Brief Articles

Synthesis and Cytotoxic Evaluation of Combretafurans, Potential Scaffolds for Dual-Action Antitumoral Agents

Tracey Pirali,[†,‡] Sara Busacca,[†,‡] Lorena Beltrami,[†] Daniela Imovilli,[†] Francesca Pagliai,[†] Gianluca Miglio,[†] Alberto Massarotti,[†] Luisella Verotta,[§] Gian Cesare Tron,*[,†] Giovanni Sorba,[†] and Armando A. Genazzani[†]

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche and Drug and Food Biotechnology Center, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy, and Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy

Received May 24, 2006

We have synthesized rigid analogues of combretastatin bearing a furan ring in place of the olefinic bridge. These compounds are cytotoxic at nanomolar concentrations in neuroblastoma cells, display a similar structure−activity relationship compared to combretastatin A4, and inhibit tubulin polymerization. We also show that the furan ring can be further functionalized. Thus, it is possible that combretafurans could act as scaffolds for the development of dual-action antitumoral agents.

Introduction

The neovasculature typical of solid tumors has recently become a primary target for the development of new drugs, and a number of the agents that have already entered clinical trials disrupt the microtubule complex by interacting with β-tubulin.[1,2] Among the drugs that possess specificity for neovasculature and that interact with tubulin is combretastatin A4[3,4] (CA-4) (**1**) (Figure 1), whose phosphate prodrug has entered clinical trials.[3] The structure−activity relationship of CA-4 is well-characterized.[3] In brief, the cis configuration of the double bond is fundamental, as are the 3,4,5-trimethoxy groups on ring A. The cis olefinic bridge is able to undergo rapid cis−trans isomerization under the influence of heat, light, and protic media. In light of this, and with the attempt to render compounds more stable, a conspicuous number of cis-restricted analogues have been synthesized and shown to retain similar biological activity compared to combretastatin. Indeed, as one would expect, some are even more potent.[5,6] For example, we have recently shown that substitution of the olefinic bridge with a furazan ring gives analogues with an identical mechanism of action and a modest increase in potency (e.g., **2**).[7] In the present manuscript we decided to exploit this finding to generate chimeric drugs that might bear a second functional group or might bear a cell-targeting residue. If this were achieved, for example, it could be conceivable to develop a chimeric drug that targets both the vasculature and the surrounding tumoral tissue (including the rim, which is thought to rely on the vasculature from the surrounding healthy tissue)[8,9] or to direct the drug to a target different from the neovasculature (i.e., the solid tumor itself or a hematologic tumor with the use of a monoclonal antibody). Because of the impossibility of using furazan itself, we opted to investigate whether furan, a substitutable ring, could also mimic the olefinic bridge. Indeed, the furan ring might be considered a bioisosteric group of the furazan ring with Grimm's substitution between the nitrogen sp^2 atom and the carbon sp^2 atom. Furthermore, furan rings can be easily functionalized through electrophilic aromatic substitution, while furazan rings are unable to undergo the same reaction.

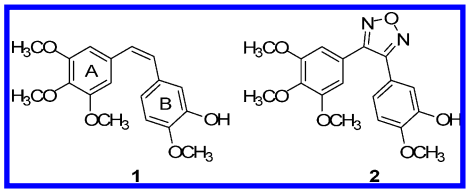


Figure 1. Combretastatin A4 (**1**) and combretafurazan (**2**).

In the present manuscript we show that combretafurans **7a**, **8a**, **8b**, synthesized through an intramolecular aldolic condensation as the key step, are active and can be functionalized at the 2 and 5 positions, rendering them a putative novel scaffold for designing a generation of dual-acting combretastatins.

Chemistry

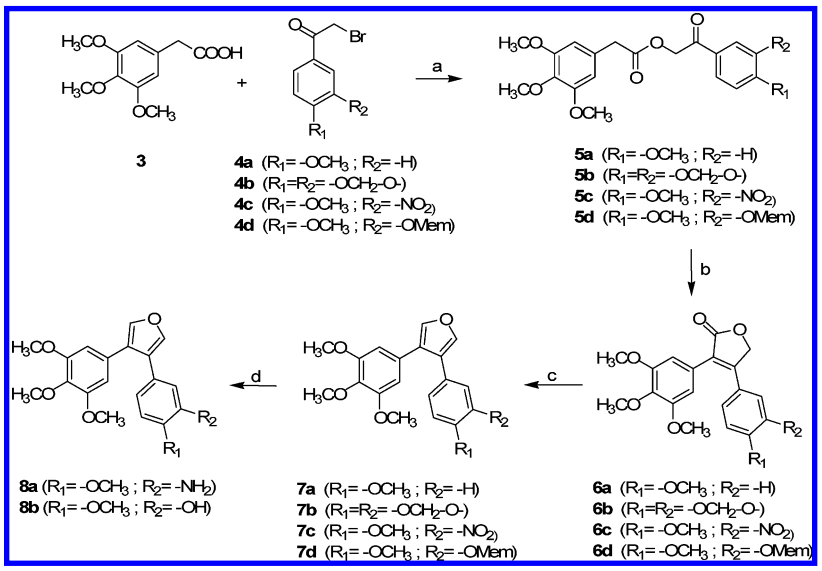
The furan nucleus was prepared in the following manner. 2-Oxo-2-phenylethyl 2-phenylacetate derivatives (**5a**−**d**) were prepared by reacting the salt of 3,4,5-trimethoxyphenylacetic (**3**) acid with the corresponding monobromine derivative of acetophenone (**4a**−**d**). The lactone ring was then prepared by an intramolecular aldolic condensation starting from derivatives **5a**−**d** (for similar approaches, see refs 10−12). Finally, the α,β unsaturated lactone was treated with the reducing agent DIBAL-H to give the desired furan derivatives (Scheme 1).

The formation of the desired unsaturated lactones **6a**−**d** was rather capricious, requiring a careful choice of the base and of the reaction conditions because initial attempts failed to be reproducible. Indeed, we were also able to separate, alongside the desired unsaturated lactone, 3,4-diphenyl-2,5-furandione (**9**) and 5-hydroxy-3,4-diphenyl-2(5*H*)-furanone derivatives (**10**) (see Supporting Information for structures).[13,14] It appeared quite clear that the presence of molecular oxygen and the base used played a pivotal role in directing the formation of the products. For these reasons, we surveyed a series of bases that differed for strength. Bases with a pK_a lower than 13 (e.g., TEA, DIPEA,

* To whom correspondence should be addressed. Phone: +39-0321-375857. Fax: +39-0321-375821. E-mail: tron@pharm.unipmn.it.
† Università degli Studi del Piemonte Orientale "A. Avogadro".
‡ These authors contributed equally to the present work.
§ Università degli Studi di Milano.

10.1021/jm060621o CCC: $33.50
Published on Web 07/29/2006

Scheme 1[a]



[a] Reagents and conditions: (a) TEA, CH_3CN; (b) KOH, 18-crown-6, CH_3CN; (c) DIBALH, THF, −10 °C; (d) Zn, CH_3COOH (**8a**); tosic acid, methanol (**8b**).

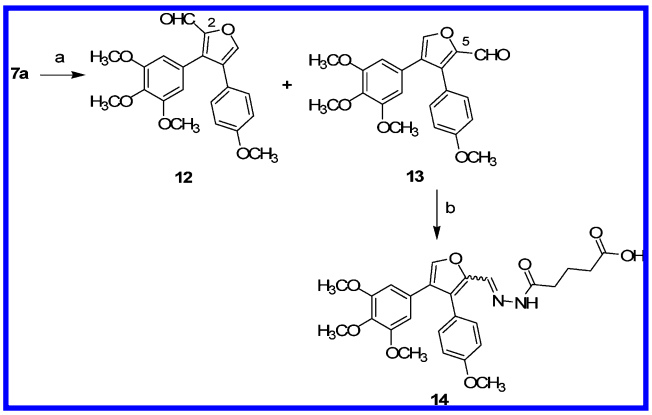
DBU)[11,15] failed to promote the cyclization, while bases with pK_a values higher than 16 (e.g., *t*-BuOK, NaH)[12,16,17] favored the deprotonation of the lactone, which subsequently reacted with oxygen or other electrophilic sites present in the reaction mixture. A good compromise was obtained by using finely pulverized potassium hydroxide (p$K_a \approx 15.7$) and a catalytic amount of 18-crown-6 ether in acetonitrile, previously degassed in order to remove the presence of oxygen. The reaction had to be carefully monitored to obtain higher yields. The reaction mixture was monitored by ^{1}H NMR, since separation in thin-layer chromatography was unsatisfactory. Under these experimental conditions, we were able to reproduce and scale up the reaction successfully, obtaining the desired unsaturated lactone in moderate to good yields (40−80%). The resulting lactone was treated at low temperatures (−10 °C) with a solution of DIBAL-H in dry THF, yielding, after acidic workup, the desired combretafuran derivatives.[18,19]

The synthesis of combretafurans bearing a methoxy (**7a**), a dioxolane ring (**7b**), a 4-methoxy-3-nitro (**7c**), or a 4-methoxy-3-amino group (**8a**) on ring B is reported in Scheme 1.

Last, the hydroxyl substituted combretafuran **8b** was prepared starting from the Mem-protected derivative **4d** as outlined in the same Scheme 1. Mem deprotection was successfully accomplished using catalytic amounts of tosic acid in MeOH. A very mild condition was necessary because furans undergo hydrolysis to dicarbonylic compounds in an acidic environment.

The products obtained were evaluated for cytotoxicity and antitubulinic action (see Biological Results and Discussion) and after establishment of their activity, the furan nucleus was functionalized by introducing a formyl group. To avoid the presence of two regioisomers, initial attempts were performed using a new combretafuran bearing a methyl group at the 2 position (**11**) (see Supporting Information for structure). Unfortunately, this derivative appeared quite unstable and unsuitable for further derivatization. We next turned our attention to **7a**, which, although 10 times less cytotoxic then **8b**, presents an easier synthetic accessibility. Formylation of **7a** using the Vilsmeier−Haack protocol (PCl_3, DMF) afforded the two regioisomers (**12** and **13**) in excellent yields. These were subsequently separated by column chromatography and HPLC (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) PCl_3, DMF; (b) 2-(4-carboxybutanoyl-)hydrazinium hydrochloride, EtOH/CH_2Cl_2.

The diastereoisomeric pair structures were assigned through two NOESY experiments, optimized with a mixing time of 1.2 s. Cross-coupling of spatially related protons was clearly visible; in **12** the aldehyde proton gave NOE with protons 2 and 6, while the furan proton gave NOE with protons 2′ and 6′. In contrast, in **13** the furan proton gave NOE with protons 2 and 6 and the methoxy groups at 3 or 5, while the aldehydic proton gave NOE with protons 2′ and 6′.

Last, we decided, as proof of principle, to synthesize an acid-labile hydrazone derivative of **13** to verify the potential of our novel scaffold to yield **14** (Scheme 2).[20]

Biological Results and Discussion

To evaluate the cytotoxic nature of the synthesized compounds, we used a neuroblastoma cell line (SH-SY5Y) that we had previously characterized as sensitive to combretastatin A4. We incubated increasing concentrations of **1** and its analogues for 48 h to establish the IC_{50} for the cell death of each compound (Table 1). Compound **1** yielded an IC_{50} of 1.6 ± 0.1 nM, a value similar to the one reported previously in this model.[7] Combretafuran **7a**, which resembles combretastatin except for the absence of the hydroxyl group on ring B, displayed an IC_{50} for cytotoxicity of 39 ± 8.9 nM, thereby demonstrating the potent nature of this novel class of analogues. For combre-

Table 1. Dose concentration Data of Combretastatin A4 (**1**) and Combretafuran Analogues on SH-SY5Y Cell Line[a]

compd	IC_{50}, nM	compd	IC_{50}, nM
1	1.6 ± 0.10	**8b**	2.9 ± 0.33
7a	39 ± 8.9	**12**	35.8 ± 20
7c	244.54 ± 150	**13**	231 ± 72
8a	5.1 ± 0.7	**14**	1670 ± 783

[a] Values are the mean ± SEM of 8−23 determinations.

tafurans, the reported SAR for the meta position of ring B[5] was maintained, with the analogue bearing the hydroxyl group being the most potent (**8b**, 2.9 ± 0.33 nM), the compound bearing the amino group displaying a slightly superior IC_{50} (**8a**, 5.1 ± 0.7 nM), and the analogue bearing the nitro group (**7c**) displaying an IC_{50} between 100 nM and 1 μM. We also tested **7b**, which presents a dioxolane moiety on ring B, but this compound was inactive up to 1 μM. Therefore, combretafuran **8b** that most closely resembles combretastatin displays just a 2-fold loss of cytotoxic action. To confirm a similar mechanism of action, we performed the in vivo tubulin polymerization assay.[7,21] This assay relies on the incubation of high amounts of inhibitor (50-fold the IC_{50}) overnight and extraction of the proteins in the presence of paclitaxel to freeze tubulin polymerization. Indeed, **7a**, at 1.5 μM (50-fold the IC_{50}) behaved identically to **1** (50 nM, 50-fold the IC_{50}; see Supporting Information). To further confirm this, we evaluated whether **8b**, the compound that most closely resembles **1**, behaved identically to its parent compound in the in vivo tubulin polymerization assay and in a cell cycle analysis, as one would expect. As expected, **8b** behaved identically to **1** (data not shown), while paclitaxel exerted the opposite effect (see Supporting Informations) in the in vivo tubulin polymerization assay. It is well-known that **1** induces a G2/M arrest of the cell cycle, and this was confirmed in our experiments (Figure 2). Surprisingly, **8b** did not elicit any significant alteration of the cell cycle (Figure 3) (see Supporting Informations for numeric analysis). Similar cell cycle profiles were obtained in cells treated with **7a** (data not shown). In summary, combretafurans are active as cytotoxic agents and inhibit tubulin polymerization but does not appear to share the G2/M block of combretastatin, thereby suggesting a distinct mechanism of action, which may or may not rely on tubulin.

Since the cytotoxic potency of these compounds was retained, we therefore decided to investigate the properties of the compounds bearing a formyl group in position 2 (**12**) or 5 (**13**) of the furan ring. Both these compounds were cytotoxic, with **12** displaying an identical IC_{50} (35.8 ± 20 nM) and **13** showing a loss of approximately 6.5-fold reduction (231 ± 72 nM) compared to **7a** (the reference compound, since it lacks the hydroxyl group). In our hands, the dose response of combretastatin and combretafurans shows a Hill slope between 1 and 2. While this was retained for **12**, the Hill slope for **11** was reproducibly higher, suggesting that this compound possesses a cytotoxic effect distinct from those of the other compounds. To strengthen these data, we performed immunocytochemistry with an antitubulin antibody to visualize the disruption of the cytoskeleton with these drugs. Indeed, **1**, **8b**, and **13** at the IC_{50} concentration for 24 h induced a disruption of the cytoskeleton that brought cells to round up, while **12** did not induce any change in tubulin organization (see Supporting Information). Surprisingly, both compounds were able to induce tubulin depolymerization in the in vivo polymerization assay (see Supporting Information). As a proof of principle, to explore the potential of the furan ring to act as scaffold, thereby allowing the generation of chimeric drugs, mutual prodrugs, or targeted

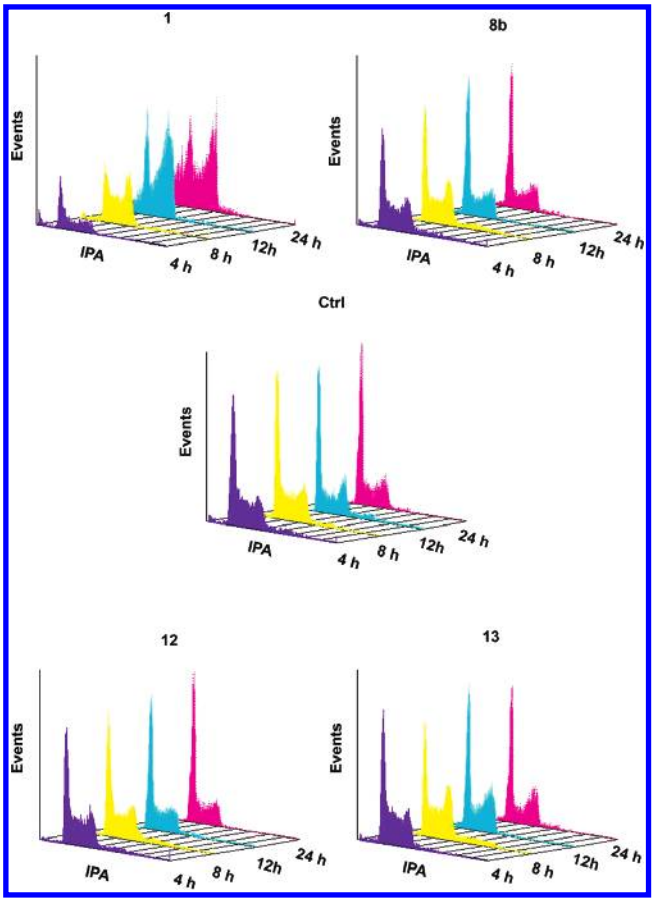


Figure 2. Cell cycle analysis of neuroblastoma cells treated for 16 h with the indicated compounds at the IC_{50} concentration. Graphs are representative of at least three experiments that yielded similar results.

compounds, we functionalized this position with a hydrazonic linker. It is well-known that these linkers are highly stable at physiological pH but undergo rapid hydrolysis at pH 5.5.[20] Because of our perplexity on the mode of action of **12**, we decided to develop **13**. This modification (**14**) was cytotoxic, although a 7-fold loss of activity compared to **13** (1.6 ± 0.7 μM) was observed. Indeed, **14** elicited an effect identical to that of **1** in the tubulin assay (i.e., depolymerization of tubulin; see Supporting Information).

Conclusions

The series of compounds we have synthesized are cytotoxic and inhibit tubulin polymerization. The potential potency of these compounds can be derived from the fact that **8b**, which resembles **1** except for the furan ring in place of the olefinic bridge, displays a cytotoxic potential of comparable strength. Further modifications, such as the addition of the formyl moiety, yield a moderate loss of potency. Considering the fact that these compounds are for designing scaffolds for chimeric or mutual prodrugs, a loss of potency might be regarded as beneficial. In fact, chimeric or mutual prodrugs rely on the fact that the two drugs should be balanced in potency to allow both actions to take place. The potency of **1** (low nanomolar) makes it difficult therefore to generate well-balanced hybrids, while **13** might allow for the use of a less potent drug (indeed, most drugs used in clinical settings at present). Indeed, one initial attempt by us to generate hybrids has failed for this very reason.[22] Furthermore, substitutions of the meta position on ring B with a hydroxyl or a nitro will also allow for a dynamic range of activity. All these compounds do not appear to interfere with the cell cycle, raising

the question of which is the cytotoxic mechanism of action of these drugs. Indeed, it has been previously shown that some combretastatin analogues can maintain cytotoxic potential while losing antitubulin activity.[5] Whether this is the case here is unclear, since we are able to see an effect on tubulin polymerization. It will nonetheless be interesting to explore further whether these drugs retain their angiotoxic potential or whether their in vivo pattern of activity will be radically modified.

Experimental Section

Chemistry. Commercially available reagents and solvents were used without further purification and were purchased from Fluka-Aldrich or Lancaster. Dichloromethane was dried by distillation from P_2O_5 and stored on activated molecular sieves (4 Å). Acetonitrile was dried on CaH and stored on activated molecular sieves (4 Å). Tetrahydrofuran (THF) and diethyl ether were distilled immediately before use from Na/benzophenone under a slight positive atmosphere of N_2. Dimethylformamide (DMF) was purified by distillation at reduced pressure, collecting the fraction having a bp of 76 °C at 39 mmHg and storing it on activated molecular sieves (4 Å). When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2.

Melting points were determined in an open glass capillary with a Stuart scientific SMP3 apparatus and are uncorrected. All the compounds were checked by IR (FT-IR Thermo Nicolet Avatar), ^{1}H and ^{13}C NMR (JEOL ECP, 300 MHz), and mass spectrometry (Thermo Finningan LCQ-deca XP-*plus*), with the instrument being equipped with an ESI source and an ion trap detector. NOE experiments were performed on a Bruker Avance 500 MHz instrument equipped with a 5 mm QNP multinuclear probe. Chemical shifts are reported in part per million (ppm). Column chromatography was performed on silica gel (Merck Kieselgel 70−230 mesh ASTM) using the indicated eluants. Thin-layer chromatography (TLC) was carried out on 5 cm × 20 cm plates with a layer thickness of 0.25 mm (Merck silica gel 60 F_{254}). When necessary, they were developed with $KMnO_4$. HPLC was carried out on Jasco Borwin HERCULE lite apparatus. Elemental Analysis (C, H, N) of the target compounds were performed by Università dell'Insubria (Como, Italy) and are within ±0.4% of the calculated values unless otherwise noted. Compounds **4b**,[23] 1-(3-hydroxy-4-methoxyphenyl)-1-ethanone,[24] 2-bromo-1-(3-hydroxy-4-methoxyphenyl)-1-ethanone,[25] and 2-(4-carboxybutanoyl)hydrazinium hydrochloride[26] were synthesized as reported in the literature.

2-(4-Methoxyphenyl)-2-oxoethyl 2-(3,4,5-Trimethoxyphenyl)-acetate (5a). To a cooled (0 °C) solution of trimethoxyphenylacetic acid (5 g, 0.022 mol, 1 equiv) in CH_3CN (50 mL), TEA (3.1 mL, 2.2 g, 0.022 mol, 1 equiv) and 2-bromo-1-(4-methoxyphenyl)-1-ethanone (**4a**) (5 g, 0.002 mol, 1 equiv) were added. The resulting solution was stirred for 4 h at 0 °C, worked up by dilution with EtOAc and washed sequentially with 2 N HCl (×1), saturated aqueous $NaHCO_3$ (×2), and brine (×1). The organic layer was dried over sodium sulfate. Filtration and evaporation of the solvent gave **5a** as white solid, which was used directly without further purification (6.8 g, 83%).

4-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (6a). To a degassed solution of **5a** (6.8 g, 0.018 mol, 1 equiv) in CH_3CN (100 mL), 18-crown-6 (143 mg, 0.54 mmol, 0.03 equiv) and KOH (1 g, 0.018 mol, 1 equiv) were added, and the reaction mixture was magnetically stirred. The resulting solution became rapidly dark-green. After 30 min, the reaction was worked up by dilution with EtOAc and washed sequentially with 2 N HCl (×2) and brine (×1). After drying over sodium sulfate and evaporation of the solvent, the crude product was purified by crystallization from methanol to give **6a** as yellow solid (6.0 g, 93%).

3-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)furan (7a). To a cooled (−20 °C) solution of **6a** (1.66 g, 4.6 mmol, 1 equiv) in dry THF (12 mL) and under a nitrogen atmosphere, a solution of 1 M DIBALH in THF was added dropwise (18.6 mL, 18.6 mmol, 4 equiv). The resulting solution was stirred for 3 h at −20 °C and quenched by slow addition of 4% H_2SO_4 p/v. After 30 min, the solution was diluted with ether and the oganic layer was washed with water (×1) and brine (×1). After drying over sodium sulfate and evaporation of the solvent, the crude furan was purified by column chromatography using 8:2 PE/EtOAc as eluant to obtain **7a** as a pale-yellow solid (1.2 g, 76%).

4-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2-furaldehyde (12) and 3-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-2-furaldehyde (13). PCl_3 (147 μL, 232 mg, 1.69 mmol, 1.1 equiv) was slowly added to dry DMF (3 mL), maintaning the temperature below 30 °C. The solution became rapidly red. 3-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)furan (522 mg, 1.53 mmol, 1 equiv), dissolved in dry DMF (5 mL), was carefully added, and the resulting solution was heated at 60 °C for 1 h, worked up by dilution with EtOAc, and washed with water (×1). The water phase was extracted thrice with EtOAc. The combined organic phases were then washed with brine (×1) and dried over sodium sulfate. After evaporation, the crude mixture was purified by column cromatography using as eluant 8:2 PE/EtOAc. The mixture obtained was further purified by HPLC (HiCHROM Kromasil silica, 250 mm × 21.2 mm × 10 μm; 7:3 PE/EtOAc; 6 mL/min; λ = 254 nm) to give **12** (185 mg, 32.7%) and **13** (191 mg, 33.7%) as yellowish solids.

5-(2-{-[3-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-2-furyl]methylidene}hydrazino)-5-oxopentanoic Acid (14). To a solution of **13** (106 mg, 0.288 mmol, 1 equiv) in ethanol (2 mL; some drops of dry CH_2Cl_2 were added to improve the solubility of the product), 2-(4-carboxybutanoyl)hydrazinium hydrochloride (105.4 mg, 0.58 mmol, 2 equiv) was added. The mixture was stirred at room temperature for 1 h, and the solvent was evaporated. The crude product was purified by column chromatography, using 5:5 PE/EtOAc and EtOAc as eluant to give **14** (*E*/*Z*, 5:1mixture) as a yellow solid (50 mg, 35%).

Acknowledgment. Financial support from Università del Piemonte Orientale and Regione Piemonte is gratefully acknowledged.

Supporting Information Available: Synthesis procedures of all other compounds, their characterization (mp, IR, MS, and ^{1}H and ^{13}C NMR data), structures of **9**−**11**, elemental analysis results of all target compounds, concentration response curves for the target compounds, representative results of the in vivo polymerization assay, and immunocytochemistry of tubulin in treated cells. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Neri, D.; Bicknell, R. Tumor vascular targeting. *Nat. Rev. Cancer* **2005**, *5*, 436−446.
(2) Jordan, M. A.; Wilson, L. Microtubules as a target for anticancer drugs. *Nat. Rev. Cancer* **2004**, *4*, 253−265.
(3) Young, S. L.; Chaplin, D. J. Combretastatin A4 phosphate: background and current clinical status. *Expert Opin. Invest. Drugs* **2004**, *13*, 1171−1182.
(4) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; et al. Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4. *Experientia* **1989**, *45*, 209−211.
(5) Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A. Medicinal chemistry of combretastatin A4: present and future directions. *J. Med. Chem.* **2006**, *49*, 3033−3044.
(6) Nam, N. H. Combretastatin A-4 analogues as antimitotic antitumor agents. *Curr. Med. Chem.* **2003**, *10*, 1697−1722.
(7) Tron, G. C.; Pagliai, F.; Del Grosso, E.; Genazzani, A. A.; Sorba, G. Synthesis and cytotoxic evaluation of combretafurazans. *J. Med. Chem.* **2005**, *48*, 3260−3268.
(8) Pedley, R. B.; Hill, S. A.; Boxer, G. M.; Flynn, A. A.; Boden, R.; et al. Eradication of colorectal xenografts by combined radioimmunotherapy and combretastatin a-4 3-O-phosphate. *Cancer Res.* **2001**, *61*, 4716−4722.
(9) Chaplin, D. J.; Hill, S. A. The development of combretastatin A4 phosphate as a vascular targeting agent. *Int. J. Radiat. Oncol., Biol., Phys.* **2002**, *54*, 1491−1496.
(10) Dikshit, D. K.; Singh, S.; Singh, M. M.; Kamboj, V. P. Synthesis and biological activity of 2,3- and 3,4-diarylfurans and 2,3,4-triaryl-2,5-dihydrofurans. *Indian J. Chem.* **1990**, *B29*, 954−960.

(11) Kim, Y.; Nam, N. H.; You, Y. J.; Ahn, B. Z. Synthesis and cytotoxicity of 3,4-diaryl-2(5*H*)-furanones. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 719−722.
(12) Rahim, M. A.; Rao, P. N. P.; Knaus, E. E. Isomeric acetoxy analogues of rofecoxib: a novel class of highly potent and selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2753−2756.
(13) Padakanti, S.; Veeramaneni, V. R.; Pattabiraman, V. R.; Pal, M.; Yeleswarapu, K. R. A simple and rapid entry to 5-alkyl (aryl)-5-hydroxy-3,4-diarylfuranones and 3a-hydroxy-1-aryl-2,3a,4,5-tetrahydronaphthofuranones via a tandem esterification and oxidative cyclization process. *Tetrahedron Lett.* **2002**, *43*, 8715−8719.
(14) Pattabiraman, V. R.; Padakanti, S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. Synthesis of 3,4-diaryl-substituted maleic anhydride/maleimide via unusual oxidative cyclization of phenacyl ester/amide. *Synlett* **2002**, 947−951.
(15) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. Design and synthesis of celecoxib and rofecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: replacement of sulfonamide and methylsulfonyl pharmacophores by an azido bioisostere. *J. Med. Chem.* **2001**, *44*, 3039−3042.
(16) Padwa, A.; Dehem, D. A facile one-step synthesis of 3,5,5-trisubstituted 2(5*H*)-furanones. *J. Org. Chem.* **1975**, *40*, 3139−3141.
(17) Gopidas, K. R.; Lohray, B. B.; Rajadurai, S.; Das, P. K.; George, M. V. Sensitized photorearrangement of 3,3,5-triaryl-2(3*H*)-furanones to 3,4,5-triaryl-2(5*H*)-furanones. Steady-state and laser flash photolysis investigations. *J. Org. Chem.* **1987**, *52*, 2831−2838.
(18) Minato, H.; Nagasaki, T. A new synthetic method for furan compounds. *Chem. and Ind.* **1965**, *21*, 899−900.
(19) Minato, H.; Nagasaki, T. A new method for the synthesis of furan compounds. *J. Chem. Soc*. **1966**, *4*, 377−379.
(20) Kratz, F.; Beyer, U.; Schuette, M. T. Drug−polymer conjugates containing acid-cleavable bonds. *Crit. Rev. Ther. Drug Carrier Syst.* **1999**, *16*, 245−288.
(21) Prinz, H.; Ishii, Y.; Hirano, T.; Stoiber, T.; Camacho Gomez, J. A.; et al. Novel benzylidene-9-(10*H*)-anthracenones as highly active antimicrotubule agents. Synthesis, antiproliferative activity, and inhibition of tubulin polymerization. *J. Med. Chem.* **2003**, *46*, 3382−3394.
(22) Coggiola, B.; Pagliai, F.; Allegrone, G.; Genazzani, A. A.; Tron, G. C. Synthesis and biological activity of mustard derivatives of combretastatins. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3551−3554.
(23) Antunes, H.; Fardelone, L. C.; Rodrigues, A. R.; Moran, P. J. S. Chemoenzymatic syntheses of (*R*)-2-bromo-, (*R*)-2-chloro- and (*R*)-2-azido-1-(1,3-benzodioxol-5-yl)-1-ethanol. *Tetrahedron: Asymmetry* **2004**, 2615−2620.
(24) Brossi, A.; Gurien, H.; Rachlin, A. I.; Teitel, S. Selective demethylation of 3,4-dimethoxy-substituited aromatic aldehydes and ketones. *J. Org. Chem.* **1967**, *32*, 1269−1270.
(25) Pratesi, P.; Lamanna, A.; Villa, L.; Grana, E.; Lilla, L. Struttura chimica e attività biologica delle catecolamine (Chemical structure and biological activity of the catecholamines). *Farmaco, Ed. Sci.* **1963**, *18*, 920−931.
(26) Chen, Q.; Sowa, D. A.; Cai, J.; Gabathuler, R. Synthesis of doxorubicin conjugates through hydrazone bonds to melanotransferrin P97. *Synth. Commun.* **2003**, *33*, 2377−2390.

JM060621O