6936 J. Med. Chem. 2009, 52, 6936–6940
DOI: 10.1021/jm900907s

Journal of Medicinal Chemistry
Brief Article

Identification of Biphenyl-Based Hybrid Molecules Able To Decrease the Intracellular Level of Bcl-2 Protein in Bcl-2 Overexpressing Leukemia Cells

Daniela Pizzirani,[#,‡] Marinella Roberti,*[,‡] Stefania Grimaudo,[∥] Antonietta Di Cristina,[∥] Rosaria Maria Pipitone,[∥] Manlio Tolomeo,[§] and Maurizio Recanatini[‡]

[#]*Department of Chemistry and Chemical Biology, Harvard University and the Broad Institute of MIT and Harvard, 12 Oxford Street, Cambridge, Massachusetts 02138,* [‡]*Dipartimento di Scienze Farmaceutiche, Università di Bologna, Via Belmeloro 6, 40126 Bologna, Italy,* [∥]*Dipartimento Biomedico di Medicina Interna e Specialistica and* [§]*Centro Interdipartimentale di Ricerca in Oncologia Clinica (C.I.R.O.C), Università di Palermo, Via del Vespro 129, 90127 Palermo, Italy*

Received November 28, 2008

With the aim of enhancing the structural complexity and diversity of an existing collection of bi- and terphenyl compounds, we synthesized hybrid molecules comprising of spirocyclic ketones (a complexity-bearing core) and bi/terphenyls (privileged fragments). Compounds **1**, **3**, **4**, and **6** showed well-defined activity on apoptosis and differentiation, making them potential leads for development as new anticancer agents and chemical probes to study signaling networks in neoplastic cells.

Introduction

Deregulated cell proliferation together with suppression of apoptosis constitutes the minimal common platform upon which all neoplastic evolution occurs. Indeed, numerous molecular and cellular mechanisms regulate these crucial events, and their identification and understanding can offer valuable insights toward the development of innovative anticancer drugs.

Given our interest in medicinal chemistry and chemical biology, over the past years we have been engaged in a project aimed at identifying novel biologically active small molecules, which can be antitumor lead candidates or valuable chemical tools to study molecular pathways in cancer cells.

We recently synthesized a library of biphenyls and terphenyls (privileged structures), and their biological evaluation showed that some derivatives were able to arrest the cell cycle in G_0-G_1 phase and also induce differentiation in leukemia cells.[1,2]

As a further development of this project, we aimed at enhancing the structural complexity and diversity of the existing collection, generating new biphenyl- and terphenyl-containing small molecules. With this goal in mind, we turned our attention to natural-product-like scaffolds as complexity-bearing cores and biologically validated starting points (BIOS[a] moieties),[3] and envisaged that the introduction of biphenyl and terphenyl privileged fragments on these scaffolds could be a promising approach to design a library of unique potential bioactive compounds (Figure 1). Thus, we have developed a two-step linear sequence relying on the combination of the three-component domino Knoevenagel/Diels–Alder/epimerization sequence (K–DA–E) for the construction of the natural product-like cores, followed by Suzuki coupling as the derivatization step. This strategy proved to be a valuable synthetic methodology for the parallel generation of a library of new molecules that are hybrids of spirocyclic ketones with biphenyls and terphenyls.[4] The spiro ring system is a widespread motif in many natural products[5,6] and notably is a novel structural feature of spiromentins, a recently reported class of natural terphenyl derivatives.[7]

To evaluate the importance of the natural product-like scaffolds and the privileged fragments forming the hybrid molecules, we prepared a series of differently substituted spirocyclic ketones. The general synthetic procedure for the preparation of the latter series (**7**–**13**, Scheme 1) and the biological evaluation of representative derivatives of the spirocyclic ketones collections (**1**–**13**, Table 1) are described.

Compounds **1**–**13** were characterized for their antiproliferative activity on HL60 and Bcr-Abl-expressing K562 (apoptosis resistant) leukemia cell lines. Two compounds (**1** and **4**) caused a block of K562 cells in G_0-G_1 after 24 h of treatment and a massive apoptotic induction after 48 h. According to their marked proapoptotic ability, **1** and **4** decreased the level of Bcl-2 which is known to play a key role in regulating apoptosis.[8,9] In chronic myeloid leukemias, the Bcr-Abl oncoprotein causes the overexpression of Bcl-2, which is known to cause leukemia cells to be resistant toward different apoptotic stimuli including chemotherapeutic drugs.[10,11] In addition, chronic myeloid leukemias are characterized by high percentage of cells in a resting state (G_0-G_1) that make them resistant to conventional chemotherapy. These novel molecules endowed with potent cytotoxic activity on resting cells and ability to down-regulate the intracellular levels of Bcl-2 could lead to the development of new therapeutic agents for the treatment of these malignancies.

Chemistry

Compounds **1**–**6** were prepared as previously described by us.[4]

*To whom correspondence should be addressed. Phone: +39-051-2099738. Fax: +39-051-2099734. E-mail: marinella.roberti@unibo.it.

[a] Abbreviations: MCRs, multicomponent reactions; K–DA–E, Knoevenagel/Diels–Alder/epimerization; BIOS, biology-oriented synthesis; FITC, fluorescein isothiocyanate; PE, phycoerythrin; IC_{50}, half maximal inhibitory concentration; AC_{50}, half maximal apoptotic concentration.

 Published on Web 09/18/2009

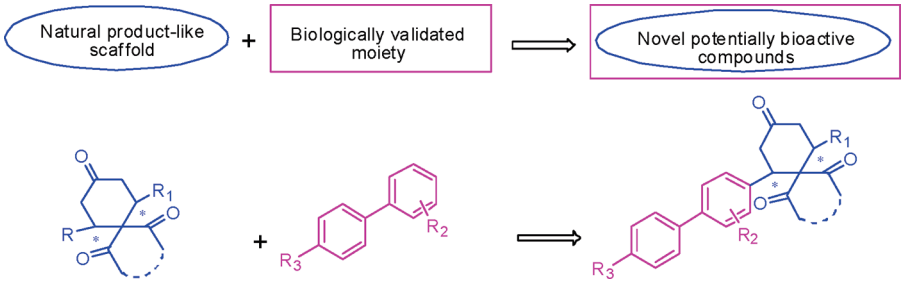
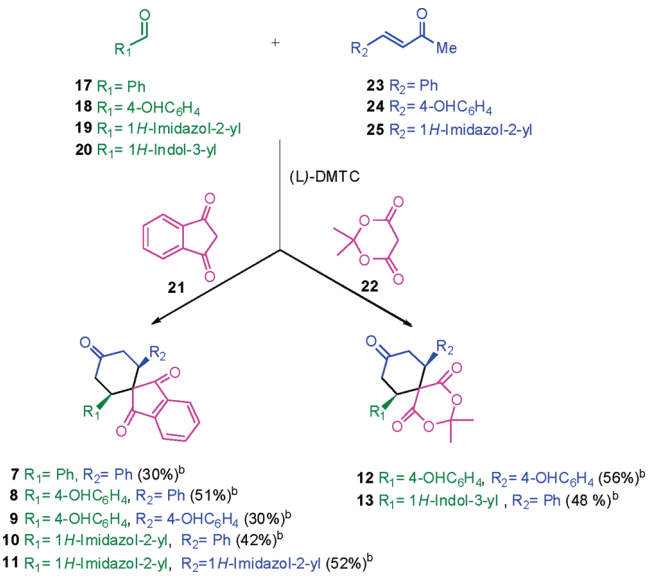


Figure 1. General design strategy of hybrid compounds.

Scheme 1[a]



[a] Reagents and conditions: aldehydes **17**−**20** (1.0 equiv), 1,3-diones **21** and **22** (1.0 equiv), L-DMTC (0.2 equiv), enones **23**−**25** (2.0 equiv), MeOH (1M), room temp, 72 h. [b] Yield refers to the purified product after flash chromatography.

The spirocyclic ketones (**7**−**13**) were synthesized in a highly diastereoselective way, taking advantage of the three-component domino K−DA−E sequence with commercially available aldehydes (**17**−**20**), 1,3-indandione **21** or Meldrum's acid **22**, and 4-substituted-3-buten-2-ones (**23**−**25**) in the presence of a catalytic amount of (L)-5,5-dimethyl thiazolidinium-4-carboxylate (DMTC), as shown in Scheme 1.

The (*E*)-4-substituted-3-buten-2-ones (**24**, **25**) were obtained through stereospecific Wittig reaction employing the appropriate stabilized ylide and commercially available aldehydes (**18**, **19**), respectively (see Supporting Information, Scheme 2).

Biology

All compounds in this study (**1**−**13**) were tested for their antiproliferative activity on sensitive acute myelogenous leukemia HL60 cells and Bcr-Abl-expressing K562 cells. The most active compounds of the series (**1**, **3**, **4**, **6**) were also evaluated for their proapoptotic activity on HL60 and K562 cells and their antiproliferative activity on normal cells (lymphocytes).

The antiproliferative activity of each compound was evaluated by counting cells with an automatic cell counter; apoptosis was evaluated by morphological assay and annexine V test. The effects of the most potent compounds on cell cycle were studied by flow cytometry after staining the cells with propidium iodide. Moreover, derivatives **1**, **3**, **4**, **6** were evaluated for their effects on the expression of Bcl-2 in K562 cells by flow cytometry after staining cells with FITC-conjugated anti-Bcl-2 monoclonal antibody. For **3** and **6** which were able to induce a stable block in G_0-G_1 phase after 72 h, we investigated their ability to induce cell differentiation by evaluating the expression of CD11c and CD61 on HL60 cells with anti-CD11c and anti-CD61 monoclonal antibodies, respectively.

Results and Discussion

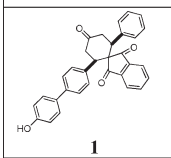
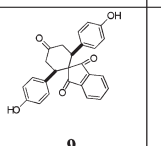
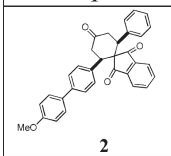
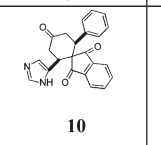
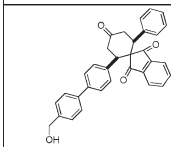
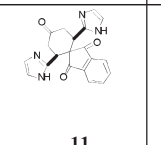
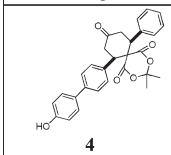
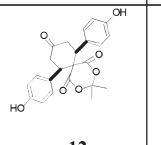
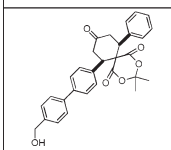
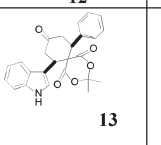
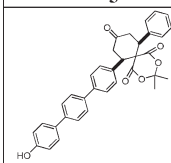
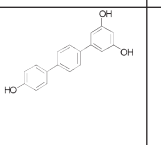
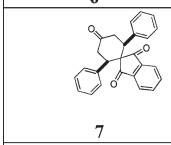
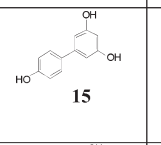
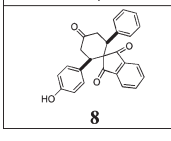
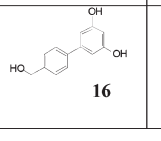
The antiproliferative activities of the compounds presented in this study are shown in Table 1 expressed as IC_{50} (concentration able to inhibit 50% of the cell growth). Terphenyl **14** and biphenyls **15** and **16** are included for comparison with our previous collection.[1,2] From Table 1, it appears that the most active compounds of the present series are **1**, **3**, **4**, and **6**, which were further tested for their proapoptotic activity (as shown in Table 2) expressed as AC_{50} (concentration able to induce apoptosis in 50% of cells). In addition, the IC_{50} values of **1**, **3**, **4**, and **6** on normal lymphocytes are shown in the same table.

Of these compounds, **3** showed antiproliferative IC_{50} of 6 and 14 μM in HL60 and K562 cells, respectively, while **6** was slightly more active in K562 than in HL60 cells (IC_{50} of 8 μM vs 16 μM) (Table 1). In contrast, the proapoptotic activity of both compounds was scarce in K562 cells (AC_{50} of 80 μM for **3** and >100 μM for **6**, Table 2). This result is consistent with the drug-induced apoptosis resistance displayed by K562 cells and may be correlated with the expression of the antiapoptotic gene Bcr-Abl. In K562 cells, compounds **1** and **4** showed AC_{50} only 2.3 and 2.0 times higher, respectively, than those observed in HL60 cells. Previous reports[12] have shown that the product of the Bcr-Abl oncogene causes a delay of drug-induced apoptosis, which generally appears after 72−96 h. In our hands, **1** and **4** induced programmed cell death after only 48 h. Noteworthy (Table 2) is the cytotoxic activity of the four derivatives on normal cells (lymphocytes) which was markedly lower than in HL60 and K562 cells.

Thus, the hybrid molecules formed by a combination of the two chemotypes provided interesting biological features, proving that this design strategy was successful to obtain new bioactive molecules. In fact, **1**, **3**, **4**, and **6** showed better IC_{50} and AC_{50} than almost all of the previously reported terphenyls and biphenyls[1,2] and the new spirocyclic ketones described here (**7**−**13**, Table 1).

A preliminary SAR analysis of the antiproliferative activity showed (Table 1) that a crucial determinant of the high activity seems to be a combination of the two different molecular moieties. Actually the spirocyclic ketones lacking

Table 1. IC_{50}[a] (μM ± SE) of **1**−**16** in Sensitive HL60 and Bcr-Abl-Expressing K562 Cells

Compound	HL60 IC_{50}[a]	K562 IC_{50}[a]	Compound	HL60 IC_{50}[a]	K562 IC_{50}[a]
 **1**	6±1	8±1	 **9**	28±3	73±9
 **2**	>100	>100	 **10**	86±9	95±12
 **3**	6±1	14 ±2	 **11**	> 100	> 100
 **4**	8±1	9±1	 **12**	87±9	>100
 **5**	20±5	38±4	 **13**	62±9	>100
 **6**	16±2	8±1	 **14**	7±1	20±2
 **7**	20±2	98±10	 **15**	> 80	> 80
 **8**	23±4	25±3	 **16**	> 80	> 80

[a] Concentration (μM) able to inhibit 50% of cell growth after 48 h of treatment.

the bi- or terphenyl fragments (**7**−**13**) are less active than the hybrids (**1**, **3**−**6**). The only exception is **2** which turned inactive if the para-OH group of **1** is methylated. Considering the biphenyls **15** and **16**, again the hybrid molecules are far more active. On the other hand, the terphenyl **14** displays an activity level comparable to that of the hybrids **1**, **3**, **4**, and **6**. However, this might be due to the presence of 1,3″,5″-OH motif (a "resveratrol-like pattern" of substitutions).[1] For the hybrid molecules **1**−**6**, other than the effects of the methylation on the antiproliferative action of compounds, no further SAR pattern is apparent in this series.

To address the mechanism of action of **1**, **3**, **4**, and **6**, their effects on cell cycle were evaluated in K562 cells. After 24 h of treatment, all four compounds induced a block of cells in G_0–G_1, as revealed by the cytometric analysis of treated

Table 2. AC_{50}[a] (μM ± SE) of Derivatives **1**, **3**, **4**, **6**, and **14**−**16** in Sensitive HL60 and Bcr-Abl-Expressing K562 Cells and IC_{50}[b] (μM ± SE) of Derivatives **1**, **3**, **4**, and **6** in Normal Lymphocytes

	AC_{50}[a]		
compd	HL60	K562	IC_{50},[b] lymphocytes
1	11 ± 2	25 ± 3	215 ± 38
3	12 ± 2	80 ± 9	286 ± 23
4	16 ± 1	33 ± 5	172 ± 15
6	32 ± 4	> 100	185 ± 20
14	25 ± 3[c]	75 ± 12[c]	nd[d]
15	> 80[c]	> 80[c]	nd[d]
16	> 80[c]	> 80[c]	nd[d]

[a] Concentration (μM) able to induce apoptosis in 50% of cells calculated after 48 h of treatment. [b] Concentration (μM) able to inhibit 50% of cell growth after 48 h of treatment. [c] From ref 2. [d] Not determined.

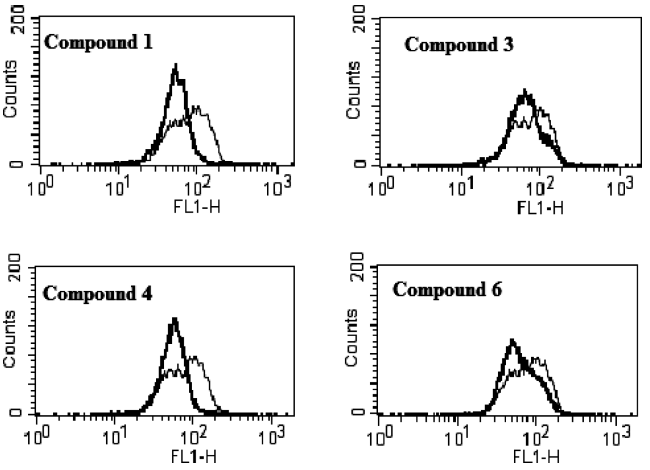


Figure 2. Effects of some representative compounds presented in this study on Bcl-2 expression. K562 cells were cultured 24 h without compounds (control) or with **1**, **3**, **4**, and **6** at 30 μM; the intracellular level of Bcl-2 was evaluated after 24 h by flow cytometry as described in Experimental Section: (thin line) control cells stained with a FITC-conjugated anti-Bcl-2 monoclonal antibody; (thick line) cells treated with each compounds and stained with a FITC conjugated anti-Bcl-2 monoclonal antibody.

cells respect to untreated cells (see Supporting Information Figure A). However, after 48 h, a marked apoptotic sub-G_0–G_1 peak appeared in cells treated with **1** and **4**, suggesting that these compounds activated apoptosis in cells that were previously blocked in G_0–G_1 phase, while cells treated with **3** and **6** remained blocked in G_0–G_1 even after 72 h without any apoptosis activation. To evaluate the importance of the biphenyl moiety on the cell cycle activity of these compounds, we carried out the same cytometric analysis for the spirocyclic ketone **7**. It turned out that **7** caused a prevalent block of cells in S and G_2–M phases after 24 h, and a block in G_2–M after 48 and 72 hours (see Supporting Information Figure A).

Since Bcl-2 plays a main role in Bcr-Abl dependent apoptotic resistance, the expression of Bcl-2 was evaluated in K562 cells before and after treatment with **1**, **3**, **4**, and **6**. As shown in Figure 2, after 24 h of exposure to 30 μM **1** or **4**, the levels of Bcl-2 expression decreased (32.8% and 31.2%, respectively). In contrast, **3** and **6** did not cause a significant modification of Bcl-2 level in K562 cells (4.3% and 4.9%, respectively). Again, these results are consistent with the marked proapoptotic activity of **1** and **4** and marginal ability to induce apoptosis in K562 cells of **3** and **6**, suggesting that the activation of apoptosis is, at least in part, dependent on the ability of **1** and **4** to reduce the intracellular levels of Bcl-2.

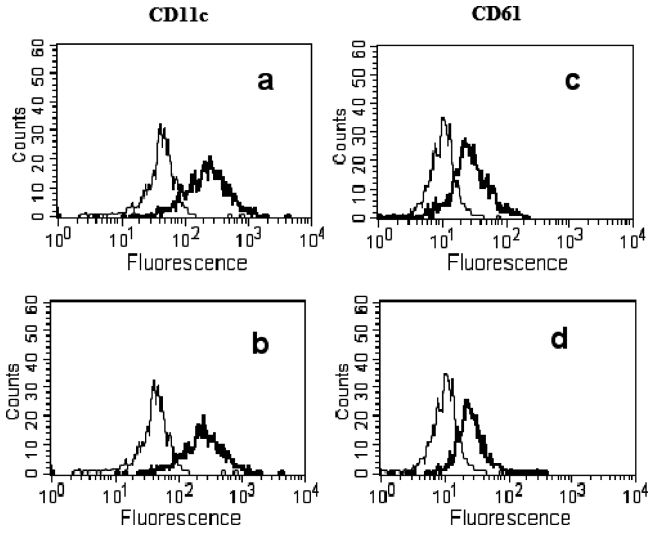


Figure 3. Expression of CD11c and CD61 in HL60 cells. HL60 cells were cultured without compounds (control) or with 10 μM **3** or **6**; the expression of CD11c and CD61 was evaluated after 5 days by flow cytometry as described in Experimental Section: (a, thin line) untreated cells stained with a PE-conjugated anti-CD11c; (a, thick line) cells treated with **3** and stained with a PE-conjugated anti-CD11c; (b, thin line) untreated cells stained with a PE-conjugated anti-CD11c; (b, thick line) cells treated with **6** and stained with a PE-conjugated anti-CD11c; (c, thin line) untreated cells stained with a FITC-conjugated anti-CD61; (c, thick line) cells treated with **3** and stained with a PE-conjugated anti-CD61; (d, thin line) untreated cells stained with a FITC-conjugated anti-CD61; (d, thick line) cells treated with **6** and stained with a FITC-conjugated anti-CD61.

High levels of Bcl-2 are found in a wide variety of human cancer, and its overexpression is associated with tumor progression, poor prognosis, and resistance to chemotherapy.[13,14] For these reasons, intensive efforts are underway to develop strategies to circumvent the cytoprotective effects of Bcl-2 in neoplastic cells.[15,16] Overexpression of Bcl-2 in K562 cells is dependent on Bcr-Abl-mediated Ras-MAPK activation.[17] Ras protein, when activated, transmits extracellular signals that promote the growth, proliferation, and survival of cells. Inhibition of Ras-MAPK pathway results in cell growth arrest and apoptosis. Although the exact mechanism by which **1** and **4** induce a decrease in intracellular level of Bcl-2 is unknown, the ability of these compounds to increase the percentage of cells in G_0-G_1 suggests a possible interaction with one or more factors involved in the Ras-MAPK pathway. Thus, **1** and **4** could be good leads to develop new agents for the treatment of malignancies characterized by high percentage of cells in resting phase and overexpression of Bcl-2, in conditions such as chronic leukemia and low-grade lymphoma.

Finally, considering the ability of **3** and **6** to induce a stable block in the G_0-G_1 phase even after 72 h,[18,19] we investigated their effect on cell differentiation in HL60 and K562 cells. Cells were exposed to 10 μM of each compound. After 120 h, the expression of CD61 (monocytic marker) and CD11c (granulocytic marker) was evaluated by flow cytometry. Both compounds induced a marked increase in CD61 and CD11c expression only in HL60 cells (Figure 3) and not in K562 cells (data not shown). The HL60 cells differentiated prevalently in monocytes. Of interest, some monocytes derived from HL60 became specialized macrophages able to phagocyte fragments of apoptotic cells (see Supporting Information Figure B). Remarkably, the characteristics of this differentiating behavior is similar to terphenyl derivative **14** previously reported by us. In fact, as discussed in Roberti et al.,[1] while the clinically used differentiating drug *all-trans*-retinoic acid (ATRA) induces prevalent granulocytic differentiation of acute promyelocytic leukemia blasts, **3** and **6**, as well as **14**, were able to also induce monocytic (i.e., functional, not only morphological) differentiation of HL60 cells. Further studies are underway to explore the possible mechanism of the differentiation-inducing effects of these compounds and their possible chemical biological applications.

Conclusion

In conclusion, we have shown that our design strategy of combining three-dimensionally complex, stereochemically rich scaffolds with biologically validated fragments (BIOS moieties) succeeded in giving novel small molecules endowed with interesting antiproliferative activity. The compounds reported here showed a well-defined activity on apoptosis or differentiation, thus representing potential leads for new anticancer agents' development and as chemical probes to study signaling networks in neoplastic cells. Thus, the effects of **1**, **4**, **3**, and **6** on apoptosis and differentiation are clearly different from those of the previously studied terphenyls[1,2] that showed mixed proapoptotic and differentiating actions.

The results presented here require further biological investigations to identify, at a molecular level, the target of the active compounds, either a macromolecule or a biochemical pathway. Noteworthy, our synthetic strategy allows a modular and easy synthesis of these compounds, making the follow-up studies more rapid and efficient by systematic structural modifications of the identified hits.[20]

Experimental Section

General Chemical Methods. Reaction progress was monitored by TLC on precoated silica gel plates (Kieselgel 60 F_{254}, Merck) and visualized by UV254 light. Flash column chromatography was performed on silica gel (particle size 40−63 μM, Merck). Tetrahydrofuran (THF) was freshly distilled over sodium/benzoketal. Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. Compounds were named relying on the naming algorithm developed by CambridgeSoft Corporation and used in ChemBioDraw Ultra 11.0, with support for the Cahn-Ingold-Prelog rules for stereochemistry. Melting points were determined on a Gallenkamp melting points apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported relative to TMS as internal standard. IR-FT spectra were obtained on a Nicolet Avatar 320 E.S.P. instrument; ν_{max} is expressed in cm^{-1}. Purity of compounds was determined by elemental analyses; purity for all the tested compounds was ≥95%.

General Parallel Procedure for the Domino K−DA−E Reaction To Obtain 7−13. In distinct reactors, 1 M solutions of the appropriate aromatic aldehyde **17−20** (1.0 equiv) and 1,3-dicarbonyl compound **21** or **22** (1.0 equiv) in MeOH (1 M) were prepared and the catalyst (L)-5,5-dimethyl thiazolidinium-4-carboxylate (L-DMTC) (0.2 equiv) was added to each reactor. The resulting mixtures were stirred for 1 h at room temperature. Then the appropriate 4-substituted 3-buten-2-ones **23−25** (2.0 equiv) were added to each reaction mixture and the suspensions were allowed to stir at room temperature for 72 h. Each crude mixture was diluted with dichloromethane and treated with saturated aqueous ammonium chloride solution. The layers were separated, and the aqueous phase was further extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under

reduced pressure. Each crude Diels−Alder product was purified using silica gel by flash chromatography (petroleum ether/EtOAc) (Scheme 1).

(2β,6β)-2-(4-Hydroxyphenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione 8. 4-Hydroxybenzaldehyde **18** (0.12 g, 1.0 mmol), 1,3-indandione **21**, and (*E*)-4-phenyl-3-buten-2-one **23** were allowed to react according to the described general procedure, and the crude Diels−Alder product was purified on silica, eluting with 8:2 petroleum ether/EtOAc. Yield, 0.19 g (51%); white solid (mp 204 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.61−2.68 (m, 2H), 3.70−3.87 (m, 4H), 6.50 (d, J = 9 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 6.95−7.02 (m, 5H), 7.42−7.53 (m, 3H), 7.66 (d, J = 7.8 Hz, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz, DEPT) δ 43.3 (CH_2), 43.6 (CH_2), 47.9 (CH), 48.6 (CH), 62.2 (C), 115.2 (CH), 122.1 (CH), 122.4 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.2 (CH), 135.4 (CH), 137.2 (C), 141.9 (C), 142.7 (C), 155.2 (C), 202.3 (C, C=O), 203.7 (C, C=O), 209.4 (C, C=O); IR ν_{max} (Nujol) cm^{-1} 1174, 1255, 1376, 1462, 1516, 1591, 1613, 1694, 1732, 3498. Anal. ($C_{26}H_{20}O_4$) C, H.

Acknowledgment. This work was supported by a PRIN2006 Project Grant from MIUR, Italy.

Note Added after ASAP Publication. This paper was published ASAP on September 18, 2009 with an error in the Results and Discussion section. The revised version was published on October 1, 2009.

Supporting Information Available: Synthesis of (*E*)-4-substituted-3-buten-2-ones (**24**, **25**); physical and spectroscopic data for derivatives **7**−**13**, **24**, **25**; detailed biological protocols; Figure A, B. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Roberti, M.; Pizzirani, D.; Recanatini, M.; Simoni, D.; Grimaudo, S.; Di Cristina, A.; Abbadessa, V.; Gebbia, N.; Tolomeo, M. Identification of a terphenyl derivative that blocks the cell cycle in the G0-G1 phase and induces differentiation in leukemia cells. *J. Med. Chem.* **2006**, *49*, 3012–3018.

(2) Pizzirani, D.; Roberti, M.; Cavalli, A.; Grimaudo, S.; Di Cristina, A.; Pipitone, R. M.; Gebbia, N.; Tolomeo, M.; Recanatini, M. Antiproliferative agents that interfere with the cell cycle at the G1→S transition: further development and characterization of a small library of stilbene-derived compounds. *ChemMedChem* **2008**, *3*, 345–355.

(3) Hubel, K.; Lessmann, T.; Waldmann, H. Chemical biology—identification of small molecule modulators of cellular activity by natural product inspired synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1361–1374.

(4) Pizzirani, D.; Roberti, M.; Recanatini, M. Domino Knoevenagel/Diels−Alder sequence coupled to Suzuky reaction: a valuable synthetic platform for chemical biology. *Tetrahedron Lett.* **2007**, *48*, 7120–7124.

(5) Brimble, M. F. Chemistry of bis-spiroacetal systems:natural products, synthesis and stereochemistry. *Curr. Org. Chem.* **2003**, *7*, 1461–1484.

(6) Zinzalla, G. M.; Ley, S. V. Chemical variation of natural product-like scaffolds: design and synthesis of spiroketal derivatives. *Org. Biol. Chem.* **2006**, *4*, 1977–2002.

(7) Liu, J. K. Natural terphenyls: developments since 1877. *Chem. Rev.* **2006**, *106*, 2209–2223.

(8) Reed, J. C. Bcl-2 family proteins. *Oncogene* **1998**, *17*, 3225–3236.

(9) Kroemer, G. The proto-oncogene Bcl-2 and its role in regulating apoptosis. *Nat. Med.* **1997**, *3*, 614–620.

(10) Sanchez-Garcia, I.; Grutz, G. Tumorigenic activity of the BCR-ABL oncogenes is mediated by BCL2. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 5287–5291.

(11) Schimmer, A. D.; Munk-Pedersen, I.; Minden, M. D.; Reed, J. C. Bcl-2 and apoptosis in chronic lymphocytic leukemia. *Curr. Treat. Options Oncol.* **2003**, *4*, 211–218.

(12) McGahon, A. J.; Brown, D. G.; Martin, S. J.; Amarante-Mendes, G. P.; Cotter, T. G.; Cohen, G. M.; Green, D. R. Downregulation of Bcr-Abl in K562 cells restores susceptibility to apoptosis: characterization of the apoptotic death. *Cell Death Differ.* **1997**, *4*, 95–104.

(13) Reed, J. C.; Miyashita, T.; Takayama, S.; Wang, H. G.; Sato, T.; Krajewski, S.; Aime-Sempe, C.; Bodrug, S.; Kitada, S.; Hanada, M. BCL-2 family proteins: regulators of cell death involved in the pathogenesis of cancer and resistance to therapy. *J. Cell. Biochem.* **1996**, *60*, 23–32.

(14) Buchholz, T. A.; Davis, D. W.; McConkey, D. J.; Symmans, W. F.; Valero, V.; Krajewski, S.; Aime-Sempe, C.; Bodrug, S.; Kitada, S.; Hanada, M. Chemotherapy-induced apoptosis and Bcl-2 levels correlate with breast cancer response to chemotherapy. *Cancer J.* **2003**, *9*, 33–41.

(15) Bettaieb, A.; Dubrez-Daloz, L.; Launay, S.; Plenchette, S.; Rebe, C.; Cathelin, S.; Solary, E. Bcl-2 proteins: targets and tools for chemosensitisation of tumor cells. *Curr. Med. Chem.: Anti-Cancer Agents* **2003**, *3*, 307–318.

(16) Gardner, C. R. Anticancer drug development based on modulation of the Bcl-2 family core apoptosis mechanism. *Expert Rev. Anticancer Ther.* **2004**, *4*, 1157–1177.

(17) Quintàs-Cardama, A.; Kantarjian, H.; Cortes, J. Flying under the radar: the new wave of BCR-ABL inibitors. *Nat. Rev. Drug Discovery* **2007**, *6*, 834–848.

(18) Tsolmon, S.; Kurita, Y.; Yamada, P.; Shigemori, H.; Isoda, H. Indoleacetic acid falcarindiol ester induces granulocytic differentiation of the human leukemia cell line HL-60. *Planta Med.* **2009**, *75*, 49–54.

(19) Dimberg, A.; Bahram, F.; Karlberg, I.; Larsson, L. G.; Nilsson, K.; Oberg, F. Retinoic acid-induced cell cycle arrest of human myeloid cell lines is associated with sequential down-regulation of c-Myc and cyclin E and posttranscriptional up-regulation of p27(Kip1). *Blood* **2002**, *99*, 2199–2206.

(20) Nielsen, T. E.; Schreiber, S. L. Towards the optimal screening collection: a synthesis strategy. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56.