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Regioselective synthesis of cytotoxic 4-(1-alkynyl)-substituted 2-(5*H*)-furanones

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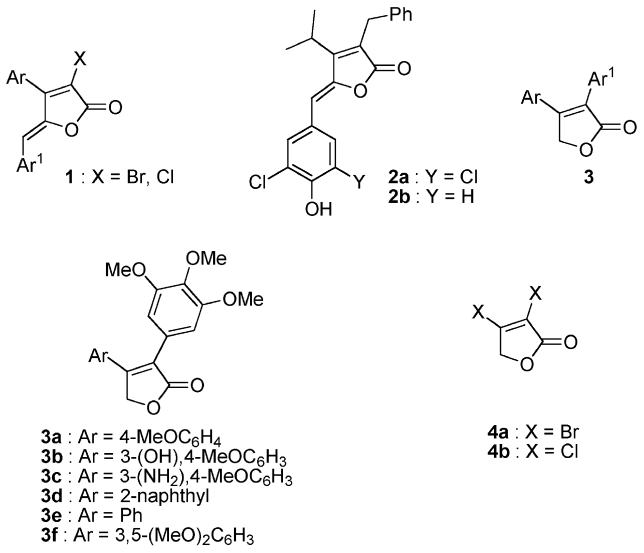
Abstract—4-(1-Alkynyl)-3-bromo- and 4-(1-alkynyl)-3-chloro-2(5*H*)-furanones have been regioselectively synthesized in moderate to good yields by a new version of the Pd/Cu-catalyzed Sonogashira reaction involving treatment of 1-alkynes with 3,4-dibromo- and 3,4-dichloro-2(5*H*)-furanone, respectively, in the presence of KF as a base. 4-(1-Alkynyl)-3-bromo-2(5*H*)-furanones have been found to be able to undergo Stille-type and Suzuki-type reactions with aryl(tributyl)tins and arylboronic acids, respectively, to give 4-(1-alkynyl)-3-aryl-2(5*H*)-furanones in modest to satisfactory yields. Some 4-(1-alkynyl)-substituted 2(5*H*)-furanones so prepared have been found to exhibit significant cytotoxic activities, especially against human leukemia cell lines.

1. Introduction

2(5*H*)-Furanone derivatives include 3,4,5-trisubstituted compounds, such as natural and unnatural (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-halo-2(5*H*)-furanones **1**[1–4] and naturally-occurring nostoclides I (**2a**) and II (**2b**),[5] that exhibit cytotoxicity against human cancer cell lines.

Moreover, 3,4-diaryl-2(5*H*)-furanones **3** have also been reported as cytotoxic agents.[4,6,7] Thus, compounds **3a**–**d** have been found to have significant cytotoxic activities against A549, SK-MEL-2 and MCF-7 cell lines[6] and compounds **3d** and **3f**, which were very recently tested in the in vitro human disease-oriented tumor cell line screening panel developed at the US National Cancer Institute (NCI), have been found to exhibit potent cytotoxicity, especially against human leukemia cell lines where they showed $\log_{10}$ GI50 values lower than -8.[7]

Recently, as part of our ongoing research program directed towards the development of efficient procedures for the preparation of unsymmetrical 3,4-disubstituted 2(5*H*)-furanone derivatives, which are cytotoxic against human tumor cell lines, we decided to investigate the use of readily available 3,4-dibromo- and 3,4-dichloro-2(5*H*)-furanone, (**4a**) and (**4b**) respectively,[8] for the selective synthesis of potentially cytotoxic 4-(1-alkynyl)-substituted 2(5*H*)-furanones of general formula **5a**, **5b**, **6** and **7**.



In fact, examples either of 3-bromo- and 3-chloro-2(5*H*)-furanones or of alkynyl-substituted heterocycles that exhibit significant cytotoxicity have been reported in the literature.[1,9–11] In this paper we wish to report an account on the results of our synthetic efforts to prepare compounds **5a**, **5b**, **6** and **7** and of some tests performed to evaluate the cytotoxic activities of some these 2(5*H*)-furanone derivatives.

Keywords: 2-(5*H*)-furanones; regioselectivity; palladium catalysis; cytotoxicity; Sonogashira reaction.
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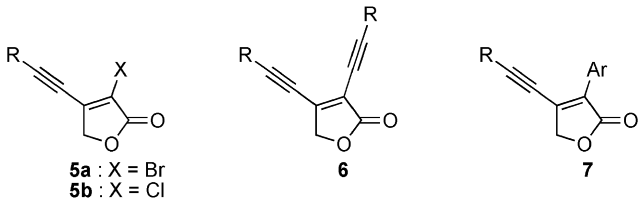
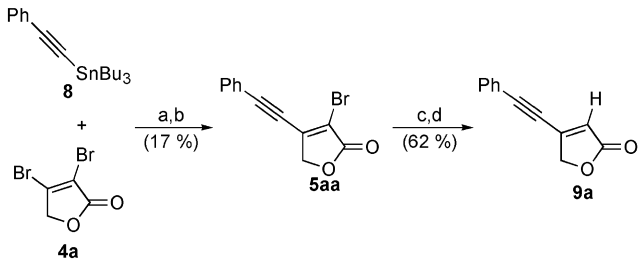


2. Results and discussion

2.1. Synthesis of 4-(1-alkynyl)-3-bromo- and 4-(1-alkynyl)-3-chloro-2(5*H*)-furanones

We began our synthetic studies by investigating the synthesis of 3-bromo-4-(phenylethynyl)-2(5*H*)-furanone (**5aa**) and in a preliminary experiment we found that reaction of **4a** with 1.05 equiv. of tributyl(phenylethynyl)tin (**8**) in a mixture of THF and acetonitrile at 40°C for 20 h, in the presence of 10 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI, provided the desired cross-coupled product **5aa** with complete regioselectivity but in modest yield (17%) (Scheme 1). The structure of compound **5aa** could be anticipated given that **4a** represents the cyclic analog of methyl (*Z*)-2,3-dibromopropenoate and that, similarly to this compound, it may exhibit regioselectivity in Pd-catalyzed cross-coupling reactions.[12] The structure of **5aa** was confirmed by its conversion to the known 2(5*H*)-furanone **9a**,[13] which was obtained in 62% yield by treatment of **5aa** with 4.0 equiv. of activated zinc dust[14] in refluxing THF for 27 h, followed by acidic hydrolysis (Scheme 1).

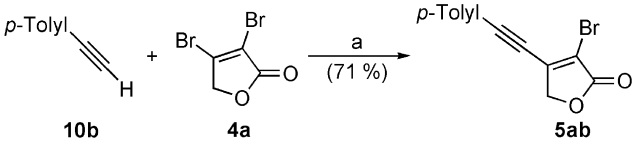


Scheme 1. (a) $PdCl_2(PPh_3)_2$ (10 mol%), CuI (10 mol%), THF, MeCN, 40°C, 16 h; (b) aq. KF, Et_2O and then MPLC on silica gel; (c) activated zinc dust (4 equiv.), THF, 27 h, reflux; (d) 5% HCl, 0°C.

The unsatisfactory yield obtained in the Pd-catalyzed reaction of **4a** with **8** prompted us to explore the preparation of **5aa** via Sonogashira reaction of **4a** with phenylacetylene (**10a**),[15] even though we were conscious that, due to the rapid decomposition of **4a** in the presence of amines, we could not perform this Pd/Cu-catalyzed reaction in the classical reaction conditions which involve the use of a base such as Et_2NH, Et_3N, *i*-Pr_2NH or EtN(*i*-Pr)$_2$.[15] As shown in Table 1, we tested some catalyst precursors and bases for the reaction between **4a** and **10a** and eventually we found that the $PdCl_2(PhCN)_2$/CuI/P(2-furyl)$_3$/KF system proved to be the best to prepare compound **5aa** (entry 3).

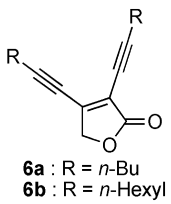
Table 1 also shows that: (i) although the cross-coupling reaction could be successfully performed in toluene (entry 4), the best results were obtained when it was performed under phase-transfer conditions,[16] i.e. in a 1:1 mixture of toluene and water in the presence of 10 mol% $BnEt_3N^+Cl^-$ (entries 1–4); (ii) the use of a base such as K_3PO_4 or K_2CO_3 in these last reaction conditions resulted in the decomposition of **4a** (entries 7 and 8); (iii) CsF and KF promoted the cross-coupling reaction (entries 3 and 6), but the use of 4.0 equiv. of KF (entry 3) allowed us to obtain **5aa** in a higher yield; and (iv) a lower yield of **5aa** was obtained when 1.5 equiv. instead of 4.0 equiv. of KF were used (compare entries 4 and 5). Moreover, very long reaction times were required for complete reaction when 1.5 equiv. of KF were used. Finally, it is worth mentioning that the reactions shown in entries 1–6 of Table 1 occurred with regioselectivity higher than 98%.

We then tested the efficiency of the $PdCl_2(RCN)_2$ (R=Ph, Me)/CuI/P(2-furyl)$_3$/KF systems for the synthesis of 3-bromo-4-[(*p*-tolyl)ethynyl]-2(5*H*)-furanone (**5ab**) and 4-[(alkyl)ethynyl]-3-bromo-2(5*H*)-furanones such as compounds **5ac**, **5ad**, **5ae**, **5af** and **5ag** from the corresponding 1-alkynes and **4a**. As shown in Scheme 2, compound **5ab** was obtained in 71% yield by reaction of **4a** with 1.2 equiv. of **10b** in a 1:1 mixture of toluene and water at 50°C for 74 h in the presence of 4.0 equiv. of KF, 10 mol% $BnEt_3N^+Cl^-$ and the *catalyst system C* previously employed to synthesize **5aa** in 85% yield (entry 3, Table 1).



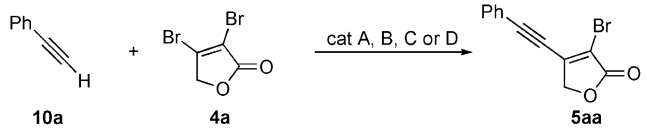
Scheme 2. (a) **10b** (1.2 equiv.), $BnEt_3N^+Cl^-$ (10 mol%), $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), P(2-furyl)$_3$ (10 mol%), KF (4 equiv.), toluene–water (1:1), 50°C, 74 h.

On the other hand, Table 2 summarizes the results obtained in the synthesis of compounds **5ac**, **5ad**, **5ae**, **5af** and **5ag**, which was performed in toluene or in a 1:1 mixture of toluene and water under phase-transfer conditions. Two aspects of these results merit comments: Firstly, all preparations reported in Table 2, save that of **5af**, occurred with satisfactory to high yields when they were performed on a ca. 2 mmol scale. However, when **5ac** was prepared on a ca. 20 mmol scale, it was isolated in a yield of 42%, significantly lower than that obtained when the reaction was performed on a 2 mmol scale (compare entry 3 with entries 1 and 2). Secondly, the selectivity of the reactions summarized in Table 2 proved sometimes to be lower than that obtained in the preparations of **5aa** and **5ab**. Thus, the crude products derived from the preparations of **5ac** and **5ag**, which are reported in entries 2 and 7, proved to be contaminated by ca. 3–5% of the corresponding symmetrical 3,4-di(1-alkynyl)-2(5*H*)-furanones **6a** and **6b**, respectively.



The first of these compounds was prepared in 27% yield by

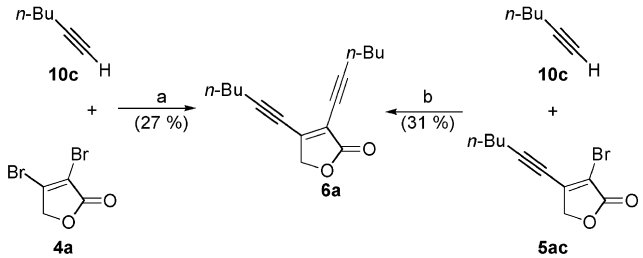
Table 1. Synthesis of **5aa** by Sonogashira reaction using different experimental conditions



Entry[a]	Catalyst system[b]	Base (equiv.)	Solvent[c]	Reaction conditions (h/°C)	Yield (%)
1	A	KF (4.0)	Toluene–water (1:1)	19/20 then 53/40	63
2	B	KF (4.0)	Toluene–water (1:1)	144/40	50
3	C	KF (4.0)	Toluene–water (1:1)	72/40	85
4	D	KF (4.0)	Toluene	75/60	47
5	C	KF (1.5)	Toluene	200/60	28
6	D	CsF (4.0)	Toluene–water (1:1)	48/40	66
7	D	K_2CO_3 (4.0)	Toluene–water (1:1)	9/40	–[d]
8	D	K_3PO_4 (4.0)	Toluene–water (1:1)	9/40	–[d]

[a] All these reactions were performed on a ca. 2 mmol scale using 1.20 equiv. of **10a** and a 7.8:8.4 ratio between the number of ml of the reaction solvent and the number of mmol of **4a**.
[b] *Catalyst system A*: $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%). *Catalyst system B*: $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), $AsPh_3$ (10 mol%). *Catalyst system C*: $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), P(2-furyl)$_3$ (10 mol%). *Catalyst system D*: $PdCl_2(MeCN)_2$ (5 mol%), CuI (10 mol%), P(2-furyl)$_3$ (10 mol%).
[c] $BnEt_3N^+Cl^-$ was used as a phase-transfer catalyst for the reactions performed in a 1:1 mixture of toluene and water.
[d] In this reaction the complete decomposition of **4a** was observed.

reaction of **4a** with 3.0 equiv. of **10c** in toluene at 90°C for 160 h in the presence of 4.0 equiv. of KF, 5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI, 10 mol% $AsPh_3$ and 5 mol% $BnEt_3N^+Cl^-$ or in 31% yield by treatment of **5ac** with 2.0 equiv. of **10c** in toluene at 90°C for 73 h in the presence of 4.0 equiv. of KF, 5 mol% $PdCl_2(MeCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$ (Scheme 3).

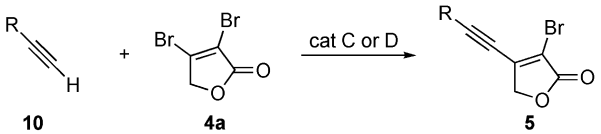


Scheme 3. (a) **10c** (3.0 equiv.), $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), $AsPh_3$ (10 mol%), KF (4 equiv.), toluene, 90°C, 160 h; (b) **10c** (2.0 equiv.), $PdCl_2(MeCN)_2$ (5 mol%), CuI (10 mol%), $AsPh_3$ (10 mol%), KF (4 equiv.), toluene, 90°C, 73 h.

It should also be noted that the structural assignment to the 4-(1-alkynyl)-3-bromo-2(5*H*)-furanones reported in Table 2 could be confirmed by conversion of one of these compounds, i.e. **5ag**, into the corresponding 4-(1-alkynyl)-2(5*H*)-furanone **9b** by a procedure very similar to that employed to prepare **9a** from **5aa** (Scheme 4).

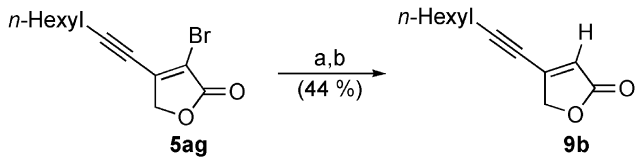
We then continued our studies on the regioselective monoalkynylation reactions of 3,4-dihalo-2(5*H*)-furanones by investigating the Sonogashira reaction of 3,4-dichloro-2(5*H*)-furanone (**4b**). We found that, unfortunately, the reaction conditions and the catalyst systems successfully used for the regioselective monoalkynylation of **4a** were unsuitable for the synthesis of 4-(1-alkynyl)-3-chloro-2(5*H*)-furanones **5b** from the corresponding 1-alkynes **10** and **4b**. Moreover, very low conversions were also obtained when **4b** was reacted with 1.2 equiv. of **10a** (i) in toluene at 100°C for 47 h, in the presence of 2 mol% Na_2PdCl_4,

Table 2. Sonogashira reaction between **4a** by Sonogashira reaction and aliphatic 1-alkynes **10**



Entry[a]	1-Alkyne		Catalyst system[b]	Solvent	Reaction conditions (h/°C)	Product	
	10	R				**5**	Yield (%)
1	**10c**	*n*-Bu	C	Toluene–water (1:1)	39/40	**5ac**	72
2	**10c**	*n*-Bu	D	Toluene	76/60	**5ac**	91
3[c]	**10c**	*n*-Bu	D	Toluene	112/65	**5ac**	42
4	**10d**	*t*-Bu	C	Toluene–water (1:1)	49/40	**5ad**	84
5	**10e**	Me_2COH	D	Toluene	51/65	**5ae**	40
6	**10f**	Me_3Si	D	Toluene	24/40 then 87/60	**5af**	30
7	**10g**	*n*-Hexyl	C	Toluene–water (1:1)	91/40	**5ag**	75

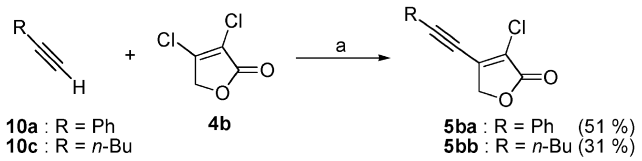
[a] Unless otherwise reported these reactions were performed on a ca. 2 mmol scale using 1.2 equiv. of 1-alkyne **10**. The reactions in toluene–water (1:1) were performed in the presence of 10 mol% $BnEt_3N^+Cl^-$.
[b] *Catalyst system C*: $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), P(2-furyl)$_3$ (10 mol%). *Catalyst system D*: $PdCl_2(MeCN)_2$ (5 mol%), CuI (10 mol%), P(2-furyl)$_3$ (10 mol%).
[c] This reaction was performed on a ca. 20 mmol scale.



Scheme 4. (a) Activated zinc dust (4 equiv.), THF, 20 h, reflux; (b) 5% HCl, 0°C.

1.5 mol% CuI, 1.4 equiv. of KF and 4 mol% *t*-Bu_3P, (ii) in a 1:1 mixture of toluene and water for 71 h at room temperature in the presence of 4.0 equiv. of KF, 5 mol% $BnEt_3N^+Cl^-$, 5 mol% $Pd(PPh_3)_4$ and 10 mol% CuI or (iii) in toluene at 80°C for 18 h in the presence of 1.0 equiv. of KF, 2.5 mol% $Pd_2(dba)_3$, 10 mol% CuI and 10 mol% P(*o*-tolyl)$_3$. Under these reaction conditions significant amounts of 1,4-diphenylbutadiyne derived from homo-coupling of **10a** were also obtained. Finally, we found that reaction of **4b** with 3.0 equiv. of **10a** in a 1:1 mixture of toluene and water at 65°C for 165 h in the presence of 4.0 equiv. of KF, 5 mol% $PdCl_2(MeCN)_2$, 10 mol% CuI, 10 mol% PCy_3 and 5 mol% $BnEt_3N^+Cl^-$ provided 3-chloro-4-(phenylethynyl)-2(5*H*)-furanone (**5ba**) in 51% yield and with complete regioselectivity (Scheme 5). Interestingly, these reaction conditions proved also to be suitable for the preparation of compound **5bb** in 31% yield by reaction of **4b** with **10c** (Scheme 5).

2.2. Synthesis of 3-aryl-4-(1-alkynyl)-2(5*H*)-furanones



Scheme 5. (a) **10a** or **10c** (3.0 equiv.), $BnEt_3N^+Cl^-$ (5 mol%), $PdCl_2(MeCN)_2$ (5 mol%), CuI (10 mol%), PCy_3 (10 mol%), KF (4 equiv.), toluene–water (1:1), 65°C, 165–167 h.

We next turned our attention to the synthesis of 3-aryl-4-(1-alkynyl)-2(5*H*)-furanones by Stille-type[17] or Suzuki-type reactions[18] of bromides **5a** with aryl(tributyl)tins or arylboronic acids, respectively. Thus, we found that reaction of **5ac** with 3.0 equiv. of aryl(tributyl)tin **11a** in NMP at 80°C for 28 h in the presence of 5 mol% $PdCl_2[P(o\text{-tolyl})_3]_2$ and 10 mol% CuI provided **7a** in 50% yield (entry 1, Table 3). On the other hand, reaction of **5aa** with 1.4 equiv. of **11b** or 1.5 equiv. of **11c** under similar experimental conditions produced compounds **7b** and **7c** in 36 and 15% yield, respectively (entries 2 and 3, Table 3).

Better results were obtained in the synthesis of compounds **7** by a Suzuki-type reaction.

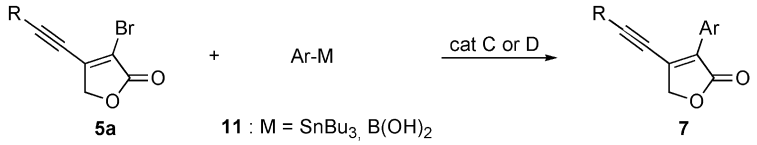
In fact, when **5ac** was treated with 2.0 equiv. of the arylboronic acid **11d** in a 1:1 mixture of toluene and water at 60°C for 23 h in the presence of 3.0 equiv. of CsF, 5 mol% $PdCl_2(PPh_3)_2$ and 5 mol% $BnEt_3N^+Cl^-$, compound **7a** could be isolated in a 59% yield. Moreover, reaction of **5aa** with 2.0 equiv. of arylboronic acid **11e** under very similar reaction conditions provided compound **7d** in 69% yield. It should be noted that we prepared this last compound since the presence of the 3,4,5-trimethoxyphenyl group at C-3 seems to be essential for the cytotoxicity of 2(5*H*)-furanone derivatives against murine and human tumor cell lines.[19]

2.3. Biological results

The cytotoxic activities of compounds **5aa**, **5ab**, **5ac**, **5ad** and **7a** were evaluated in vitro against the NCI three-cell lines panel consisting of MCF7 (breast), SF-268 (CNS), and NCI-H460 (lung). The protocol used involved inoculation and preincubation of each cell line on a microtiter plate. Tests agents were then added at a single concentration (1.00×10^{-4} M) and the culture incubated for 48 h. End-point determinations were made with sulforhodamine B, a protein-binding dye. Results for each test (Table 4) are reported as the percent of growth of the treated cells when compared to the untreated control cells.

Compounds which reduced the growth of any one of the cell lines to 32% or less were considered to be active and some of them were passed on for evaluation over a 5-log dose range in the NCI's in vitro human disease-oriented tumor cell line screening panel that consisted of 60 human tumor cell lines arranged in nine subpanels, representing diverse histologies.[20] Results from Table 4 indicate that compounds **5aa**, **5ac**, **5ad**,

Table 3. Synthesis of 4-(1-alkynyl)3-aryl-2(5*H*)-furanones **7**



Entry[a]	Reagents					Catalyst system[b]	Solvent	Reaction conditions (h/°C)	Product	
	5a	R	**11** (equiv.)	Ar	M				**7**	Yield (%)
1	**5ac**	*n*-Bu	**11a** (3.0)	4-$MeOC_6H_4$	$SnBu_3$	E	NMP	28/80	**7a**	50
2	**5aa**	Ph	**11b** (1.4)	2-$MOMOC_6H_4$	$SnBu_3$	E	NMP	28/80	**7b**	36
3	**5aa**	Ph	**11e** (1.5)	2-furyl	$SnBu_3$	E	NMP	28/80	**7c**	15
4	**5ac**	*n*-Bu	**11d** (2.0)	4-$MeOC_6H_4$	$B(OH)_2$	F	toluene–water (1:1)	23/60	**7a**	59
5	**5aa**	Ph	**11e** (2.0)	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	F	toluene–water (1:1)	70/60	**7d**	69

[a] The coupling reactions involving arylboronic acids were performed in the presence of 3.0 equiv. CsF and 5 mol% $BnEt_3N^+Cl^-$.
[b] *Catalyst system E*: $PdCl_2[P(o\text{-tolyl})_3]_2$ (5 mol%), CuI (10 mol%). *Catalyst system F*: $PdCl_2(PPh_3)_2$ (5 mol%).

Table 4. Primary anticancer assay of 4-(1-alkynyl) substituted 2(5*H*)-furanone derivatives

Compound	Percentage of growth inhibition		
	NCI-H460 (lung)	MC F 7 (breast)	SF-268 (CNS)
5aa	1	1	39
5ab	64	101	98
5ac	1	2	1
5ad	1	1	55
5ba	3	0	43
7a	80	114	105
7d	6	54	67

5ba and **7d** passed the three-cell lines primary screening, but only **5ac** was found to be significantly cytotoxic against the three cell lines. Compounds **5aa**, **5ac** and **5ad** were further evaluated for potential anticancer activity in the 60 human tumor cell line panel.

For each compound, dose-response curves for each cell lines were measured with five different drug concentrations. The $\log_{10}$ GI_{50} values (GI_{50} being the molar drug concentration required for half growth inhibition) obtained with leukemia cell lines, along with the mean graph mid-point (MGM) values, are summarized in Table 5. The MGM is based on a calculation of the average $\log_{10}$ GI_{50} for all of the cell lines tested in which GI_{50} values below and above the test range (10^{-4}–10^{-8} M) are taken as the minimum (10^{-8} M) and maximum (10^{-4} M) drug concentration used in the screening test.

The data summarized in Table 5 indicate the indisputable cytotoxicity of compounds **5aa**, **5ab** and **5ac**, which showed MGM $\log_{10}$ GI_{50} values below-5, and the potent cytotoxic activities of **5aa** and **5ac** against the following human leukemia cells: CCRF-CEM, HL-60(TB), K-562, RPMI-8226, and SR. These cell lines were relatively more sensitive to compounds **5aa** and **5ac** than were other tumor cell lines.

3. Conclusions

In summary, we have shown that 4-(1-alkynyl)-3-bromo-2(5*H*)-furanones **5a** and the corresponding 3-chloro derivatives **5b** can be regioselectively and efficiently prepared by modified versions of the Sonogashira reaction between 1-alkynes and 3,4-dibromo-2(5*H*)-furanone (**4a**) and 3,4-dichloro-2(5*H*)-furanone (**4b**), respectively, which involve the use of KF as a base. We have also shown that compounds **5a** are useful precursors to 4-(1-alkynyl)-3-aryl-2(5*H*)-furanones **7**. Interestingly, some compounds of general formula **5a** have been found to exhibit significant cytotoxic activities, especially against human leukemia cell lines.

4. Experimental

Melting points and boiling points are uncorrected. Precoated Merck 60 F_{254} aluminum silica gel sheets were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani DDS 1000 data station. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040 mm) were performed on a Büchi B-680 system using a Knauer K-2400 differential refractometer as detector. Electron impact mass spectra were measured at 70 eV by GLC/MS. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas-chromatograph. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer 1725-X FT-IR spectrophotometer. All reactions of air and water sensitive materials were performed in flame-dried glassware under a positive atmosphere of argon using standard syringe, cannula and septa techniques. Solvents were dried and distilled before use. The following compounds were prepared by published procedures: $PdCl_2(PPh_3)_2$,[21] $Pd(PPh_3)_4$,[22] $PdCl_2(PhCN)_2$,[21] $PdCl_2(MeCN)_2$,[23] 3,4-dibromo-2(5*H*)-furanone (**4a**),[2,4] 3,4-dichloro-2(5*H*)-furanone (**4b**),[3,4] tributyl(4-methoxyphenyl)tin (**11a**).[24] (2-Methoxymethoxy)phenyl bromide [bp 98–99°C/8 Torr], which was used for the preparation of tributyl[(2-methoxymethoxy)phenyl]tin (**11b**), was prepared in 90% yield from commercially available 2-bromophenol according to the procedure used for the synthesis of 2-bromo-5-methoxymethoxy-1,4-naphthoquinone.[25]

Tributyl(phenylethynyl)tin (**8**), tributyl(2-furyl)tin (**11c**), 4-methoxyphenylboronic acid (**11d**) and 3,4,5-trimethoxyphenylboronic acid (**11e**) are commercially available reagents.

4.1. General

4.1.1. Synthesis of 3-bromo-4-phenylethynyl-2(5*H*)-furanone (5aa) by Pd-catalyzed reaction between tributyl (phenylethynyl)tin (8) and 4a. A flame-dried flask flushed with argon was charged with $PdCl_2(PPh_3)_2$ (0.133 g, 0.19 mmol), CuI (0.036 g, 0.19 mmol), **4b** (1.90 mmol), **8**

Table 5. Cytotoxicity of compounds **5aa**, **5ac** and **5ad**

Compound	$\log_{10}$ GI_{50},[a] Leukemia					MGM[b]
	CCRF-CEM	HL-60(TB)	K-562	RPMI-8226	SR	
5aa	−6.09	−7.70	−5.58	−6.86	−6.73	−5.32
5ac	−6.62	−6.48	−6.43	−6.80	−6.44	−5.70
5ad	−5.67	−6.28	−5.38	−6.66	>−4.00	−5.49

[a] Log molar drug concentration required for 50% growth inhibition.
[b] Mean graph midpoint for all human cancer cell lines tested (ca. 60).

(0.78 g, 1.99 mmol) and a deaerated 10:1 mixture of THF and CH_3CN (10 ml) and the mixture was stirred at 40°C for 16 h. It was then allowed to cool to 20°C and poured into a saturated NH_4Cl solution (50 ml) and extracted with AcOEt (4×50 ml). The organic extract was stirred for 4 h with an aqueous semisaturated KF solution (100 ml) and filtered through Celite. The filtrate was extracted with AcOEt (3×20 ml), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (50:50+1% AcOEt) as eluent, to give **5aa** (85 mg, 17% yield) as a pale yellow crystalline solid. Mp 141–142°C. MS, *m/z* (%): 264 (39, M^+), 262 (39, M^+), 235 (29), 233 (30), 153 (100), 126 (85), 125 (28), 102 (13), 75 (28). IR (KBr): ν 2201, 1760, 1585, 1437, 1345, 1261, 1096, 1032, 990, 802, 687 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.88 (2H, s, H-5), 7.45 (3H, m, Harom), 7.60 ppm (2H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.3, 78.9, 108.7, 114.7, 120.6, 128.7 (2C), 130.6, 132.2 (2C), 143.3, 168.6 ppm. Anal. calcd for $C_{12}H_7BrO_2$: C, 62.37; H, 3.05. Found: C, 62.30; H, 2.99.

4.1.2. Conversion of compound 5aa into 4-phenylethynyl-2(5*H*)-furanone (9a). A suspension of zinc dust (0.71 g, 10.9 mmol, Aldrich cat. No 20,998-8) in deaerated THF (15 ml) containing 1,2-dibromoethane (0.037 ml, 0.43 mmol) was heated under argon to 65°C for 1 min and cooled to room temperature. Chlorotrimethylsilane (0.042 ml, 0.33 mmol) was added. After 15 min at room temperature, a solution of **5aa** (0.71 g, 2.71 mmol) in THF (5 ml) was added dropwise and the mixture was stirred under reflux for 27 h, cooled to room temperature and allowed to settle. The clear solution of the organozinc derivative so obtained was poured into 5% HCl (70 ml) cooled at 0°C and extracted with AcOEt (4×50 ml). The organic extract was washed with brine (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of toluene and AcOEt (96:4) as eluent, to give **9a** (0.31 g, 62% yield) as a pale yellow solid. Mp 85–87°C. MS, *m/z* (%): 184 (95, M^+), 155 (20), 127 (22), 126 (100), 98 (6), 87 (6), 77 (10), 74 (11), 63 (9). IR (KBr): ν 2200, 1776, 1747, 1611, 1445, 1312, 1152, 1152, 1029, 882, 850 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (2H, d, J=2.2 Hz, H-5), 6.26 (1H, t, J=2.2 Hz, H-3), 7.43 (3H, m, Harom), 7.54 ppm (2H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.9, 79.2, 104.9, 120.7, 122.0, 128.6 (2C), 130.2, 131.9 (2C), 147.0, 173.1 ppm. The physical and spectral properties of this compound were in agreement with those previously reported.[13]

4.2. General procedures for the synthesis of 4-(1-alkynyl)-3-bromo-2(5*H*)-furanones 5a from 1-alkynes 10 and 4a

A mixture of compound **4a** (0.48 g, 2.0 mmol) and a 1-alkyne **10** (2.4 mmol) in a deaerated 1:1 mixture of toluene and water (15.6–16.8 ml) or deaerated toluene (16.0 ml) was reacted under argon with 4.0 equiv. of KF in the presence of *catalyst system A*, *B*, *C*, or *D* for the period of time and at the temperature indicated in Table 1 or 2. *Catalyst system A* consisted of $Pd(PPh_3)_4$ (5 mol%) and CuI (5 mol%); *catalyst system B* consisted of $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%) and $AsPh_3$ (10 mol%); *catalyst system C* consisted of $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%) and P(2-furyl)$_3$ (10 mol%) and *catalyst system D* consisted of $PdCl_2(CH_3CN)_2$ (5 mol%), CuI (10 mol%) and P(2-furyl)$_3$ (10 mol%). The reactions in a 1.1 mixture of toluene and water were performed in the presence of $BnEt_3N^+Cl^-$ (10 mol%). After completion of the reaction, the reaction mixture was allowed to cool to 20°C, poured into a saturated aqueous NH_4Cl solution (75 ml) and extracted with AcOEt (4×30 ml). The organic extract was washed with brine (30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. Tables 1 and 2 summarize the results obtained in the synthesis of **5aa** and **5ac**–**5ag**, respectively. Entries 6–8 of Table 1 summarize the attempts we made to perform the cross-coupling reaction between **4a** and **10a** using CsF, K_2CO_3 or K_3PO_4 respectively, instead of KF as a base. The procedure involving treatment of **4a** with **10** and 4.0 equiv. of KF in a 1:1 mixture of toluene and water in the presence of 10 mol% $BnEt_3N^+Cl^-$ and the *catalyst system C* was used to prepare **5aa** (entry 3, Table 1) and **5ac**, **5ad** and **5ag** (entries 1, 4 and 7, respectively, Table 2). On the other hand, the procedure involving treatment of **4a** with **10** in toluene in the presence of 4.0 equiv. of KF and *catalyst system D* was used to prepare **5ac**, **5ae** and **5af** (entries 2, 5 and 6, respectively, Table 2). As shown in entry 3 of Table 2, compound **5ac** was also synthesized on a 20 mmol scale using a procedure very similar to that employed in entry 2. Finally, it must be mentioned that compound **5ab** was prepared by a procedure very similar to that used in entry 3 of Table 1 to prepare **5aa** (Scheme 2).

4.2.1. 3-Bromo-4-phenylethynyl-2(5*H*)-furanone (5aa). The crude reaction product, which was obtained by Pd/Cu-catalyzed reaction of **4a** with **10a** (entry 3, Table 1), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (50:50+1% AcOEt) as eluent, to give **5aa** in 85% yield. The physical and spectral properties of this compound were in agreement with those of **5aa** prepared by Pd-catalyzed reaction between tributyl(phenylethynyl)tin (**8**) and **4a**.

4.2.2. 3-Bromo-4-(*p*-tolyl)ethynyl-2(5*H*)-furanone (5ab). The crude reaction product, obtained by reaction of *p*-tolylacetylene (**10b**) with **4a** at 50°C for 74 h in a 1:1 mixture of toluene and water, in the presence of 4.0 equiv. of KF, 10 mol% $BnEt_3N^+Cl^-$ and *catalyst system C* (Scheme 2), was purified by MPLC on silica gel, with a mixture of toluene and AcOEt (99:1), followed by recrystallization from CH_2Cl_2 and hexane, to give **5ab** as a light brown solid in 71% yield. Mp 115–117°C. MS, *m/z* (%): 278 (81, M^+), 276 (90, M^+), 249 (51), 247 (52), 167 (100), 152 (20), 140 (94), 139 (92), 63 (64). IR (KBr): ν 2204, 1767, 1594, 1445, 1326, 1205, 1179, 1028, 984, 834, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 4.87 (2H, s, H-5), 7.22 (2H, m, Harom), 7.47 ppm (2H, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 72.3, 78.6, 109.2, 114.0, 117.5, 129.4 (2C), 132.1 (2C), 141.3, 143.4, 168.7 ppm. Anal. calcd for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.22; H, 3.09.

4.2.3. 3-Bromo-4-(1-hexynyl)-2(5*H*)-furanone (5ac). The

crude reaction product, which was obtained by reaction of **4a** with 1-hexyne (**10c**) in toluene in the presence of *catalyst system D* (entry 2, Table 2), was purified by MPLC on silica gel, with a mixture of hexane and Et_2O (80:20) as eluent, to give **5ac** as a pale orange liquid in 91% yield. MS, *m/z* (%): 244 (49, M^+), 242 (62, M^+), 227 (38), 187 (24), 143 (61), 135 (59), 119 (86), 117 (47), 91 (100), 79 (44), 63 (32). IR (film): ν 2227, 1785, 1765, 1614, 1341, 1288, 1171, 1039, 984, 749, 719 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (3H, t, J=7.1 Hz, H-6′), 1.54 (4H, m, H-4′ and H-5′), 2.52 (2H, m, t, J=6.7 Hz, H-3′), 4.77 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 19.9, 21.9, 29.9, 71.0, 72.6, 112.3, 113.5, 144.4, 168.9 ppm. Anal. calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.32; H, 4.49.

4.2.4. 3-Bromo-4-(3,3-dimethyl-1-butynyl)-2(5*H*)-furanone (5ac). The crude reaction product, which was obtained by reaction of **4a** with 3,3-dimethyl-1-butyne (**10d**) in a 1:1 mixture of toluene and water in the presence of *catalyst system C* (entry 4, Table 2), was purified by MPLC on silica gel, with a mixture of hexane and Et_2O (80:20) as eluent, to give **5ad** as a colorless solid in 84% yield. Mp 79–80°C. MS, *m/z* (%): 244 (20, M^+), 242 (21, M^+), 229 (42), 227 (43), 171 (42), 169 (43), 133 (11), 119 (100), 105 (35), 91 (54), 77 (33). IR (KBr): ν 2212, 1774, 1758, 1608, 1437, 1342, 1305, 1158, 1028, 988, 748 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (9H, s, *t*-Bu), 4.75 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.9, 30.2 (2C), 69.7, 72.5, 113.8, 119.7, 144.2, 168.9 ppm. Anal. calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.31; H, 4.44.

4.2.5. 3-Bromo-4-(3-hydroxy-3-methyl-1-butynyl)-2(5*H*)-furanone (5ae). The crude reaction product, which was obtained by reaction of **4a** with 3-hydroxy-3-methyl-1-butyne (**10e**) in toluene in the presence of *catalyst system D* (entry 5, Table 2), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and AcOEt (90:10) as eluent, to give **5ae** as a yellow solid in 40% yield. Mp 73–75°C. MS, *m/z* (%): 246 (3, M^+), 244 (2, M^+), 231 (90), 229 (100), 173 (41), 171 (42), 165 (71), 121 (19), 91 (19), 77 (78), 63 (35). IR (KBr): ν 3470, 2215, 1777, 1615, 1368, 1346, 1288, 1142, 1042, 986, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64 (6H, s, CH_3), 4.79 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.8 (2C), 65.8, 71.9, 72.3, 113.5, 115.2, 143.0, 168.6 ppm. Anal. calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.03; H, 3.63.

4.2.6. 3-Bromo-4-(trimethylsilylethynyl)-2(5*H*)-furanone (5af). The crude reaction product, which was obtained by reaction of **4a** with trimethylsilylacetylene (**10f**) in toluene in the presence of *catalyst system D* (entry 6, Table 2), was purified by MPLC on silica gel, with a mixture of hexane and Et_2O (85:15) as eluent, to give **5af** as a light brown solid in 30% yield. Mp 41–44°C. MS, *m/z* (%): 260 (5, M^+), 258 (5, M^+), 245 (99), 243 (100), 187 (11), 185 (12), 179 (13), 107 (9), 91 (10), 77 (8). IR (KBr): ν 2016, 1780, 1769, 1600, 1434, 1343, 1262, 1253, 1032, 988, 847 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.29 (9H, $SiMe_3$), 4.78 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.6 (3C), 72.4, 92.9, 115.7, 117.2, 143.0, 168.6 ppm. Anal. calcd for $C_9H_{11}BrO_2Si$: C, 41.71; H, 4.28. Found: C, 41.64; H, 4.15.

4.2.7. 3-Bromo-4-(1-octynyl)-2(5*H*)-furanone (5af). The crude reaction product, which was obtained by reaction of **4a** with 1-octyne (**10f**) in a 1. 1 mixture of toluene and water in the presence of *catalyst system C* (entry 7, Table 2), was purified by MPLC on silica gel, with a mixture of hexane and Et_2O (80:20) as eluent, to give **5af** as an orange liquid in 75% yield. MS, *m/z* (%): 243 (33), 241 (31), 229 (39), 227 (38), 202 (32), 165 (62), 143 (46), 141 (36), 105 (57), 95 (43), 91 (100). IR (film): ν 2228, 1786, 1766, 1613, 1448, 1340, 1171, 1038, 984, 749, 719 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (3H, t, J=6.7 Hz, H-8′), 1.46 (8H, m, H-4′, H-5′, H-6′ and H-7′), 2.51 (2H, t, J=6.9 Hz, H-3′), 4.75 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 20.2, 22.5, 27.8, 28.4, 31.2, 71.1, 72.6, 112.3, 113.6, 144.3, 168.9 ppm. Anal. calcd for $C_{12}H_{15}BrO_2$: C, 53.16; H, 5.57. Found: C, 53.07; H, 5.48.

4.2.8. Synthesis of 3,4-di(1-hexynyl)-2(5*H*)-furanone (6a). Two procedures were used for the synthesis of this compound. The first of these involved treatment of **4a** (0.49 g, 2.05 mmol) with 1-hexyne (**10c**) (0.51 g, 6.15 mmol) in deaerated toluene (16 ml) at 90°C for 160 h under argon, in the presence of KF (0.48 g, 8.2 mmol), $PdCl_2(PhCN)_2$ (26.6 mg, 0.10 mmol), CuI (39.0 mg, 0.20 mmol), and $AsPh_3$ (62.8 mg, 0.20 mmol). The mixture was then allowed to cool to room temperature and worked up using a procedure very similar to that used for the preparation of compounds **5a**. Purification of the crude reaction mixture by MPLC on silica gel, with toluene as eluent, gave **6a** (0.14 g, 27% yield) as a light brown liquid. MS, *m/z* (%): 244 (100, M^+), 202 (44), 187 (33), 173 (32), 157 (50), 143 (52), 129 (67), 128 (67), 115 (87), 91 (84), 77 (49). IR (film): ν 2216, 1789, 1611, 1456, 1375, 1337, 1125, 1041, 1031, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (6H, m, H-6′ and H-6″), 1.49 (8H, m, H-4′, H-4″, H-5′ and H-5″), 2.49 (4H, m, H-3′ and H-3″), 4.75 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (2C), 19.6, 19.9, 21.9 (2C); 30.0, 30.3, 70.2 (2C), 71.6, 102.3 (2C), 111.2, 118.5, 145.2, 171.2 ppm. Anal. calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.49; H, 8.13. The second procedure for the preparation of **6a** involved treatment of **5ac** (0.50 g, 2.05 equiv.) with **10ac** (0.34 g, 4.10 mmol) in deaerated toluene (16 ml) at 90°C for 73 h under argon, in the presence of KF (0.48 g, 8.2 mmol), $PdCl_2(MeCN)_2$ (26.6 mg, 0.10 mmol), CuI (39.0 mg, 0.20 mmol) and $AsPh_3$ (62.8 mg, 0.20 mmol). This procedure furnished **6a** in 31% yield.

4.2.9. Conversion of compound 5ag into 4-(1-octynyl)-2(5*H*)-furanone (9b). Compound **5ag** (0.70 g, 2.60 mmol) was reacted with activated zinc dust (0.68 g, 10.4 mmol, Aldrich cat. No. 20,998-8) in refluxing THF for 20 h, followed by acidic hydrolysis according to a procedure very similar to that used to prepare **9a** from **5aa**. Purification of the crude reaction mixture by MPLC on silica gel, with a mixture of hexane and Et_2O (75:25) as eluent, furnished **9b** (0.22 g, 44% yield) as a pale yellow liquid. MS, *m/z* (%): 163 (30), 149 (20), 119 (25), 107 (18), 105 (56), 92 (36), 91 (100), 79 (46), 77 (36), 69 (31), 63 (43). IR (film): ν 2224, 1780, 1751, 1610, 1449, 1292, 1145, 1042, 881, 852, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (3H, t, J=6.6 Hz, H-8′). 1.40 (8H, m, H-4′, H-5′, H-6′ and H-7′), 2.45 (2H, t, J=6.9 Hz, H-3′), 4.77 (2H, t, J=2.2 Hz, H-5),

6.09 ppm (1H, t, J=0, 2.2 Hz, H-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.9, 22.5, 27.9, 28.6, 31.2, 71.4, 73.2, 108.3, 121.2, 148.2, 173.6 ppm. Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.26.

4.3. General procedure for the synthesis of 4-(1-alkynyl)-3-chloro-2(5*H*)-furanones 5b

A mixture of compound **4b** (0.61 g, 4.0 mmol) and a 1-alkyne **10** (3.0 mmol) in a deaerated 1:1 mixture of toluene and water (32 ml) was reacted under argon at 65°C for 165–167 h with 4.0 equiv. of KF in the presence of $PdCl_2(MeCN)_2$ (5 mol%), CuI (10 mol%), PCy_3 (10 mol%) and $BnEt_3N^+Cl^-$ (5 mol%). The reaction mixture was then allowed to cool to 20°C, poured into a saturated aqueous NH_4Cl solution (75 ml) and extracted with AcOEt (4×30 ml). The organic extract was washed with brine (30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was used to prepare compounds **5ba** and **5bb**.

4.3.1. 3-Chloro-4-(phenylethynyl)-2(5*H*)-furanone (5ba). The crude reaction product, which was obtained by reaction of **4b** with **10a**, was purified by MPLC on silica gel, with a mixture of toluene and AcOEt (99:1) as eluent, to give **5ba** as a yellow solid in 51% yield. Mp 145–148°C. MS, *m/z* (%): 220 (44, M^+), 218 (100, M^+), 191 (32), 189 (93), 161 (39), 160 (59), 153 (17), 126 (27), 99 (11), 80 (11). IR (KBr): ν 2207, 1764, 1618, 1438, 1220, 1127, 1036, 1015, 975, 763, 749 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.91 (2H, s, H-5), 7.44 (3H, m, Harom), 7.58 ppm (2H, s, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 69.9, 70.7, 108.7, 120.5, 127.8, 128.6 (2C), 130.5, 132.1 (2C), 138.8, 167.8 ppm. Anal. calcd for $C_{12}H_7ClO_2$: C, 65.92; H, 3.23. Found: C, 65.75; H, 3.15.

4.3.2. 3-Chloro-4-(1-hexynyl)-2(5*H*)-furanone (5bb). The crude reaction product, which was obtained by reaction of **4b** with **10c**, was purified by MPLC on silica gel, with a mixture of hexane and Et_2O (80:20) as eluent, to give **5bb** as an orange liquid in 31% yield. MS, *m/z* (%): 200 (14, M^+), 198 (47, M^+), 183 (54), 163 (32), 143 (30), 135 (50), 119 (80), 91 (92), 77 (100). IR (film): ν 2229, 1776, 1736, 1623, 1446, 1373, 1242, 1178, 1044, 1011, 752 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (3H, t, J=7.1 Hz, H-6′), 1.52 (4H, m, H-4′ and H-5′), 2.53 (2H, t, J=7.0 Hz, H-3′), 4.79 ppm (2H, s, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 19.8, 21.9, 29.9, 69.9, 71.0, 112.3, 124.4, 139.9, 168.2 ppm. 60.46; H, 5.58. Found: C, 60.32; H, 5.44.

4.3.3. Tributyl[(2-methoxymethoxy)phenyl]tin (11b). A 0.45 M THF solution of the Grignard reagent derived from (2-methoxymethoxy)phenyl bromide (110 ml, 49.5 mmol) was reacted with tributyltin chloride (14.51 g, 44.6 mmol) for 20 h at 65°C. It was then cooled to room temperature, poured into water (300 ml) and extracted with Et_2O (4×40 ml). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was fractionally distilled to give **11b** (13.53 g, 71% yield) as a colorless liquid. Bp 160–162°C/0.8 mbar. MS, *m/z* (%): 371 (100), 369 (77), 367 (49), 213 (88), 211 (79), 197 (59), 195 (59), 179 (78), 177 (82), 175 (83), 91 (73). IR (film): ν 2955, 2926, 1576, 1464, 1435, 1224, 1189, 1154, 1081, 924, 756 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (9H, t, J=7.4 Hz, Sn–C–C–C–CH_3), 1.29 (18H, Sn(CH_2–CH_2–CH_2–C)$_3$, 3.46 (3H, s, OCH_3), 5.15 (2H, s, OCH_2O), 7.04 (2H, m, Harom), 7.31 ppm (2H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8 (3C), 13.7 (3C), 27.4 (3C), 29.2 (3C), 55.8, 94.0, 112.0, 121.8, 129.6, 130.4, 136.9, 161.6 ppm. Anal. calcd for $C_{20}H_{36}O_2Sn$: C, 56.23; H, 8.49. Found: C, 56.12; H, 8.36.

4.4. General procedures for the synthesis of 4-(1-alkynyl)-3-aryl-2(5*H*)-furanones 7

Two general procedures were used to prepare compounds **7** from the corresponding 4-(1-alkynyl)-3-bromo-2(5*H*)-furanones **5a**. The first procedure involved the Pd-catalyzed reaction of compounds **7** with aryl(tributyl)tins. According to this procedure, a flame-dried flask flushed with argon was charged with $PdCl_2[P(o\text{-tolyl})_3]_2$ (78.6 mg, 0.10 mmol), CuI (38.1 mg, 0.20 mmol), a compound **5a** (2.0 mmol) and dry NMP (2.0 ml). A deaerated solution of an organotin compound **11** (1.4–3.0 equiv.) in NMP (2.5 ml) was added and the mixture was stirred under argon at 80°C for 28 h. The reaction between **5ac** and tributyl(4-methoxyphenyl)tin (**11a**) was carried out using a 1:3 molar ratio between these compounds, but the reactions of **5aa** with tributyl[(2-methoxymethoxy)phenyl]tin (**11b**) and tributyl(2-furyl)tin (**11c**) were performed using a 1:1.4 and 1:1.5 molar ratio, respectively, between the furanone derivative and the organotin compound. The reaction mixture was then allowed to cool to room temperature, diluted with AcOEt (50 ml) and stirred for 3–4 h with a 8 M aqueous KF solution (50 ml). The mixture was filtered through Celite and the filtrate was extracted with AcOEt (4×25 ml). The extract was washed with brine (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was used to prepare compounds **7a**, **7b** and **7c** (entries 1–3, Table 3).

A second procedure involved the Pd-catalyzed reaction of compounds **5a** with arylboronic acids **11**. According to this procedure, a flame dried flask was charged with $PdCl_2(PPh_3)_2$ (64.9 mg, 0.093 mmol), $BnEt_3N^+Cl^-$ (21.2 mg, 0.093 mmol), CsF (0.84 g, 5.55 mmol), a compound **5a** (1.85 mmol), an arylboronic acid **11** (3.70 mmol) and a deaerated 1:1 mixture of toluene and water (26 ml), and the mixture was stirred under argon at 60°C for the period of time indicated in Table 3. It was then cooled to room temperature, extracted with AcOEt (4×50 ml) and filtered through Celite. The filtrate was washed with brine (30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was used to prepare compounds **7a** and **7d** (entries 4 and 5, Table 3).

4.4.1. 4-(1-Hexynyl)-3-(4-methoxyphenyl)-2(5*H*)-furanone (7a). The crude reaction product, which was obtained by Pd-catalyzed reaction of **5ac** with **11a** (entry 1, Table 3), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (60:40+1% AcOEt), to give **7a** as a pale yellow solid in 50% yield. Mp 76–78°C. MS, *m/z* (%): 270 (100, M^+), 227 (13), 213 (24), 185 (11), 183 (17), 171 (33), 169 (12), 1390 (11), 128 (8), 121 (11), 77 (7). IR (KBr): ν

2217, 1752, 1606, 1459, 1370, 1296, 1254, 1181, 1047, 954 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (3H, t, J=7.1 Hz, H-6′), 1.53 (4H, m, H-4′ and H-5′), 2.52 (2H, t, J=6.8 Hz, H-3′), 3.84 (3H, s, OCH_3), 4.77 (2H, s, H-5), 6.95 (2H, m, Harom), 8.11 ppm (2H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 19.8, 22.0, 30.1, 55.2, 71.0, 73.3, 108.9, 113.6 (2C), 122.2, 129.1, 129.2 (2C), 136.4, 160.1, 172.8 ppm. Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.43; H, 6.66. This same compound was synthesized in 59% yield by Pd-catalyzed reaction of **5ac** with **11d** (entry 4, Table 3).

4.4.2. 3-[(2-Methoxymethoxy)phenyl]-4-phenylethynyl-2(5*H*)-furanone (7b). The crude reaction product, which was obtained by Pd-catalyzed reaction of **5aa** with **11b** (entry 2, Table 3), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (90:10+1% AcOEt), to give **7b** in 36% yield as a pale yellow solid. Mp 76–79°C. MS, *m/z* (%): 320 (13, M^+), 290 (34), 289 (100), 275 (42), 260 (39), 231 (77), 202 (73), 200 (25), 189 (63), 127 (22), 105 (33). IR (KBr): ν 2201, 1755, 1636, 1594, 1337, 1257, 1229, 1153, 1080, 1038, 994 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.46 (3H, s, OCH_3), 4.98 (2H, s, H-5), 5.19 (2H, s, O–CH_2–O), 7.09 (1H, dt, J=7.3, 1.1 Hz, Harom), 7.38 ppm (8H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.1, 71.3, 80.5, 95.1, 105.3, 114.9, 119.3, 121.2, 121.5, 128.5 (2C), 129.8, 130.7, 130.8, 131.5, 131.9 (2C), 140.6, 155.5, 171.9 ppm. Anal. calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.78; H, 4.95.

4.4.3. 3-(2-Furyl)-4-phenylethynyl-2(5*H*)-furanone (7c). The crude reaction product, which was obtained by Pd-catalyzed reaction of **5aa** with **11c** (entry 3, Table 3), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (55:45+1% AcOEt), to give **7c** as a pale yellow solid in 15% yield. Mp 79–82°C. MS, *m/z* (%): 250 (95, M^+), 222 (37), 193 (77), 165 (100), 163 (19), 139 (13), 115 (10), 82 (15), 76 (25), 63 (19). IR (KBr): ν 2195, 1766, 1640, 1340, 1261, 1099, 1049, 1037, 1017, 970, 802 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.93 (2H, s, H-5), 6.55 (1H, dd, J=3.4, 1.7 Hz, Harom), 7.30 (1H, d, J=3.4 Hz, Harom), 7.42 (3H, m, Harom), 7.59 ppm (3H, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 70.2, 71.2, 81.4, 106.5, 111.7, 112.7, 121.6, 121.9. 128.5 (2C), 129.9, 131.9 (2C), 144.1, 146.1, 170.4 ppm. Anal. calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.65; H, 3.97.

4.4.4. 3-(3,4,5-Trimethoxyphenyl)-4-phenylethynyl-2(5*H*)-furanone (7d). The crude reaction product, which was obtained by Pd-catalyzed reaction of **5aa** with **11e** (entry 5, Table 3), was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (95:5+1% AcOEt), to give **7d** as a pale yellow solid in 69% yield. Mp 162–165°C. MS, *m/z* (%): 350 (62, M^+), 335 (18), 293 (13), 253 (12), 189 (13), 165 (21), 163 (16), 129 (100), 115 (19), 82 (15), 63 (3). IR (KBr): ν 2188, 1740, 1607, 1415, 1372, 1306, 1249, 1131, 1107, 997, 753 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (6H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.94 (2H, s, H-5), 7.50 ppm (7H, m, Harom). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.1 (2C), 60.9, 70.7, 81.3, 105.4 (2C), 106.5, 121.1, 124.9, 128.7 (2C), 130.0, 130.2, 131.7 (2C), 136.4, 139.2, 152.9 (2C), 172.11 ppm. Anal. calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.86; H, 5.09.

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