1 **2**

α-Alkylidene-γ-lactones and lactams are also valuable synthetic intermediates wildly employed in organic synthesis. Apart from being excellent Michael acceptors[17,18] they can act as dipolarophiles in 1,3-dipolar cycloadditions,[19] be partners in cross methathesis reactions[20] and be utilized in the synthesis of many kinds of natural products and biologically important substances.[21,22] Not surprisingly, a variety of methodologies for their synthesis have been reported in the literature and the number of publications dedicated to this subject is steadily increasing. The most common methodology is the reaction of allyl derivatives, mainly metal derivatives

Keywords: α-Alkylidene-γ-lactones; α-Alkylidene-γ-lactams; Horner–Wadsworth–Emmons olefination; ^{1}H, ^{13}C ^{31}P NMR; Cytotoxic activity.
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of 2-alkoxycarbonylallyl, with carbonyl compounds followed by intramolecular cyclization.[23–26] An interesting variant of this method is the intramolecular Hosomi-Sukurai reaction of 2-(ethoxycarbonyl)allylsilanes and related functionalized allylsilanes with aldehydes.[27] Another elegant approach is the Pd-catalyzed, homogeneous intramolecular alkoxy-carbonylation of propargyl or homopropargyl alcohols.[28] Alkenylalumination of oxiranes [29] and other methods were also developed.[1,30–32] Several approaches to α-methylidene-γ-lactams were also reported.[33,34]

Quite recently, yet another methodology, which employs the Wittig or Horner–Wadsworth–Emmons olefination for the introduction of the alkylidene moiety onto γ-lactone or γ-lactam ring has emerged as a very versatile and promising tool.[35] Using this approach we synthesized a variety of 3-alkylidenedihydrofuran-2(3*H*)-ones,[36,37] 3-methylidenepyrrolidin-2-ones[16,38] as well as 4-methylideneisoxazolidin-5-ones.[39]

Herein, we demonstrate further application of this methodology, this time in the synthesis of a series of 5-aryl-3-alkylidenedihydrofuran-2(3*H*)-ones **6a**–**g**″, **11a**,**b** as well as 5-aryl-3-methylidenepyrrolidi-2-nones **10a**–**c**, **12**. Furthermore, all target compounds were evaluated for their cytotoxic activity against the mouse leukemia cell line L-1210 and two human leukemia cell lines NALM-6 and HL-60. Synthesis of 5-aryl substituted 3-methylidenefuran-2-ones was particularly attractive in view of the cytotoxicity evaluations of 5-alkyl and 5-arylmethyl substituted 3-methylidenefuran-2-ones, performed recently in our laboratory.[16] According to these evaluations 5-arylmethyl substituted methylidenefuranones had remarkably higher cytotoxicities against NALM-6 cell line than their 5-alkyl analogs. Current investigations open up the opportunity to check whether the presence of an aryl group connected directly to the lactone ring would also enhance cytotoxicity. Therefore, structure–activity relationships of the newly obtained compounds, in comparison with 5-alkyl and 5-arylmethyl-3-methylidenedihydrofuran-2(3*H*)-ones, previously obtained in our laboratory, will be discussed.

2. Chemistry

Target furanones **6a**–**g**″ and pyrrolidinones **10a**–**c** were synthesized starting from the corresponding 4-aryl-2-diethoxyphosphoryl-4-oxobutanoates **3a**–**g**. These substrates can be efficiently prepared from 1-aryl-2-bromoalkan-1-ones and ethyl diethoxyphosphorylacetate, applying the methodology which has been recently worked out in our laboratory.[40] Oxobutanoates **3e**–**g** (R^1 = Me) were used as mixtures of diastereomers in close to 60:40 ratio.

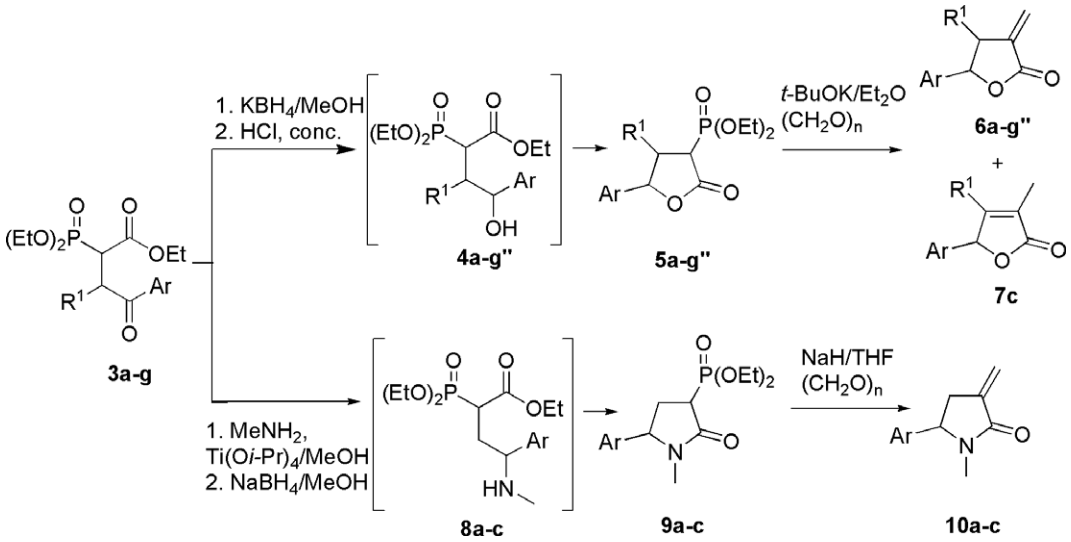
Reduction of the carbonyl group in oxobutanoates **3a**–**g** followed by spontaneous lactonization of the initially formed 5-aryl-2-diethoxyphosphoryl-4-hydroxybutanoates **4a**–**g**, gave, after standard work up, crude 5-aryl-3-diethoxyphosphoryl-3,4-dihydrofuran-2(5*H*)-ones **5a**–**g**, as mixtures of two diastereomers, in the ratios shown in Table 1 (Scheme 1). These compounds were then purified and dihydrofuranones **5e**–**g** also separated into single diastereomers by column chromatography. Yields are given in Table 1. Analysis of IR, ^{1}H, ^{13}C and ^{31}P NMR spectra of dihydrofuranones **5a**–**g** confirmed their structures unambiguously.

It is worth to stress that dihydrofuranones **5e**–**g** were formed as mixtures of only two, out of four possible diastereomers. Reasonable explanation of this observation was epimerization on the C3 carbon atom in the strongly basic conditions of the reaction and the formation of more stable diastereomers with *trans* alignment of phosphoryl and methyl groups. Careful analysis of the well resolved signals of these stereoisomers in ^{1}H and ^{13}C NMR spectra confirmed this supposition and also allowed us to propose their relative configuration. Particularly characteristic were the chemical shifts of the protons of the methyl group and protons H5, as well as coupling constants ^3J(P-CH$_3$), ^3J(P-C5), ^3J(H3–H4) and ^3J(H4–H5). These values are given in Table 2. Protons of the methyl groups of the minor diastereomers adsorbed at the unexpectedly low frequency, for example, in **5f** the methyl protons of the major and minor diastereomer had chemical shift 1.28 ppm and 0.76 ppm,

Table 1. Synthesis of 3,4-dihydrofuran-2(5*H*)-ones **5a**–**g**″, methylidenedihydrofuran-2-ones **6a**–**g**″, pyrrolidin-2-ones **9a**–**c** and methylidenepyrrolidin-2-ones **10a**–**c**

	Ar	R^1	**5**		**6**		**9**		**10**
			Yield[a] (%)	Diastereomers ratio[b]	Yield[a] (%)	**6**/**7** ratio	Yield[a] (%)	Diastereomers ratio[c]	Yield[a] (%)
a	Ph	H	86	60:40	55	>99:1	77	70:30	79
b	4-BrC_6H_4	H	86	60:40	45	>99:1	92	60:40	65
c	4-MeOC_6H_4	H	73	60:40	61[d]	60:40	58	60:40	59
d	1-Naphthyl	H	90	60:40	30	>99:1	—	—	—
e′	Ph	Me	55	65:35	66	>99:1	—	—	—
e″			30		65	>99:1			
f′	4-BrC_6H_4	Me	40	55:45	52	>99:1	—	—	—
f′			50		51	>99:1			
g′	4-MeOC_6H_4	Me	47	55:45	61	>99:1	—	—	—
g″			38		66	>99:1			

[a] Yield of isolated, pure product based on **3**, **5** or **9**, respectively.
[b] Taken from ^{31}P NMR of the crude product.
[c] Taken from ^{1}H NMR of the crude product.
[d] Overall yield for **6c** and **7c**.



Scheme 1.

Table 2. Selected chemical shifts and coupling constants for (*r*-3,*t*-4,*t*-5)-**5e′**–**g′** and (*r*-3,*t*-4,*c*-5)-**5e″**–**g″**

	δ (^{1}H) H5 (ppm)	δ (^{1}H) CH_3 (ppm)	^3J(P-CH_3) (Hz)	^3J(P-C5) (Hz)	^3J(H3–H4) (Hz)	^3J(H4–H5) (Hz)
(*r*-3,*t*-4,*c*-5)-**5e′**	4.86	1.28	1.2 (~90°)	13.9 (150–160°)	11.0 (150–160°)	6.6 (160–170°)
(*r*-3,*t*-4,*t*-5)-**5e″**	5.86	0.74	0 (110–120°)	3.7 (130–140°)	3.9 (120–130°)	6.6 (10–20°)
(*r*-3,*t*-4,*c*-5)-**5f′**	4.82	1.28	0	14.5	11.0	9.0
(*r*-3,*t*-4,*t*-5)-**5f″**	5.82	0.76	0	3.7	3.5	6.3
(*r*-3,*t*-4,*c*-5)-**5g′**	4.86	1.25	0	14.5	11.4	9.2
(*r*-3,*t*-4,*t*-5)-**5g″**	5.84	0.78	0	4.3	3.5	6.6

respectively. This anomaly can be rationalized by assuming the *cis* arrangement of the methyl and aromatic groups in the minor diastereomers. In this arrangement the methyl protons are placed in the shielding area of the benzene ring. Furthermore, chemical shifts of the H5 protons in the spectra of the minor diastereomers were surprisingly high, for example, in **5f** these shifts were 5.82 and 4.82 ppm for the minor and major diastereoisomers, respectively. This, in turn can be explained by the deshielding effect of the diethoxyphosphoryl group exerted on the *cis*-oriented proton H5. These observations allowed us to assign the *r*-3,*t*-4,*c*-5 and *r*-3,*t*-4,*t*-5 configurations for the major and minor diastereomers of **5e**–**g**, respectively. Also, coupling constants ^3J(P-CH_3), ^3J(P-C5), ^3J(H3–H4) and ^3J(H4–H5) validated this assignment. Dihedral angles estimated from these coupling constants, using Karplus equation,[41,42] had values given in parentheses in Table 2 and were in good agreement with the dihedral angles taken from the corresponding cochranes orbit size molecular models of (*r*-3,*t*-4,*c*-5)-**5e′**–**g′** and (*r*-3,*t*-4,*t*-5)-**5e″**–**g″**, in which the diethoxyphosphoryl and aryl groups were assumed to occupy *pseudo*-equatorial positions.

Correctness of the above configurational assignments was unambiguously confirmed by the NOE experiments performed on both diastereoisomers of **5f**. Obtained results are shown in Figure 1.

Data from the ^{1}H and ^{13}C NMR spectra of the diastereomeric mixtures of dihydrofuranones **5a**–**d** were less useful for the configurational assignments. However, based on the correlation described above, mainly deshielding effect of the diethoxyphosphoryl group, the *trans* configuration was assigned to the major diastereomers in which proton H5 had higher chemical shift, for example, for **5a** these shifts were 5.71 ppm and 5.44 ppm for the major and minor diastereomers, respectively.

Dihydrofuranones **5a**–**g″** were next used in the Horner–Wadsworth–Emmons olefination of formaldehyde. Reaction of these compounds with paraformaldehyde in the presence of *t*-BuOK as a base gave, after standard work-up, crude 5-aryl-3-methylidene-4,5-dihydrofuran-2-ones **6a**–**g″**, which were purified by column chromatography (Scheme 1 and Table 1). Only the reaction of furanone **5c** gave the mixture of methylidenefuranone **6c** and its rearrangement product **7c**. Our efforts to separate this mixture were unsuccessful. Reason for the facile rearrangement of **6c** are not fully understood. Structures of all synthesized compounds were unequivocally confirmed by their IR, ^{1}H, and ^{13}C spectra. As expected, methylidenedihydrofuranones **6e′**–**g″** were obtained as single diastereomers with preserved *trans* or *cis* configuration of the starting dihydrofuranones **5e′**–**g″**, for example, ^{1}H NMR spectra of all *cis*-**6e″**–**g″** revealed characteristic low-frequency absorption of the

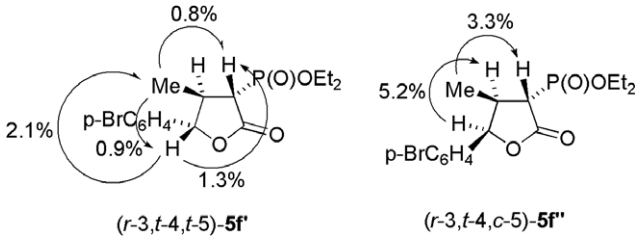
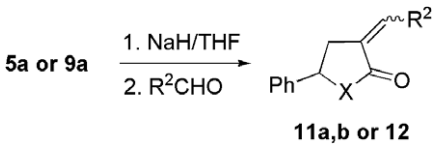


Figure 1. NOE experiments performed on diastereomeric dihydrofuranones **5f′** and **5f″**.

methyl group (0.79–0.88 ppm) caused by the shielding effect of the *cis*-oriented aryl group.

On the other hand, reductive amination of oxobutanoates **3a**–**c** using methylamine along with titanium (IV) isopropoxide, followed by addition of sodium borohydride, standard work up and purification by column chromatography, furnished pure 5-aryl-3-diethoxyphosphoryl-1-methylpyrrolidin-2-ones **9a**–**c** in good to excellent yields (Scheme 1 and Table 1). Disappointingly, oxobutanoate **3d** treated the same way gave only 20% yield of the pyrolidinone **9d** along with substrate and other products which were difficult to separate. Also oxobutanoates **3e**–**g** did not give expected pyrrolidinones but only difficult to analyze mixtures of products. Pyrrolidinones **9a**–**c** were obtained as mixtures of diastereomers in the ratios given in Table 1. IR, ^{1}H, ^{13}C and ^{31}P NMR spectra of **9a**–**c** confirmed their structures but were not conclusive enough to attribute the relative configurations to the major and minor diastereomers. Olefination of formaldehyde using pyrrolidinones **9a**–**c** and NaH as a base gave, after work up and column chromatography, expected 5-aryl-3-methylidenepyrrolidin-2-ones **10a**–**c** in good yields (Table 1).

Dihydrofuranone **5a** and pyrrolidinone **9a** were also used in the olefination of isobutyraldehyde or benzaldehyde (Scheme 2). Applying standard procedure (NaH, THF) and work up, followed by purification by column chromatography, 3-alkylidene-5-phenyldihydrofuran-2-ones **11a**,**b** and 3-(2-methylpropylidene)-5-phenylpyrrolidin-2-one **12** were obtained in good yields as a mixture of *E* and *Z* diastereoisomers or as single isomers (Table 3). Configurational assignments were made using



Scheme 2.

Table 3. Synthesis of furanones **11a**,**b** and pyrrolidinone **12**

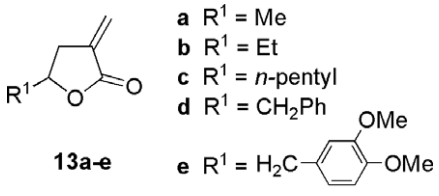
Compound	X	R^2	Yield[a] (%)	*E*/*Z*[b]
11a	O	*i*-Pr	88	15:85
11b	O	Ph	50	>99:1
12	NMe	*i*-Pr	59	<1:99

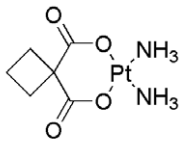
[a] Yield of isolated, pure product based on **5a** or **9a**, respectively.
[b] Taken from ^{1}H NMR of the crude product.

the diagnostic deshielding effect of the carbonyl group exerted on the *cis*-oriented vinyl proton.[41,43] Opposite *E*/*Z* stereochemistry observed for **11a** and **11b** (15:85 and >99:1, respectively), although surprising at first, can be rationalized taking into account conjugating ability of the phenyl group. Inspection of the corresponding molecular models revealed that in (*Z*)-**11b** thermodynamically preferred coplanar arrangement of phenyl and α,β-unsaturated lactone moieties causes severe steric repulsions between phenyl and carbonyl groups. Therefore, more stable (*E*) stereoisomer is formed exclusively. In (*Z*)-**11a** the isopropyl group can adopt conformation lacking significant steric interactions, due to free rotation about the bond connecting this group to the unsaturated system.

3. Pharmacological results

All target compounds **6a**,**b**,**d**–**g″**, **10a**–**c**, **11a**,**b**, **12** were evaluated in vitro against mouse leukemia cell line L-1210 and two human leukemia cell lines HL-60 and NALM-6. Cytotoxic activity of these compounds is expressed as the concentration (μM) required to inhibit tumor cell proliferation by 50% after a 48 h exposure of the cells to a tested compound (IC_{50} values). Results are given in Table 4. Cytotoxicities of 5-alkyl and 5-arylmethyl-3-methylidene-dihydrofuran-2(3*H*)-ones **13a**–**e** prepared recently in our laboratory are also given for comparison. Carboplatin was used as a reference compound.[44]





carboplatin

Presented results are very encouraging because four of the obtained furanones, **6d**, **6e″**, **6f′** and **6g′** showed IC_{50} values against all three tested cell lines lower than 8.09 μM and can be considered highly potent according to the *Kupchan's* classification ($IC_{50} \leqslant 15$ μM).[45]

Several conclusions, which can be drawn from the data given in Table 4 confirm the observations described in our recent paper[16] where cytotoxicities of 5-alkyl or 5-arylmethylfuranones **13a**–**e** and other 5-alkyl or 5-arylmethylfuran-2-ones and pyrrolidin-2-ones were tested. These conclusions can be summarized as follows: (i) the cytotoxicities of methylidenefuranones **6a**–**g″** are much higher than methylidenepyrrolidin-2-ones **10a**–**c**, (ii) the activities of methylidenefuranone **6d** and methylidenepyrrolidin-2-one **10a** are evidently higher than the activities of alkylidenefuranones **11a**,**b** and isopro-

Table 4. Cytotoxic Activity of compounds **6a**,**b**,**d**–**g**″, **10a**–**c**, **11a**,**b**, **12** and **13a**–**e**

Compound	Cytotoxicity IC_{50}[a] (μM)		
	L-1210	HL-60	NALM-6
6a	1.4 ± 0.12	36.9 ± 13.6	9.13 ± 0.34
6b	1.3 ± 0.10	20.3 ± 2.6	85.3 ± 8.0
6d	4.3 ± 0.24	4.42 ± 0.52	3.86 ± 0.49
6e′	28.0 ± 1.92	8.97 ± 0.36	7.91 ± 0.37
6e″	4.0 ± 0.21	8.09 ± 0.6	5.42 ± 0.44
6f′	1.55 ± 0.05	5.05 ± 0.28	4.02 ± 0.24
6f″	7.5 ± 0.33	41.8 ± 7.3	43.9 ± 6.8
6g′	3.65 ± 0.35	5.69 ± 0.1	5.23 ± 0.46
6g″	14.2± 2.12	37.9 ± 6.7	38.6 ± 6.6
10a	>50	988.7± 19.3	552.9 ± 46.9
10b	>50	220.1 ± 27.9	141.4 ± 26.9
10c	>50	611.3 ± 18.2	522.6 ± 21.0
11a	>50	158.9 ± 44.6	482.9 ± 42.3
11b	>50	>1000	497 ± 38.6
12	>50	81.3 ± 6.8	351.1 ± 31.8
13a[b]	32.5 ± 4.8	77.4 ± 6.5	41.0 ± 1.8
13b[b]	6.0 ± 1.6	39.5 ± 17.3	51.6 ± 24.0
13c[b]	20.0 ± 3.2	99.4 ± 31.5	23.6 ± 12.9
13d[b]	15.5 ± 2.9	42.7 ± 11.1	5.4 ± 0.3
13e[b]	4.3 ± 0.8	46.3 ± 1.8	6.0 ± 1.4
Carboplatin **14**	9.7 ± 1.2	2.9 ± 0.1	0.7 ± 0.3

[a] IC_{50}, 50% inhibitory concentration represents the mean from dose–response curves of at least three experiments.
[b] Data taken from Ref. 16.

pylidenepyrrolidinone **12**, respectively, (iii) cytotoxicities of methylidenefuranones **6a**,**b**,**d**–**g**″, against L-1210 cell line are generally higher than against HL-60 or NALM-6 cell lines.

Our studies also show that 5-aryl or 5-arylmethyl substituted furanones are more potent antiproliferative agents than 5-alkyl analogs, for example, activities of **6a** and **13d**, which differ only by the methylene group (phenyl and methylphenyl substituents, respectively), against HL-60 and NALM-6 cell lines are very similar and much higher than activities of **13a** (methyl substituent) against the same cell lines. This observation indicates that the presence of an aryl substituent in position 5, whether attached directly to the furanone ring or through the methylene tether, is very important for the activity. However, cytotoxicities of 5-aryl substituted furanones **6a**–**g**″ against HL-60 cell lines are generally considerably higher than the cytotoxicities of 5-arylmethylfuranones **13d**,**e**. The highest cytotoxicity against both, HL-60 and NALM-6 cell lines was found for **6d** having a bulk naphthyl ring in position 5. Comparison of the cytotoxicities of the diastereomeric 4-methyl-5-aryl substituted furanones **6f**′ and **6f**″ as well as **6g**′ and **6g**″ shows another, very interesting relationship: *trans*-furanones **6f**′,**g**′ are significantly more potent than the *cis* stereoisomers **6f**″,**g**″. Evidently, the spatial arrangement of the substituents plays an important role in the interaction with the bionucleophiles.

4. Conclusions

Simple and effective synthesis of biologically important 3-alkylidene-5-aryldihydrofuran-2-ones **6a**–**g**″, **11a**,**b** and 3-alkylidene-5-arylpyrrolidin-2-ones **10a**–**c**, **12** was achieved starting from easily available intermediates—4-aryl-2-diethoxyphosphoryl-4-oxobutanoates **3a**–**g**. Furthermore, 3-methyl substituted furanones **6e**′–**g**″ were obtained as pure *trans* and *cis* stereoisomers. Relative configurations of all diastereomers were assigned using ^1H and ^{13}C NMR analysis, including NOE experiments. Several of the target 5-arylfuranones **6d**,**e**″,**f**′,**g**′ proved to be highly potent against L-1210, HL-60 and NALM-6 cell lines with the activity comparable to or higher than 5-arylmethylfuranones **13d**,**e** previously prepared in our laboratory and much higher than the activity of 5-alkylfuranones **13a**–**c**. Moreover, significant differences in the cytotoxicities of *trans*-**6f**′,**g**′ and *cis*-**6f**″,**g**″ were found, with *trans* isomers being eight times more active than *cis* isomers.

5. Experimental

5.1. Chemistry

Organic solvents and reagents were purified by the appropriate standard procedures. Column chromatography was performed on FLUKA® silica gel 60 (230–400 mesh). IR spectra were recorded on Specord M 80 spectrometer. ^1H NMR (250 MHz), ^{13}C NMR (62.9 MHz), and ^{31}P NMR (101 MHz) spectra were recorded on a Bruker DPX-250 spectrometer with TMS as an internal standard for ^1H NMR and ^{13}C NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR. ^{31}P NMR spectra were recorded using broad-band proton decoupling. NOE experiments were performed on Bruker Avance II Plus (700 MHz) spectrometer.

5.1.1. General procedure for the preparation of 5-aryl-3-diethoxyphosphoryl-2-furanones (5a–g). To a stirred solution of 2-dietoxyphosphoryl-4-oxoalkanoates (**3a**–**g**) (5.0 mmol) in methanol (20 mL) potasium borohydride (0.405 g, 7.5 mmol) was added at 0 °C. Stirring was continued for appropriate period of time. The resulting mixture was acidified to pH 1.5 with concentrated HCl, then the water (15 mL) was added and methanol was evaporated under reduced pressure. The residue was extracted with chloroform (4× 20 mL). The combined organic layers were washed with water (20 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography ($CHCl_3$/acetone, 98:2) affording pure product.

5.1.1.1. 3-Diethoxyphosphoryl-5-phenyl-dihydrofuran-2(3*H*)-one (5a). Oil, yield = 86%; IR (film, cm^{-1}): 1772, 1516, 1168, 1024; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.13–1.41 (m, 6H major and minor, $(CH_3CH_2O)_2P(O)$), 2.35–2.70 (m, 1H major and minor, *H*-3), 2.80–3.20 (m, 1H major and minor, *H*-4), 3.20–3.49 (m, 1H major and minor, *H*-4), 3.80–4.27 (m, 4H major and minor, $(CH_3CH_2O)_2P(O)$), 5.44 (dd, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 9.7 Hz, 1H minor, *H*-5), 5.71 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 8.9 Hz, 1H major, *H*-5), 7.34–7.37 (m, 5H major and minor, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.05 (d, $^3J_{PC}$ = 5.9 Hz, CH_3CH_2O, CH_3CH_2O),

32.98 (d, $^2J_{PC}$ = 3.1 Hz, *C*-4), 33.04 (d, $^2J_{PC}$ = 4.4 Hz, *C*-4), 39.83 (d, $^1J_{PC}$ = 152.1 Hz, *C*-3), 39.94 (d, $^1J_{PC}$ = 138.7 Hz, *C*-3), 62.65 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 62.77 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.13 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.41 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 79.97 (d, $^3J_{PC}$ = 12.0 Hz, *C*-5), 80.16 (d, $^3J_{PC}$ = 3.1 Hz, *C*-5), 125.07 (s, 2× *C*-Ar), 125.44 (s, 2× *C*-Ar), 128.34 (s, *C*-Ar, *C*-Ar), 128.43 (s, 2× *C*-Ar), 128.49 (s, 2× *C*-Ar), 138.10 (s, *C*-Ar), 138.32 (s, *C*-Ar), 170.98 (d, $^2J_{PC}$ = 2.3 Hz, *C*-2), 171.16 (d, $^2J_{PC}$ = 4.4 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.84 minor, 21.08 major; (40:60); Anal. Calcd for $C_{14}H_{19}O_5P$: C, 56.37; H, 6.42. Found: C, 56.41; H, 6.36.

5.1.1.2. 5-(4-Bromophenyl)-3-diethoxyphosphoryl-dihydrofuran-2(3*H*)-one (5b). Oil, yield = 86%; IR (film, cm^{-1}): 1770, 1512, 1168, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.12–1.50 (m, 6H major and minor, $(CH_3CH_2O)_2P(O)$), 2.25–2.60 (m, 1H major and minor, *H*-3), 2.82–3.10 (m, 1H major and minor, *H*-4), 3.10–3.44 (m, 1H major and minor, *H*-4), 4.05–4.45 (m, 4H major and minor $(CH_3CH_2O)_2P(O)$), 5.40 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 10.0 Hz, 1H minor, *H*-5), 5.66 (t, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 10.0 Hz, 1H major, *H*-5), 7.20–7.23 (m, 2H major and minor, *H*-Ar), 7.51–7.60 (m, 2H major and minor, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.14 (d, $^3J_{PC}$ = 6.7 Hz, CH_3CH_2O, CH_3CH_2O), 32.89 (d, $^2J_{PC}$ = 3.1 Hz, *C*-4), 33.11 (d, $^2J_{PC}$ = 3.1 Hz, *C*-4), 39.88 (d, $^1J_{PC}$ = 153.97 Hz, *C*-3), 40.00 (d, $^1J_{PC}$ = 138.12 Hz, *C*-3), 62.68 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 62.93 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.36 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.61 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 79.24 (d, $^3J_{PC}$ = 11.9 Hz, *C*-5), 79.55 (d, $^3J_{PC}$ = 2.5 Hz, *C*-5), 122.37 (s, *C*-Ar), 122.50 (s, *C*-Ar), 126.90 (s, 2× *C*-Ar, 2× *C*-Ar), 127.24 (s, *C*-Ar), 131.73 (s, 2× *C*-Ar), 137.32 (s, *C*-Ar), 137.48 (s, *C*-Ar, *C*-Ar), 170.82 (d, $^2J_{PC}$ = 2.3 Hz, *C*-2), 171.00 (d, $^2J_{PC}$ = 4.4 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.44 minor, 20.46 major; (40:60); Anal. Calcd for $C_{14}H_{18}BrO_5P$: C, 44.58; H, 4.81. Found: C, 44.54; H, 4.79.

5.1.1.3. 3-Diethoxyphosphoryl-5-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one (5c). Oil, yield = 73%; IR (film, cm^{-1}): 1768, 1512, 1168, 1028; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20–1.45 (m, 6H major and minor, $(CH_3CH_2O)_2P(O)$), 2.25–2.60 (m, 1H major and minor, *H*-3), 2.75–3.10 (m, 1H major and minor, *H*-4), 3.20–3.40 (m, 1H major and minor, *H*-4), 3.81 (s, CH_3O), 4.10–4.32 (m, 4H major and minor, $(CH_3CH_2O)_2P(O)$), 5.37 (dd, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 10.1 Hz, 1H minor, *H*-5), 5.66 (t, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 9.0 Hz, 1H major, *H*-5), 6.81–7.01 (m, 2H major and minor, *H*-Ar), 7.18–7.33 (m, 2H major and minor, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.03 (d, $^3J_{PC}$ = 5.6 Hz, CH_3CH_2O, CH_3CH_2O), 32.94 (d, $^2J_{PC}$ = 3.9 Hz, *C*-4, *C*-4), 40.03 (d, $^1J_{PC}$ = 151.58 Hz, *C*-3), 40.14 (d, $^1J_{PC}$ = 137.75 Hz, *C*-3), 54.94 (s, CH_3O), 62.45 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 62.70 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.12 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.36 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 80.07 (d, $^3J_{PC}$ = 12.6 Hz, *C*-5), 80.30 (d, $^3J_{PC}$ = 2.5 Hz, *C*-5), 113.78 (s, 2× *C*-Ar), 113.83 (s, 2× *C*-Ar), 126.83 (s, 2× *C*-Ar, 2× *C*-Ar), 127.21 (s, *C*-Ar, *C*-Ar), 129.85 (s, *C*-Ar), 130.05 (s, *C*-Ar), 159.61 (s, *C*-Ar), 159.70 (s, *C*-Ar), 170.94 (d, $^2J_{PC}$ = 2.3 Hz, *C*-2), 171.13 (d, $^2J_{PC}$ = 4.4 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.65 minor, 20.85 major; (40:60); Anal. Calcd for $C_{15}H_{21}O_6P$: C, 54.88; H, 6.45. Found: C, 54.78; H, 6.50.

5.1.1.4. 3-Diethoxyphosphoryl-5-(1-naphtyl)-dihydrofuran-2(3*H*)-one (5d). Oil, yield = 90%; IR (film, cm^{-1}): 1776, 1512, 1392, 1368, 1260, 1164, 1028; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.45 (m, 6H major and minor, $(CH_3CH_2O)_2P(O)$), 2.42–2.70 (m, 1H major and minor, *H*-3), 3.05–3.50 (m, 2H major and minor, *H*-4), 4.10–4.45 (m, 4H major and minor, $(CH_3CH_2O)_2P(O)$), 6.12 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 8.2 Hz, 1H minor, *H*-5), 6.43 (t, $^3J_{HH}$ = 7.0 Hz, 1H major, *H*-5), 7.32–7.60 (m, 4H major and minor, *H*-Ar), 7.70–7.95 (m, 3H major and minor, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.23 (d, $^3J_{PC}$ = 4.9 Hz, CH_3CH_2O, CH_3CH_2O), 32.44 (d, $^2J_{PC}$ = 3.7 Hz, *C*-4, *C*-4), 39.36 (d, $^1J_{PC}$ = 141.5 Hz, *C*-3), 39.88 (d, $^1J_{PC}$ = 151.6 Hz, *C*-3), 62.66 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 62.84 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.17 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.53 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 77.60 (d, $^3J_{PC}$ = 4.9 Hz, *C*-5), 77.73 (d, $^3J_{PC}$ = 1.9 Hz, *C*-5), 121.40 (s, *C*-Ar, *C*-Ar), 122.19 (s, *C*-Ar), 122.26 (s, *C*-Ar), 125.09 (s, *C*-Ar), 125.16 (s, *C*-Ar), 125.69 (s, *C*-Ar), 125.83 (s, *C*-Ar), 126.38 (s, *C*-Ar), 126.50 (s, *C*-Ar), 128.74 (s, *C*-Ar), 128.76 (s, *C*-Ar), 128.79 (s, *C*-Ar), 128.87 (s, *C*-Ar), 129.20 (s, *C*-Ar), 129.34 (s, *C*-Ar), 133.47 (s, *C*-Ar), 133.52 (s, *C*-Ar), 133.88 (s, *C*-Ar), 134.08 (s, *C*-Ar), 171.36 (d, $^2J_{PC}$ = 3.7 Hz, *C*-2, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.36 minor, 20.89 major; (40:60); Anal. Calcd for $C_{18}H_{21}O_5P$: C, 62.07; H, 6.08. Found: C, 62.13; H, 6.00.

5.1.1.5. *r*-3-Diethoxyphosphoryl-*t*-4-methyl-*c*-5-phenyl-dihydrofuran-2(3*H*)-one (5e′). Oil, yield = 55%; IR (film, cm^{-1}): 1776, 1456, 1256, 1160, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3), 1.29–1.41 (m, 6H, $(CH_3CH_2O)_2P(O)$), 2.65–2.98 (m, 1H, *H*-4), 2.94 (dd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HP}$ = 28.5 Hz, 1H, *H*-3), 4.09–4.37 (m, 4H, $(CH_3CH_2O)_2P(O)$), 4.86 (d, $^3J_{HH}$ = 6.6 Hz, 1H, *H*-5), 7.33–7.40 (m, 5H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.93 (d, $^3J_{PC}$ = 1.24 Hz, CH_3), 16.15 (d, $^3J_{PC}$ = 5.0 Hz, CH_3CH_2O), 16.33 (d, $^3J_{PC}$ = 5.0 Hz, CH_3CH_2O), 41.97 (d, $^2J_{PC}$ = 2.5 Hz, *C*-4), 47.03 (d, $^1J_{PC}$ = 150.9 Hz, *C*-3), 62.45 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.37 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 87.16 (d, $^3J_{PC}$ = 13.9 Hz, *C*-5), 126.23 (s, 2× *C*-Ar), 128.50 (s, 2× *C*-Ar), 128.86 (s, *C*-Ar), 136.89 (s, *C*-Ar), 170.70 (s, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.49; Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.69; H, 6.78. Found: C, 57.80; H, 6.79.

5.1.1.6. *r*-3-Diethoxyphosphoryl-*t*-4-methyl-*t*-5-phenyl-dihydrofuran-2(3*H*)-one (5e″). Oil, yield = 30%; IR (film, cm^{-1}): 1776, 1456, 1252, 1164, 1028; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.74 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.32–1.44 (m, 6H, $(CH_3CH_2O)_2P(O)$), 2.88 (dd, $^3J_{HH}$ = 3.9 Hz, $^2J_{HP}$ = 23.8 Hz, 1H, *H*-3), 3.15–3.28 (m, 1H, *H*-4), 4.08–4.27 (m, 4H $(CH_3CH_2O)_2P(O)$), 5.86 (d, $^3J_{HH}$ = 6.6 Hz, 1H, *H*-5), 7.07–7.47 (m, 5H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.01 (s,

CH_3), 16.19 (s, ($CH_3CH_2O)_2$), 37.41 (s, *C*-4), 48.02 (d, $^1J_{PC}$ = 137.1 Hz, *C*-3), 62.79 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2 OP(O)), 63.58 (d, $^2J_{PC}$ = 6.9 Hz, $CH_3CH_2OP(O)$), 82.99 (d, $^3J_{PC}$ = 3.7 Hz, *C*-5), 125.22 (s, 2× *C*-Ar), 128.04 (s, *C*-Ar), 128.35 (s, 2× *C*-Ar), 135.40 (s, *C*-Ar), 171.23 (s, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 19.95; Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.69; H, 6.78. Found: C, 57.78; H, 6.81.

5.1.1.7. *c*-5-(4-Bromophenyl)-*r*-3-diethoxyphosphoryl-*t*-4-methyl-dihydrofuran-2(3*H*)-one (5f′). Oil, yield = 40%; IR (film, cm^{-1}): 1780, 1252, 1160, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.27–1.41 (m, 6H, ($CH_3CH_2O)_2P(O)$), 2.70–2.88 (m, 1H, *H*-4), 2.89 (dd, $^3J_{HH}$ = 11.3 Hz, $^2J_{HP}$ = 23.4 Hz, 1H, *H*-3), 4.12–4.38 (m, 4H, ($CH_3CH_2O)_2P(O)$), 4.82 (d, $^3J_{HH}$ = 9.0 Hz, 1H, *H*-5), 7.20–7.26 (m, 2H, *H*-Ar), 7.49–7.60 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.91 (s, CH_3), 16.14 (d, $^3J_{PC}$ = 5.6 Hz, CH_3CH_2O), 16.23 (d, $^3J_{PC}$ = 5.6 Hz, CH_3CH_2O), 41.93 (d, $^2J_{PC}$ = 1.9 Hz, *C*-4), 46.88 (d, $^1J_{PC}$ = 150.9 Hz, *C*-3), 62.46 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.49 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 86.32 (d, $^3J_{PC}$ = 14.5 Hz, *C*-5), 122.87 (s, *C*-Ar), 127.88 (s, 2× *C*-Ar), 131.93 (s, 2× *C*-Ar), 136.01 (s, *C*-Ar), 170.48 (s, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.31; Anal. Calcd for $C_{15}H_{20}BrO_5P$: C, 46.05; H, 5.15. Found: C, 46.21; H, 5.07.

5.1.1.8. *t*-5-(4-Bromophenyl)-*r*-3-diethoxyphosphoryl-*t*-4-methyl-dihydrofuran-2(3*H*)-one (5f″). Oil, yield = 50%; IR (film, cm^{-1}): 1776, 1256, 1164, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.32–1.49 (m, 6H, ($CH_3CH_2O)_2P(O)$), 2.86 (dd, $^3J_{HH}$ = 3.4 Hz, $^2J_{HP}$ = 23.8 Hz, 1H, *H*-3), 3.13–3.21 (m, 1H, *H*-4), 4.11–4.33 (m, 4H ($CH_3CH_2O)_2P(O)$), 5.82 (d, $^3J_{HH}$ = 6.3 Hz, 1H, *H*-5), 7.11–7.21 (m, 2H, *H*-Ar), 7.40–7.72 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.85 (s, CH_3), 16.19 (s, CH_3CH_2O), 37.22 (d, $^2J_{PC}$ = 4.4 Hz, *C*-4), 48.10 (d, $^1J_{PC}$ = 137.1 Hz, *C*-3), 62.83 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 63.65 (d, $^2J_{PC}$ = 6.9 Hz, CH_3CH_2O), 82.27 (d, $^3J_{PC}$ = 3.7 Hz, *C*-5), 121.91 (s, *C*-Ar), 126.91 (s, 2× *C*-Ar), 131.50 (s, 2× *C*-Ar), 134.45 (s, *C*-Ar), 170.95 (s, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 19.59; Anal. Calcd for $C_{15}H_{20}BrO_5P$: C, 46.05; H, 5.15. Found: C, 45.92; H, 5.12.

5.1.1.9. *r*-3-Diethoxyphosphoryl-*t*-4-methyl-*c*-5-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one (5g′). Oil, yield = 47%; IR (film, cm^{-1}): 1772, 1252, 1172, 1028; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3), 1.32–1.42 (m, 6H, ($CH_3CH_2O)_2P(O)$), 2.75–3.02 (m, 1H, *H*-4), 2.86 (dd, $^3J_{HH}$ = 11.4 Hz, $^2J_{HP}$ = 29.4 Hz, 1H, *H*-3), 3.82 (s, 3H, CH_3O), 4.11–4.40 (m, 4H ($CH_3CH_2O)_2P(O)$), 4.86 (d, $^3J_{HH}$ = 9.2 Hz, 1H, *H*-5), 6.90–6.95 (m, 2H, *H*-Ar), 7.28–7.33 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.70 (s, CH_3), 16.09 (d, $^3J_{PC}$ = 5.6 Hz, CH_3CH_2O), 16.18 (d, $^3J_{PC}$ = 3.6 Hz, CH_3CH_2O), 41.75 (d, $^2J_{PC}$ = 1.8 Hz, *C*-4), 47.03 (d, $^1J_{PC}$ = 151.0 Hz, *C*-3), 55.03 (s, CH_3O), 62.33 (d, $^2J_{PC}$ = 6.2 Hz, $CH_3CH_2OP(O)$), 63.30 (d, $^2J_{PC}$ = 6.2 Hz, $CH_3CH_2OP(O)$), 87.07 (d, $^3J_{PC}$ = 14.5 Hz, *C*-5), 113.87 (s, 2× *C*-Ar), 127.84 (s, 2× *C*-Ar), 128.56 (s, *C*-Ar), 130.58 (s, *C*-Ar), 170.62 (s, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.67; Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77. Found: C, 56.31; H, 6.92.

5.1.1.10. *r*-3-Diethoxyphosphoryl-*t*-4-methyl-*t*-5-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one (5g″). Oil, yield = 38%; IR (film, cm^{-1}): 1776, 1516, 1252, 1164, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.78 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 1.31–1.42 (m, 6H, ($CH_3CH_2O)_2P(O)$), 2.87 (dd, $^3J_{HH}$ = 3.5 Hz, $^2J_{HP}$ = 23.8 Hz, 1H, *H*-3), 3.11–3.25 (m, 1H, *H*-4), 3.80 (s, 3H, CH_3O), 4.12–4.38 (m, 4H ($CH_3CH_2O)_2P(O)$), 5.84 (d, $^3J_{HH}$ = 6.6 Hz, 1H, *H*-5), 6.87–6.96 (m, 2H, *H*-Ar), 7.13–7.18 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.85 (s, CH_3), 16.05 (d, $^3J_{CP}$ = 3.6 Hz, ($CH_3CH_2O)_2$), 37.39 (d, $^2J_{PC}$ = 1.8 Hz, *C*-4), 47.68 (d, $^1J_{PC}$ = 137.8, *C*-3), 54.92 (s, CH_3O), 62.62 (d, $^2J_{PC}$ = 7.5 Hz, CH_3CH_2O), 63.41 (d, $^2J_{PC}$ = 6.2 Hz, CH_3CH_2O), 82.84 (d, $^3J_{PC}$ = 4.3 Hz, *C*-5), 113.61 (s, 2× *C*-Ar), 126.46 (s, 2× *C*-Ar), 127.19 (s, *C*-Ar), 130.53 (s, *C*-Ar), 171.19 (d, $^2J_{CP}$ = 3.14 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.10; Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77. Found: C, 56.19; H, 6.53.

5.1.2. General procedure for the preparation of 5-aryl-3-methylidene-2-furanones (6a–g). A solution of 5-aryl-3-diethoxyphosphoryl-2-furanones (**5a**–**g**) (1.0 mmol) in Et_2O (5 mL) was added to a suspension of *t*-BuOK (0.146 g, 1.2 mmol) in Et_2O (3 mL), and the reaction mixture was stirred at room temperature for 0.5 h. Next, the paraformaldehyde (0.150 g, 5.0 mmol) was added and the mixture was stirred for 1.5 h then the brine (5 mL) was added, layers were separated, and water layer was washed with Et_2O (2× 10 mL). Combined organic extracts were dried ($MgSO_4$) and evaporated to give crude products which were purified by column chromatography ($CHCl_3$).

5.1.2.1. 3-Methylene-5-phenyl-dihydrofuran-2(3*H*)-one (6a)[46,47]. Oil, yield = 55% (lit. yield 88%[49]).

5.1.2.2. 5-(4-Bromophenyl)-3-methylene-dihydrofuran-2(3*H*)-one (6b)[47]. Oil, yield = 45%; IR (film, cm^{-1}): 1772, 1252, 1136; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.86 (ddt, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 6.5 Hz, $^2J_{HH}$ = 17.0 Hz, 1H, *H*-4), 3.40 (ddt, $^4J_{HH}$ = 2.8 Hz, $^3J_{HH}$ = 8.0 Hz, $^2J_{HH}$ = 17.0 Hz, 1H, *H*-4), 5.48 (dd, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *H*-5), 5.71 (t, $^4J_{HH}$ = 2.8 Hz, 1H, CH_2=C), 6.32 (t, $^4J_{HH}$ = 2.8 Hz, 1H, CH_2=C), 7.19–7.24 (m, 2H, *H*-Ar), 7.50–7.54 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 36.15 (s, *C*-4), 77.17 (s, *C*-5), 122.53 (s, *C*-Ar), 122.82 (s, CH_2=C), 127.04 (s, 2× *C*-Ar), 131.99 (s, 2× *C*-Ar), 133.71 (s, *C*-Ar), 138.84 (s, CH_2=*C*), 169.80 (s, *C*-2); Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58. Found: C, 52.28; H, 3.62.

5.1.2.3. 5-(4-Methoxyphenyl)-3-methylene-dihydrofuran-2(3*H*)-one (6c) and 5-(4-methoxyphenyl)-3-methylfuran-2(5*H*)-one (7c) (60:40). Oil, yield = 61%.

5.1.2.3.1. 5-(4-Methoxyphenyl)-3-methylene-dihydrofuran-2(3*H*)-one (6c)[46,47]. ^{1}H NMR[48] (250 MHz, $CDCl_3$): δ = 2.91 (ddt, $^4J_{HH}$ = 2.9 Hz, $^3J_{HH}$ = 6.6 Hz,

$^{2}J_{HH}$ = 17.0 Hz, 1H, *H*-4), 3.36 (ddt, $^{4}J_{HH}$ = 2.5 Hz, $^{3}J_{HH}$ = 7.9 Hz, $^{2}J_{HH}$ = 17.0 Hz, 1H, *H*-4), 3.81 (s, 3H, C*H*$_3$O), 5.47 (dd, $^{3}J_{HH}$ = 6.6 Hz, $^{3}J_{HH}$ = 7.9 Hz, 1H, *H*-5), 5.68 (dd, $^{4}J_{HH}$ = 2.5 Hz, $^{4}J_{HH}$ = 2.9 Hz, 1H, C*H*$_2$=C), 6.30 (dd, $^{4}J_{HH}$ = 2.5 Hz, $^{4}J_{HH}$ = 2.9 Hz, 1H, C*H*$_2$=C), 6.86–6.93 (m, 2H, *H*-Ar), 7.24–7.27 (m, 2H, *H*-Ar).

5.1.2.3.2. 5-(4-Methoxyphenyl)-3-methylfuran-2(5*H*)-one (7c). ^{1}H NMR[48] (250 MHz, $CDCl_3$): δ = 3.18 (s, 3H, C*H*$_3$), 3.82 (s, 3H C*H*$_3$O), 5.50 (d, $^{3}J_{HH}$ = 1.4 Hz, 1H, H-5), 6.15 (d, $^{3}J_{HH}$ = 1.4 Hz, 1H, H-4), 6.86–6.93 (m, 2H, *H*-Ar), 7.24–7.27 (m, 2H, *H*-Ar).

5.1.2.4. 3-Methylene-5-(naphthalen-1-yl)-dihydrofuran-2(3*H*)-one (6d)[46]. Oil, yield = 30%; (lit. yield = 87%[46]).

5.1.2.5. *t*-4-Methyl-3-methylene-*r*-5-phenyl-dihydrofuran-2(3*H*)-one (6e′)[47]. Oil, yield = 66%; IR (film, cm^{-1}): 1768, 1256, 1136; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, C*H*$_3$), 2.91–3.01 (m, 1H, *H*-4), 4.90 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, *H*-5), 5.62 (d, $^{4}J_{HH}$ = 3.0 Hz, 1H, C*H*$_2$=C), 6.31 (d, $^{4}J_{HH}$ = 3.0 Hz, 1H, C*H*$_2$=C), 7.28–7.46 (m, 5H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.87 (s, *C*H$_3$), 42.39 (s, *C*-4), 84.90 (s, *C*-5), 119.93 (s, *C*H$_2$=C), 124.34 (s, 2× *C*-Ar), 127.76 (s, *C*-Ar), 127.78 (s, 2× *C*-Ar), 137.38 (s, CH$_2$=*C*), 139.49 (s, *C*-Ar), 169.02 (s, *C*-2); Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.41; H, 6.35.

5.1.2.6. *c*-4-Methyl-3-methylene-*r*-5-phenyl-dihydrofuran-2(3*H*)-one (6e″)[46]. Oil, yield = 65%; (lit. yield = 86%[46]).

5.1.2.7. *r*-5-(4-Bromophenyl)-*t*-4-methyl-3-methylene-dihydrofuran-2(3*H*)-one (6f′)[26,47]. Oil, yield = 52%; IR (film, cm^{-1}): 1772, 1256, 1132; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, C*H*$_3$), 2.82–2.94 (m, 1H, *H*-4), 4.86 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H, *H*-5), 5.60 (d, $^{4}J_{HH}$ = 3.0 Hz, 1H, C*H*$_2$=C), 6.32 (d, $^{4}J_{HH}$ = 3.0 Hz, 1H, C*H*$_2$=C), 7.20–7.57 (m, 2H, *H*-Ar), 7.48–7.57 (m, 2H, *H*-Ar); ^{13}C NMR: 15.80 (s, *C*H$_3$), 43.41 (s, *C*-4), 85.12 (s, *C*-5), 121.36 (s, *C*H$_2$=C), 122.82 (s, *C*-Ar), 127.54 (s, 2× *C*-Ar), 131.99 (s, 2× *C*-Ar), 137.46 (s, CH$_2$=*C*), 140.03 (s, *C*-Ar), 169.75 (s, *C*-2); Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 53.99; H, 4.31.

5.1.2.8. *r*-5-(4-Bromophenyl)-*c*-4-methyl-3-methylene-dihydrofuran-2(3*H*)-one (6f″)[26]. Oil, yield = 51%; IR (film, cm^{-1}): 1764, 1252, 1136; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, $^{3}J_{HH}$ = 7.1 Hz, 3H, C*H*$_3$), 3.35–3.51 (m, 1H, *H*-4), 5.57 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H, *H*-5), 5.59 (d, $^{4}J_{HH}$ = 2.6 Hz, 1H, C*H*$_2$=C), 6.34 (d, $^{4}J_{HH}$ = 2.6 Hz, 1H, C*H*$_2$=C), 7.04–7.10 (m, 2H, *H*-Ar), 7.48–7.61 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.42 (s, *C*H$_3$), 38.66 (s, *C*-4), 81.32 (s, *C*-5), 122.11 (s, *C*H$_2$=C), 122.35 (s, *C*-Ar), 127.60 (s, 2× *C*-Ar), 131.63 (s, 2× *C*-Ar), 135.34 (s, CH$_2$=*C*), 139.63 (s, *C*-Ar), 170.18 (s, *C*-2); Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 54.11; H, 4.36.

5.1.2.9. *r*-5-(4-Methoxyphenyl)-*t*-4-methyl-3-methylene-dihydrofuran-2(3*H*)-one (6g′)[46,47]. Oil, yield = 61%; (lit. yield = 76%[46]).

5.1.2.10. *r*-5-(4-Methoxyphenyl)-*c*-4-methyl-3-methylene-dihydrofuran-2(3*H*)-one (6g″)[26,46]. White crystal, mp 82 °C; yield = 66%; (lit. yield = 13%[46]).

5.1.3. General procedure for the preparation of 5-aryl-3-diethoxyphosphorylpyrrolidin-2-ones (9a–c). To a stirred solution of titanium (IV) isopropoxide (1.84 g, 6.5 mmol), 2 N solution of methyl amine in methanol (3.25 mL, 6.5 mmol) was added, then 2-dietoxyphosphoryl-4-oxoalkanoate (**3a**–**c**) (5.0 mmol) in methanol (20 mL) was added at room temperature. The reaction mixture was stirred for 3 h, then sodium borohydride (0.189 g, 5.0 mmol) was added in one portion. Stirring was continued for 24 h. The water (15 mL) was added and methanol was evaporated under reduced pressure. The residue was extracted with chloroform (4× 20 mL). The combined organic layers were washed with water (20 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography ($CHCl_3$/acetone, 90:10) affording pure product.

5.1.3.1. 3-Diethoxyphosphoryl-1-methyl-5-phenylpyrrolidin-2-one (9a). Oil, yield = 77%; IR (film, cm^{-1}): 1688, 1392,1252, 1136, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22–1.67 (m, 6H, (C*H*$_3$CH$_2$O)$_2$P(O) major and minor), 2.05–2.29 (m, 1H major and minor, *H*-4), 2.55–2.91 (m, 1H major and minor, *H*-4), 2.68 (s, 3H, C*H*$_3$N) 3.04–3.14 (m, 1H major and minor, *H*-3), 4.12–4.35 (m, 4H major and minor, (CH$_3$C*H*$_2$O)$_2$P(O)), 4.33–4.67 (m, 1H major and minor, *H*-5), 7.21–7.43 (m, 5H major and minor, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.23 (d, $^{3}J_{PC}$ = 6.9 Hz, *C*H$_3$CH$_2$O), 16.33 (d, $^{3}J_{PC}$ = 6.9 Hz, *C*H$_3$CH$_2$O), 28.41 (s, *C*H$_3$N), 28.55 (s, *C*H$_3$N), 30.10 (d, $^{2}J_{PC}$ = 4.4 Hz, *C*-4), 30.83 (d, $^{2}J_{PC}$ = 4.4 Hz, *C*-4), 40.47 (d, $^{1}J_{PC}$ = 142.8 Hz, *C*-3), 40.58 (d, $^{1}J_{PC}$ = 150.3 Hz, *C*-3), 62.02 (d, $^{2}J_{PC}$ = 6.2 Hz, CH$_3$*C*H$_2$O), 62.12 (d, $^{2}J_{PC}$ = 6.9 Hz, CH$_3$*C*H$_2$O), 62.96, 63.06, 63.10, 63.14, 63.24 (*C*-5, CH$_3$*C*H$_2$OP(O)), 126.34 (s, 2× *C*-Ar), 126.92 (s, 2× *C*-Ar), 128.21 (s, *C*-Ar), 128.29 (s, *C*-Ar), 128.87 (s, 2× *C*-Ar), 128.97 (s, 2× *C*-Ar), 140.01 (s, *C*-Ar), 140.08 (s, *C*-Ar), 169.69 (d, $^{2}J_{PC}$ = 5.0 Hz, *C*-2), 169.76 (d, $^{2}J_{PC}$ = 4.4 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 24.81 minor, 25.00 major; (30:70); Anal. Calcd for $C_{15}H_{22}NO_4P$: C, 57.87; H, 7.12. Found: C, 57.62; H, 7.33.

5.1.3.2. 5-(4-Bromophenyl)-3-diethoxyphosphoryl-1-methylpyrrolidin-2-one (9b). Oil, yield = 92%; IR (film, cm^{-1}): 1692, 1392,1256, 1132, 1024; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31–1.64 (m, 6H, (C*H*$_3$CH$_2$O)$_2$-P(O) major and minor), 2.00–2.32 (m, 1H major and minor, *H*-4), 2.62 (s, 3H, C*H*$_3$N minor), 2.67 (s, 3H, C*H*$_3$N major), 2.57–2.91 (m, 1H major and minor, *H*-4), 3.01–3.20 (m, 1H, *H*-3 major and minor), 4.14–4.31 (m, 4H major and minor, (CH$_3$ C*H*$_2$O)$_2$P(O)), 4.62–4.66 (m, 1H, *H*-5 major and minor), 7.07–7.24 (m, 2H *H*-Ar major and minor), 7.51–7.54 (m, 2H, *H*-Ar major and minor); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.21 (d,

$^{3}J_{PC}$ = 6.9 Hz, CH_3CH_2O), 16.31 (d, $^{3}J_{PC}$ = 6.7 Hz, CH_3CH_2O), 29.46 (s, CH_3N), 29.97 (s, CH_3N), 30.12 (d, $^{2}J_{PC}$ = 3.1 Hz, *C*-4), 30.87 (d, $^{2}J_{PC}$ = 3.4 Hz, *C*-4), 40.64 (d, $^{1}J_{PC}$ = 143.5 Hz, *C*-3), 40.68 (d, $^{1}J_{PC}$ = 149.1 Hz, *C*-3), 62.64 (d, $^{2}J_{PC}$ = 6.2 Hz, CH_3 CH_2O), 62.82 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_3CH_2O), 62.56 (d, $^{3}J_{PC}$ = 3.4 Hz, *C*-5), 63.36 (d, $^{2}J_{PC}$ = 6.2 Hz, CH_3CH_2O), 63.62 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_3CH_2O), 122.38 (s, *C*-Ar), 122.51 (s, *C*-Ar), 126.92 (s, 2× *C*-Ar), 127.32 (s, *C*-Ar), 131.73 (s, 2× *C*-Ar), 137.30 (s, *C*-Ar), 137.46 (s, *C*-Ar), 169.58 (d, $^{2}J_{PC}$ = 4.4 Hz, *C*-2), 169.82 (d, $^{2}J_{PC}$ = 3.4 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 24.39 major and minor; Anal. Calcd for $C_{15}H_{21}BrNO_4P$: C, 46.17; H, 5.42. Found: C, 46.31; H, 5.57.

5.1.3.3. 5-(4-Methoxyphenyl)-3-diethoxyphosphoryl-1-methylpyrrolidin-2-one (9c). Oil, yield = 58%; IR (film, cm^{-1}): 1684, 1398,1256, 1132, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32–1.41 (m, 6H, $(CH_3CH_2O)_2$-P(O) major and minor), 2.09–2.30 (m, 1H major and minor, *H*-4), 2.59 (s, 3H, CH_3N minor), 2.65 (s, 3H, CH_3N major), 2.67–2.89 (m, 1H major and minor, *H*-4), 2.99–3.19 (m, 1H, *H*-3 major and minor), 3.82 (s, 3H, CH_3O major and minor) 4.14–4.31 (m, 4H major and minor, $(CH_3CH_2O)_2P(O)$), 4.60–4.66 (m, 1H, *H*-5 major and minor), 6.89–6.93 (m, 2 H *H*-Ar major and minor), 7.10–7.14 (m, 2H, *H*-Ar major and minor); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.24 (d, $^{3}J_{PC}$ = 6.3 Hz, CH_3CH_2O), 16.33 (d, $^{3}J_{PC}$ = 6.4 Hz, CH_3CH_2O), 28.25 (s, CH_3N), 28.42 (s, CH_3N), 30.15 (d, $^{2}J_{PC}$ = 3.4 Hz, *C*-4), 30.97 (d, $^{2}J_{PC}$ = 3.9 Hz, *C*-4), 40.58 (d, $^{1}J_{PC}$ = 145.7 Hz, *C*-3), 40.64 (d, $^{1}J_{PC}$ = 145.9 Hz, *C*-3), 55.16 (s, CH_3O), 61.92 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_3CH_2O), 62.07 (d, $^{2}J_{PC}$ = 7.2 Hz, CH_3CH_2O), 62.56 (d, $^{3}J_{PC}$ = 3.3 Hz, *C*-5), 63.00 (d, $^{2}J_{PC}$ = 6.5 Hz, $CH_3CH_2OP(O)$), 63.12 (d, $^{2}J_{PC}$ = 7.6 Hz, $CH_3CH_2OP(O)$), 114.19 (s, 2× *C*-Ar), 114.29 (s, 2× *C*-Ar), 127.65 (s, *C*-Ar), 128.23 (s, *C*-Ar), 131.84 (s, 2× *C*-Ar), 131.98 (s, 2× *C*-Ar), 159.46 (s, *C*-Ar), 159.52 (s, *C*-Ar), 169.44 (d, $^{2}J_{PC}$ = 3.2 Hz, *C*-2), 169.56 (d, $^{2}J_{PC}$ = 3.8 Hz, *C*-2); ^{31}P NMR (101 MHz, $CDCl_3$): δ = 24.67 minor, 24.78 major; (40:60); Anal. Calcd for $C_{16}H_{24}NO_5P$: C, 56.30; H, 7.09. Found: C, 56.21; H, 7.22.

5.1.4. General procedure for the preparation of 5-aryl-3-methylidenepyrrolidin-2-ones (10a–c). A solution of 5-aryl-3-diethoxyphosphorylpyrrolidin-2-one (**9a**–**c**) (1.0 mmol) in THF (5 mL) was added to a suspension of NaH (0.033 g, 1.1 mmol) in THF (3 mL) at 0 °C, and the reaction mixture was stirred for 0.5 h. Next, paraformaldehyde (0.330 g, 1.1 mmol) was added at 0 °C and the mixture was stirred for 1.5 h at room temperature. After cooling to 0 °C, brine (5 mL) was added, layers were separated, and water layer was washed with CH_2Cl_2 (2× 10 mL). Combined organic extracts were dried ($MgSO_4$) and evaporated to give crude product which was purified by column chromatography ($CHCl_3$).

5.1.4.1. 1-Methyl-3-methylene-5-phenylpyrrolidin-2-one (10a)[15,49]. Oil, yield = 79%; IR (film, cm^{-1}): 1692, 1432, 1284, 1080; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (ddt, $^{4}J_{HH}$ = 2.6 Hz, $^{3}J_{HH}$ = 5.0 Hz, $^{2}J_{HH}$ = 17.2 Hz, 1H, *H*-4), 2.78 (s, 3H, CH_3N), 3.23 (ddt, $^{4}J_{HH}$ = 2.6 Hz, $^{3}J_{HH}$ = 8.5 Hz, $^{2}J_{HH}$ = 17.2 Hz, 1H, *H*-4), 4.52 (dd, $^{3}J_{HH}$ = 5.0 Hz, $^{3}J_{HH}$ = 8.5 Hz, 1H, *H*-5), 5.36 (t, $^{4}J_{HH}$ = 2.6 Hz, 1H, CH_2=C), 6.08 (t, $^{4}J_{HH}$ = 2.6 Hz, 1H, CH_2=C), 7.18–7.22 (m, 2H, *H*-Ar), 7.33–7.43 (m, 3H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.53 (s, CH_3N), 34.79 (s, *C*-4), 61.40 (s, *C*-5), 115.43 (s, CH_2=C), 126.27 (s, 2× *C*-Ar), 128.18 (s, *C*-Ar), 129.02 (s, 2× *C*-Ar), 138.75 (s, CH_2=*C*), 140.90 (s, *C*-Ar), 168.39 (s, *C*-2); Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00. Found: C, 76.75; H, 7.22.

5.1.4.2. 5-(4-Bromophenyl)-1-methyl-3-methylenepyrrolidin-2-one (10b). Oil, yield = 65%; IR (film, cm^{-1}): 1688, 1484, 1392, 1076; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.58 (ddt, $^{4}J_{HH}$ = 2.7 Hz, $^{3}J_{HH}$ = 5.1 Hz, $^{2}J_{HH}$ = 17.3 Hz, 1H, *H*-4), 2.75 (s, 3H, CH_3N), 3.22 (ddt, $^{4}J_{HH}$ = 2.4 Hz, $^{3}J_{HH}$ = 8.5 Hz, $^{2}J_{HH}$ = 17.3 Hz, 1H, *H*-4), 4.47 (dd, $^{3}J_{HH}$ = 5.1 Hz, $^{3}J_{HH}$ = 8.5 Hz, 1H, *H*-5), 5.36 (dd, $^{4}J_{HH}$ = 2.4 Hz, $^{4}J_{HH}$ = 2.7 Hz, 1H, CH_2=C), 6.08 (dd, $^{4}J_{HH}$ = 2.4 Hz, $^{4}J_{HH}$ = 2.7 Hz, 1H, CH_2=C), 7.04–7.09 (m, 2H, *H*-Ar), 7.48–7.53 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.52 (s, CH_3N), 34.62 (s, *C*-4), 60.82 (s, *C*-5), 115.87 (s, CH_2=C), 122.05 (s, *C*-Ar), 127.95 (s, 2× *C*-Ar), 132.19 (s, 2× *C*-Ar), 138.20 (s, CH_2=*C*), 139.97 (s, *C*-Ar), 168.30 (s, *C*-2); Anal. Calcd for $C_{12}H_{12}BrNO$: C, 54.16; H, 4.54. Found: C, 54.00; H, 4.55.

5.1.4.3. 5-(4-Methoxyphenyl)-1-methyl-3-methylenepyrrolidin-2-one (10c). Yellow crystal, mp 95 °C, yield = 59%; IR (film, cm^{-1}): 1684, 1512, 1436, 1284, 1080; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (ddt, $^{4}J_{HH}$ = 2.7 Hz, $^{3}J_{HH}$ = 5.0 Hz, $^{2}J_{HH}$ = 17.3 Hz, 1H, *H*-4), 2.73 (s, 3H, CH_3N), 3.19 (ddt, $^{4}J_{HH}$ = 2.7 Hz, $^{3}J_{HH}$ = 8.3 Hz, $^{2}J_{HH}$ = 17.3 Hz, 1H, *H*-4), 3.81 (s, 3H, CH_3O), 4.45 (dd, $^{3}J_{HH}$ = 5.0 Hz, $^{3}J_{HH}$ = 8.3 Hz, 1H, *H*-5), 5.34 (t, $^{4}J_{HH}$ = 2.7 Hz, 1H, CH_2=C), 6.06 (t, $^{4}J_{HH}$ = 2.7 Hz, 1H, CH_2=C), 6.87–6.92 (m, 2H, *H*-Ar), 7.09–7.12 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.41 (s, CH_3N), 34.93 (s, *C*-4), 55.27 (s, CH_3O), 60.90 (s, *C*-5), 114.36 (s, 2× *C*-Ar), 115.30 (s, CH_2=C), 127.56 (s, 2× *C*-Ar), 132.82 (s, CH_2=*C*), 138.96 (s, *C*-Ar), 159.49 (s, *C*-Ar), 168.30 (s, *C*-2); Anal. Calcd for $C_{13}H_{15}NO$: C, 71.87; H, 6.96. Found: C, 72.03; H, 6.90.

5.1.5. General procedure for the preparation of 3-alkylidene-5-aryl-2 furanones (11a–b). A solution of 3-diethoxyphosphoryl-5-phenyl-2-furanone (**5a**) (0.300 g, 1.0 mmol) in THF (5 mL) was added to a suspension of NaH (0.033 g, 1.1 mmol) in THF (3 mL), and the reaction mixture was stirred at room temperature for 0.5 h. Next, appropriate aldehyde (1.1 mmol) was added and the mixture was refluxed for 1.5 h. After cooling to room temperature, brine (5 mL) was added, layers were separated, and water layer was washed with CH_2Cl_2 (2× 10 mL). Combined organic extracts were dried ($MgSO_4$) and evaporated to give crude product which was purified by column chromatography ($CHCl_3$).

5.1.5.1. (*Z*)-3-(2-Methylpropylidene)-5-phenyl-dihydrofuran-2(3*H*)-one (*Z*)-(11a). Oil, yield = 88%; IR (film, cm^{-1}): 1756, 1364, 1200; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (d, $^{3}J_{HH}$ = 6.8 Hz, $(CH_3)_2CH$), 2.85 (ddd,

$^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^2J_{HH}$ = 16.0 Hz, 1H, *H*-4), 3.28 (ddd, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^2J_{HH}$ = 16.0 Hz, 1H, *H*-4), 3.70–3.86 (m, $(CH_3)_2CH$), 5.45 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *H*-5), 5.69 (dt, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, C*H*=C), 7.30–7.43 (m, 5H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.24 (s, CH_3), 22.37 (s, CH_3), 26.31 (s, $(CH_3)_2CH$), 37.77 (s, *C*-4), 77.80 (s, *C*-5), 121.99 (s, *C*-Ar), 125.30 (s, 2× *C*-Ar), 128.25 (s, *C*-Ar) 128.62 (s, 2× *C*-Ar), 140.05 (s, CH=*C*), 150.82 (s, CH=*C*), 169.29 (s, *C*-2); Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.83; H, 7.55.

5.1.5.2. (*Z*) and (*E*)-3-(2-Methylpropylidene)-5-phenyldihydrofuran-2(3*H*)-one (*Z*,*E*)-(11a). Oil, ^{1}H NMR[48] (250 MHz, $CDCl_3$): δ = 1.04 (d, $^3J_{HH}$ = 6.8 Hz, $(CH_3)_2CH$ Z_{isomer}), 1.05 (d, $^3J_{HH}$ = 6.6 Hz, $(CH_3)_2CH$ E_{isomer}), 2.77 (ddd, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 6.4 Hz, $^2J_{HH}$ = 16.7 Hz, 1H, *H*-4 E_{isomer}), 2.85 (ddd, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^2J_{HH}$ = 16.0 Hz, 1H, *H*-4 Z_{isomer}), 3.28 (ddd, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^2J_{HH}$ = 16.0 Hz, 1H, *H*-4 Z_{isomer}), 3.33 (ddd, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 8.1 Hz, $^2J_{HH}$ = 16.7 Hz, 1H, *H*-4 Z_{isomer}), 3.70–3.86 (m, $(CH_3)_2CH$ Z_{isomer} + E_{isomer}), 5.45 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *H*-5 Z_{isomer}), 5.52 (dd, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, *H*-5 E_{isomer}), 5.69 (dt, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, C*H*=C Z_{isomer}), 6.03 (dt, $^4J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 10.1 Hz, 1H, C*H*=C E_{isomer}), 7.30–7.43 (m, 5H, *H*-Ar Z_{isomer} + E_{isomer}).

5.1.5.3. (*E*)-3-Benzylidene-5-phenyl-dihydrofuran-2(3*H*)-one (11b)[50]. Oil, yield = 50%; IR (film, cm^{-1}): 1732, 1320, 1232, 1192; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.96 (ddd, $^4J_{HH}$ = 2.7 Hz, $^3J_{HH}$ = 6.0 Hz, $^2J_{HH}$ = 17.5 Hz, 1H, *H*-4), 3.64 (ddd, $^4J_{HH}$ = 2.7 Hz, $^3J_{HH}$ = 8.3 Hz, $^2J_{HH}$ = 17.5 Hz, 1H, *H*-4), 5.62 (dd, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, *H*-5), 7.32–7.63 (m, 10H, *H*-Ar), 7.67 (t, $^4J_{HH}$ = 2.7 Hz, 1H, C*H*=C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 36.44 (s, *C*-4), 78.06 (s, *C*-5), 124.02 (s, *C*-Ar), 125.28 (s, 2× *C*-Ar), 128.46 (s, CH=*C*) 128.80 (s, 2× *C*-Ar), 128.85 (s, *C*-Ar), 129.87 (s, 2× *C*-Ar), 129.95 (s, 2× *C*-Ar), 134.45 (s, *C*-Ar) 136.86 (s, *C*H=C), 140.21 (s, *C*-Ar), 171.86 (s, *C*-2); Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.76; H, 5.65.

5.1.6. The preparation of (*E*)-1-methyl-3-(2-methylpropylidene)-5-phenylpyrrolidin-2-one (12). A solution of 3-diethoxyphosphoryl-5-phenylpyrrolidin-2-one (**9a**) (0.311 g, 1.0 mmol) in THF (5 mL) was added to a suspension of NaH (0.033 g, 1.1 mmol) in THF (3 mL) at 0 °C, and the reaction mixture was stirred for 0.5 h at that temperature. Next, isobutyraldehyde (0.080 g, 1.1 mmol) was added and the resulting mixture was refluxed for 1.5 h. After cooling to 0 °C, brine (5 mL) was added, layers were separated, and water layer was washed with CH_2Cl_2 (2× 10 mL). Combined organic extracts were dried ($MgSO_4$) and evaporated to give crude product which was purified by column chromatography ($CHCl_3$). Oil, yield = 59%; IR (film, cm^{-1}): 1752, 1368, 1204; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (d, $^3J_{HH}$ = 6.7 Hz, CH_3), 1.02 (d, $^3J_{HH}$ = 6.7 Hz, CH_3), 2.58 (ddd, $^4J_{HH}$ = 2.3 Hz, $^3J_{HH}$ = 4.5 Hz, $^2J_{HH}$ = 16.5 Hz, 1H, *H*-4), 2.70 (s, CH_3N), 3.13 (ddd, $^4J_{HH}$ = 2.3 Hz, $^3J_{HH}$ = 8.6 Hz, $^2J_{HH}$ = 16.5 Hz, 1H, *H*-4), 4.04 (dq, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 9.9 Hz, 1H, $(CH_3)_2CH$), 4.44 (dd, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, *H*-5), 5.65 (dt, $^4J_{HH}$ = 2.3 Hz, $^3J_{HH}$ = 9.9 Hz, 1H, C*H*=C), 7.12–7.21 (m, 2H, *H*-Ar), 7.32–7.35 (m, 2H, *H*-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.20 (s, $(CH_3)_2CH$), 23.63 (s, *C*H), 26.48 (s, CH_3N), 34.54 (s, *C*-4), 69.88 (s, *C*-5), 124.45 (s, CH_2=*C*), 124.62 (s, 2× *C*-Ar), 126.26 (s, CH_2=*C*), 127.02 (s, 2× *C*-Ar), 139.62 (s, *C*-Ar), 142.36 (s, *C*-Ar), 167.28 (s, *C*-2); Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.73; H, 8.58.

5.2. Pharmacology

5.2.1. Cells and cytotoxicity assays. Mouse leukemia L-1210 cells were cultured in RPMI 1640 medium (Sigma, St. Louis, MO) supplement with 10% fetal calf serum (Gibco, Berlin, Germany), gentamycin (50 μg/mL) and 0.02 M Hepes buffer (Gibco). Cytostatic effects were assayed by measuring inhibitory effects on L-1210 cell proliferation. In this assay, cells were seeded in 2 mL aliquots onto a 24-well plate (NUNC, Denmark) at a concentration 1.5×10^3 cells/mL. After 24 h, drug solution was added and incubation was carried out for an additional 46 h. The cell number relative to control was determined by a tetrazolium dye method.[51]

Human leukemia promyelocytic HL-60 and lymphoblastic NALM-6 cell lines were used. Leukemia cells were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen, Paisley, UK) and antibiotics (100 μg/mL streptomycin and 100 U/mL penicillin). Cells were grown in 37 °C in a humidified atmosphere of 5% CO_2 in air. Cytotoxic activity was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylterazolium bromide, Sigma, St. Louis, USA] assay.[52] Exponentially growing leukemia cells were seeded at 8×10^3/well on 96-well plate (Nunc, Roskilde, Denmark). Stock solutions of the analyzed compounds were freshly prepared in DMSO and diluted with complete culture medium to obtain the concentration range from 10^{-7} to 10^{-3} M. Cells were exposed to the test compounds for 46 h, then MTT reagent was added and incubation was continued for 2 h. After incubation, MTT-formazan crystals were dissolved in 20% SDS and 50% DMF at pH 4.7 and absorbance was read at 562 and 630 nm on an ELISA-plate reader (ELX 800, Bio-Tek, USA). As a control, cultured cells were grown in the absence of drugs. The values of IC_{50} (the concentration of the tested compound required to reduce the cells survival fraction to 50% of the control) were calculated from concentration–response curves and used as a measure of cellular sensitivity to a given treatment. Data points represent means of at least 6 repeats ± SD.

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