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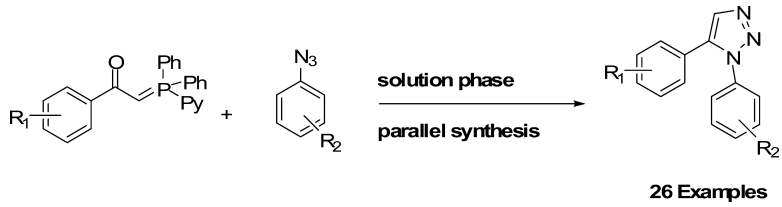

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Solution-Phase Parallel Synthesis and Biological Evaluation of Combretatriazoles

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Combretastatin A-4 is an antitumoral and antitubulin agent that is active only in its cis configuration. In the present manuscript, we have synthesized cis-locked combretastatins containing a triazole ring (combretatriazoles). To achieve this, we have developed a column chromatography-free parallel solution-phase synthesis that exploits the reaction between azides and α-keto phosphorus ylids, which is known to regioselectively generate the 1,5-disubstituted triazoles. The prepared compounds were screened as antitubulinic agents, allowing us to identify three new compounds with high potency, two of which show a new mechanism of action that induces cells to appear multinucleated and display a high number of mitotic spindles.

Introduction

Tubulin has been shown to be a good target for antitumoral drugs and for drugs targeting the neovasculature. Indeed, alongside drugs already used for these indications (e.g., paclitaxel, vincristine), a number of new molecules have entered clinical trials. Among these, combretastatin A-4 (**1**) (Figure 1) is an excellent example, and it has now entered phase II clinical trials as the phosphate prodrug.[1] Combretastatin A-4 is a simple molecule, and it is therefore no surprise that a number of studies have addressed its structure−activity relationship to improve our understanding of its action and generate more potent and specific drugs.[2]

Combretastatin A-4 is active in its cis conformation, yet isomerization of the active cis double bond of **1** to the inactive trans form is frequent and is favored by heat, light, and proton media, and this transformation also takes place in normal physiological buffer during in vitro metabolism experiments.[3] This phenomenon is among the reasons for which a number of authors have replaced the olefinic bridge with heterocycle moieties.[2,4,5] As expected, some of these molecules (presumably those that maintain the correct orientation of the two polyoxygenate aromatic rings) display an increase in potency over combretastatin. Yet, one could also envisage that these heterocycles, if properly suited into the binding pocket, might also increase the specificity or might confer different pharmacodynamic properties to the compound. Last, the heterocycle can also be used as a scaffold for the generation of dual-acting drugs.[6]

Although this strategy might work, until now, this procedure has generated compounds that require an increase in the number of synthetic steps with respect to **1**. Recently, we used the concept of click chemistry to synthesize 1,4-disubstituted triazole analogues with cytotoxic[7] and estrogenic properties[8] in a rapid and effective manner. As expected, when this substitution was performed on the olefinic bridge of **1** (yielding therefore what might be called 1,4-disubstituted triazole combretastatin), these compounds (Figure 2) were neither cytotoxic[7] nor effective at altering tubulin polymerization (data not shown).

In the present contribution, we decided to investigate whether 1,5-disubstituted triazoles might be effective tubulin inhibitors and whether this strategy might provide a means to generate libraries. In this instance, instead of using the click chemistry reaction catalyzed by a ruthenium complex (a catalyst which should yield only the 1,5-regioisomer)[9] because it did not yield regioselectivity with these substrates, our attention was directed toward the reaction between azides and α-keto phosphorus ylids, which is also known to regioselectively generate the 1,5-disubstituted triazole. This reaction, developed in the 1960s,[10] despite its broadness in scope and selectivity, has received scanty attention in a medicinal chemistry context,[11] but it has an important advantage because it does not require metal catalysis.

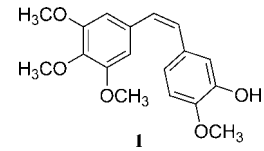

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Figure 1. Combretastin A-4.

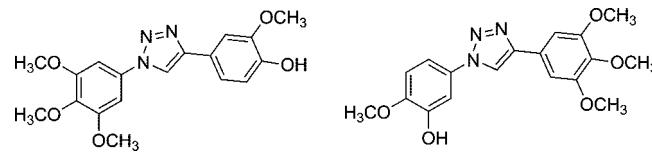

Figure 2. 1,4-Disubstituted triazoles analogues of combretastatin.[7]

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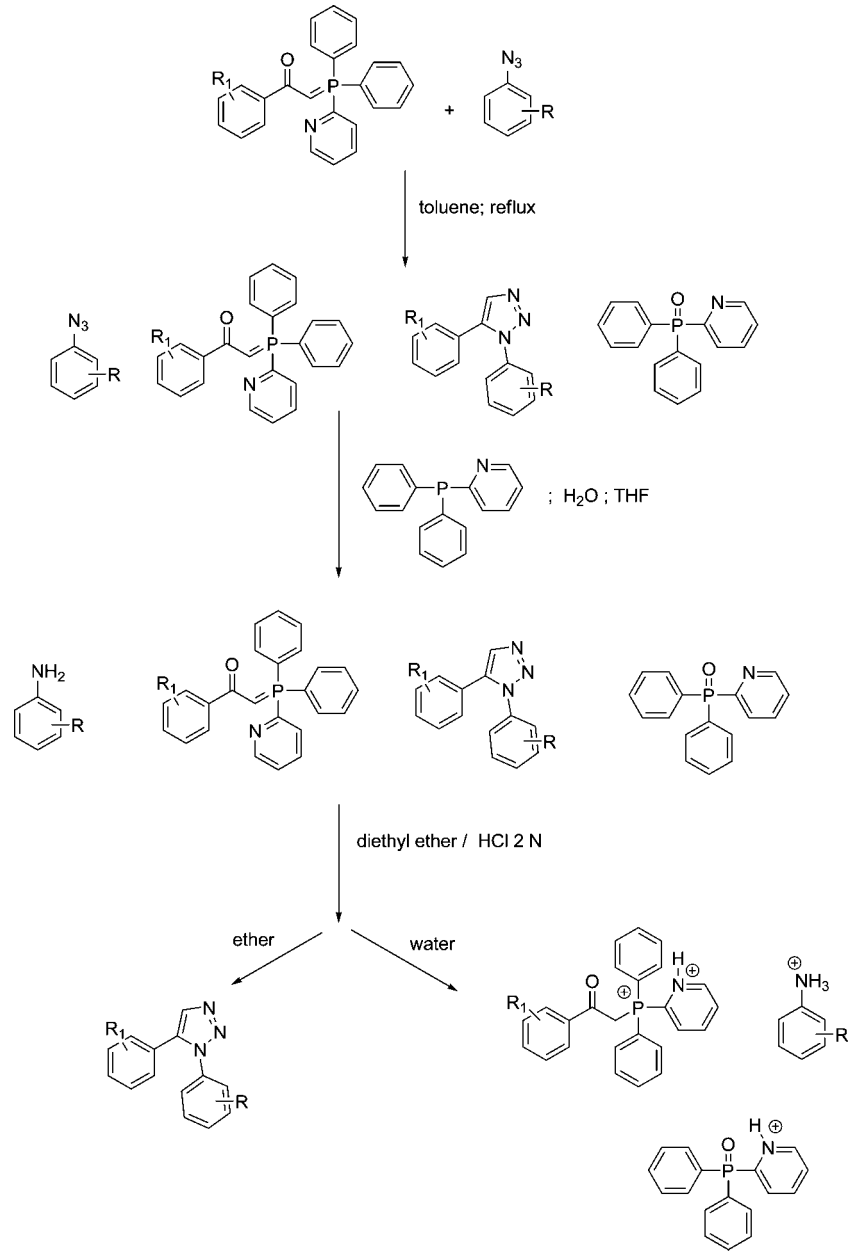
Scheme 1. Scheme of Purification of the 1,5-Disubstituted Triazoles



Indeed, we now show that 1,5-disubstituted triazole combretastatins synthesized in this manner are active as cytotoxic and antitubulin agents. Furthermore, the generation of a small library has also allowed the synthesis of a new class of structurally similar molecules that appear to have a different, yet promising, mechanism of action, providing evidence that this approach can allow for the generation of combretastatin analogues and can explore the chemical space.

Results

To generate 1,5-disubstituted triazole combretastatins, we first attempted to use the ruthenium-catalyzed chemistry,[9] but this proved ineffective for our objective because we obtained a mixture of the 1,4- and the 1,5-regioisomers in almost equal quantity (data not shown). Naturally, this lack of selectivity was observed also when we heated the corresponding azides and alkynes.[12] These reasons prevented the use of these strategies in a rapid parallel combinatorial approach to generate a vast number of derivatives.

For this reason, our attention was directed toward the reaction between azides and α-keto phosphorus ylids. To set up a parallel combinatorial approach and to purify the final products without using chromatography, we decided to use diphenyl-pyridinyl α-keto phosphorus ylids, which could be easily removed with an acidic wash. The strategy followed is illustrated in Scheme 1. A slight excess of azide and phosphorus ylid were dissolved in toluene and reacted in cap-screw vials, with heating at 90 °C for three days. Evaporation of the solvent was followed by Staudinger reduction of the unreacted azide with diphenyl-2-pyridyl-phosphine in THF/water at room temperature. After evaporation of the solvent, the crude was subjected to an acidic workup to remove diphenyl-2-pyridyl-phosphine oxide and the eventually unreacted phosphorus ylid to give the desired 1,5-disubtitued triazole. Different phenyl azides with electron-withdrawing or -releasing groups were used (Figure 3) to probe the allowed substitutions, while 3,4,5-trimethoxyphenyl

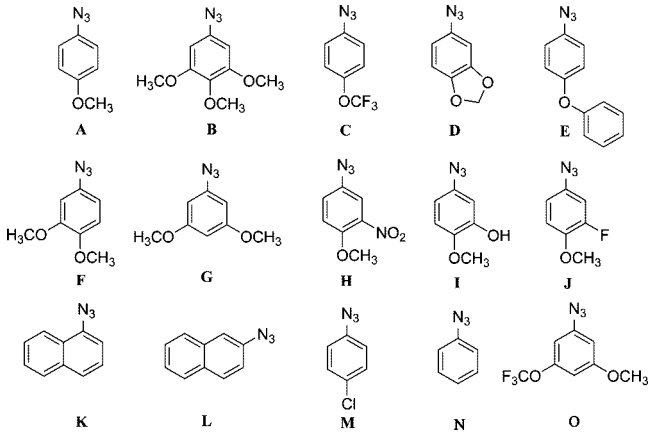


Figure 3. Azide building blocks.

(**5**; Scheme 2) and 3-benzyloxy-4-methoxyphenyl (**9**; Scheme 3) were used as aryl groups in the phosphorus ylids. These latter compounds were synthesized starting from their corresponding acetophenone derivatives, which were α-brominated and then transformed into the corresponding phosphonium salts using diphenyl-2-pyridyl-phosphine. Ylids were obtained using a biphasic system (CH_2Cl_2/water) in the presence of sodium bicarbonate as base (Schemes 2 and 3). With these compounds in our hands, we synthesized a library of triazole derivatives (26 analogues) (Schemes 4 and 5). Protection of the phenolic group was required for series **9** because, in its absence, the reaction gave a complex mixture of products (data not shown). For this reason, we opted for the benzylic moiety as protecting group. This choice was driven by the knowledge that this group is stable in the acidic conditions required during the workup procedures. Because the removal of this protecting group by hydrogenolysis is not easily automatizable, other protecting groups (stable at acidic conditions) may be taken into consideration for the generation of larger libraries.

The products were analyzed by NMR and HPLC-MS. All products were the expected compounds with purities ranging between 72−98% (see Supporting Information). This purity allowed us to pursue the initial biological evaluations.

Biological Results and Conclusion

To evaluate the synthesized compounds, we first screened the unpurified compounds of both series on a neuroblastoma cell line (SHSY-5Y; Table 1). Most of the products of series **5** were not cytotoxic up to 1 μM, with a few devoid of cytotoxic effects up to 10 μM. Compounds **5Hbis**, **5I**, and **5L** displayed high nanomolar IC_{50} values. In contrast, a number of compounds of series **10** appeared to exert potent cytotoxic effects, with 3 of these (**10B**, **10G**, and **10L**) displaying approximate IC_{50} values below 30 nM.

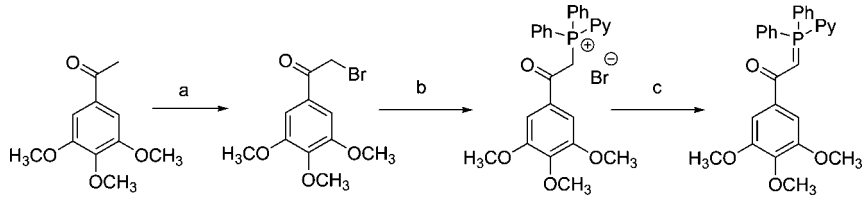
We therefore decided to concentrate on compounds **10B**, **10G**, and **10L** to characterize them further. These three compounds were re-prepared and purified by column chromatography (overall yield on two synthetic steps **10B** (45%), **10G** (48%), and **10L** (30%)), and their purity evaluated by HPLC (≥95%) (see Supporting Information). A full-dose response curve was performed. In the present experiments, combretastatin A-4 (**1**) displayed an IC_{50} of approximately 3.0 ± 0.3 nM, which is comparable to what we have published previously in this cell line.[6] Compound **10B** displayed an IC_{50} of 4.7 ± 0.7 nM; compound **10G** displayed an IC_{50} of 1.9 ± 2.0 nM, and compound **10L** displayed an IC_{50} of 12.2 ± 1.2 nM (Figure 4). These dose−response curves thereby confirm the potency of the unpurified compounds.

To investigate their mechanism of action, we performed cell cycle analysis of cells treated with these compounds for 24 h at the IC_{50} value (Figure 5). Tubulin inhibitors have a typical cell cycle signature, with a marked G2/M arrest. As expected, **1** did indeed induce a G2/M cell arrest, as did compound **10B**. To our surprise, though, this analysis did not yield any striking difference in cell cycle between compounds **10G** and **10L** versus control.

To investigate this further, we decided to visualize the tubulin cytoskeleton via confocal microscopy, and cells were treated for 8, 16, or 24 h in the presence of the compounds at the IC_{50} concentration. Treatment of cells with **1** or **10B** led to a rearrangement and disorganization of microtubules already after 8 h, while treatment with the other two compounds did not modify the organized cytoskeletal structure (Figure 6). This suggests that **10G** and **10L** are unable to impair tubulin polymerization/depolymerazion at interphase. Yet, both **10G** and **10L** induced a very peculiar immunocytochemical pictures that were particularly evident after 16 h of treatment (Figure 7). In brief, about 30% of cells appeared multinucleated and displayed a high number of aberrant mitotic spindles. This immunohistochemical picture was not observable in control cells or in cells treated with **1**. At present the cellular target that should elicit this effect is unknown, and we therefore envisage investigating this further in the future. Yet, it once again suggests that **10G** and **10L** act as cytotoxic agents in a different manner than combretastatin. Yet, when performing tubulin polymerization assays on whole cells, by incubating SH-SY5Y cells for 16 h at a concentration 50-fold the IC_{50} and performing SDS-Page-Western blotting on polymerized and unpolymerized tubulin, we found that **10B**, **10G**, and **10L** all behaved as depolymerizing agents (like combretastatin A-4; data not shown). This would suggest that, as expected, all these compounds can bind tubulin and interfere with polymerization, but for **10G** and **10L** the primary mechanism of action must be found elsewhere. This effect on tubulin was strengthened by molecular modeling aimed at investigating the binding mode of **10B**, **10G**, and **10L** on the colchicine binding site. Equivalent compounds bearing a double bond in place of the triazole ring have been reported previously; **10B** is equivalent to combretastin A-4, and the equivalent of **10G** has been shown to be cytotoxic at low concentrations and be an antitubulin agent.[13a] The equivalent of **10L** has been shown to be cytotoxic but effects on tubulin have not been investigated.[13b]

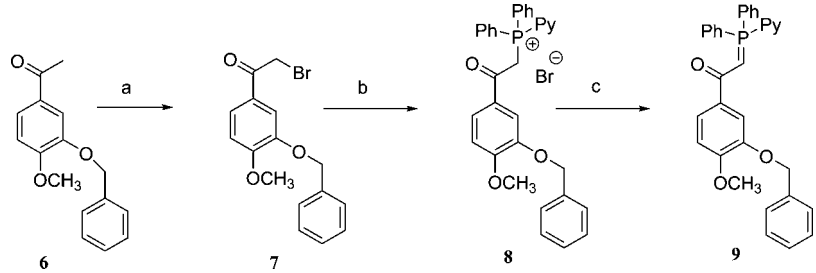
Docking studies show that the binding mode for **10B** is in agreement with X-ray structure complex of DAMA−colchicine−tubulin.[14] The triazole group was located in a small pocket near βA250 and βD251 with the N-2 and N-3 atoms of the 1,2,3-triazole ring forming hydrogen bonds with the NH atoms of the aminoacid amides. In agreement with the pharmacophoric model previously

Scheme 2. Synthesis of Ylid **5**[a]



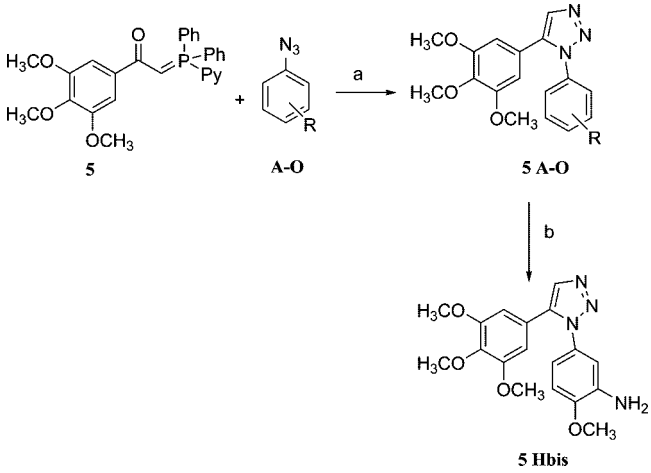
[a] Reagents and conditions: (a) Bromine, diethyl ether, 0 °C; (b) diphenyl-2-pyridyl-phosphine, toluene, r.t. (86%); (c) $NaHCO_3$, CH_2Cl_2/H_2O, r.t. (85%).

Scheme 3. Synthesis of Ylid **9**[a]



[a] Reagents and conditions: (a) Bromine, ethanol, 0 °C; (b) diphenyl-2-pyridyl-phosphine, toluene, r.t. (90%); (c) $NaHCO_3$, CH_2Cl_2/H_2O, r.t. (61%).

Scheme 4. Synthesis of Triazoles **5A**−O and **5Hbis**[a]



[a] Reagents and conditions: (a) toluene, 90 °C; (b) H_2, Pd/C 10%, MeOH, r.t.

published by Nguyen et al.,[15] **10B** forms two further hydrogen bonds, one between the phenolic group of the ring B and the −NH of αV181 and another one between the methoxy group of the ring A and the −SH of *β*C241 (Figure 8). This interaction is absent in the compounds **10G** and **10L**. This model would be in accord with the binding mode postulated by others using a different molecular modeling software for 2-methoxy-5-[1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl]aniline[16] another active triazole-combretastin analogue. Yet, while this model would also explain the loss of activity of **10A**, **10H**, and **10I**, and the different mechanism of action of **10G** and **10L**, it would not fully account for the loss of potency of **10F** and **10J** (see Supporting Information for the docking binding mode). It is therefore likely that, while the correct positioning of the triazole can play a role in binding, the loss of potency/activity is most likely caused by the absence of the trimethoxyphenyl group, which has been shown previously to be crucial.[17]

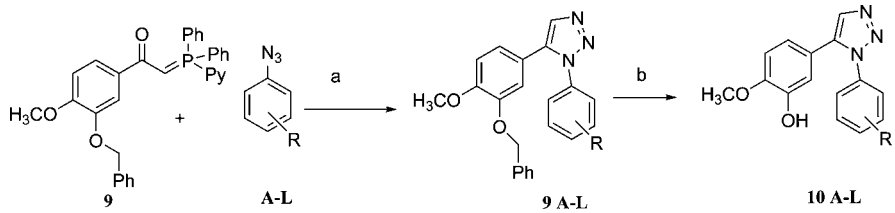
While we were submitting this manuscript, Odlo and coworkers[16] described some of the molecules described here (**5A**, **5H**, **5I**, **5Hbis**, **10A**, and **10I**). These were obtained either by the 1,3-dipolar cycloaddition between magnesium acetylides and azides[18] or by the classical thermal cycloaddition[19] (for those that did not react in the former protocol). The process developed by us appears to be more versatile and amenable to combinatorial chemistry because it appears more tolerant to different functional groups. Yet, in the context of combrestatin analogues, the described strategy cannot be used with the nitrogen-bearing heterocycles, although some of these have been shown to be able to replace the 3-hydroxy-4-methoxy phenyl ring of combretastatin.[2] The cytotoxic data presented for the four compounds of series **5** and the two compounds of series **10** appear in general accord with our data. Odlo and co-workers find a discrepancy between the cytotoxic and antitubulin activities of the compounds, as we found for compounds **10G** and **10L**. In our contribution, we were more fortunate because we found a true antitubulin agent in **10B** and show some preliminary evidence for a new mechanism of action for **10G** and **10L**.

In conclusion, our manuscript provides for a new method amenable to parallel synthesis of cis-constrained stilbenoids and describes three new compounds with high cytotoxic potency. One of these displays the biological signature of antitubulin agents, while the other two induce cells to appear multinucleated and display a high number of mitotic spindles, suggestive of a different mechanism of action.

Experimental Section

Chemistry. Commercially available reagents and solvents were used without further purification and were purchased from Fluka-Aldrich or Acros. Dichloromethane was dried by distillation from P_2O_5 and stored on activated molecular sieves (4 Å). Toluene was dried by distillation from sodium and stored on activated molecular sieves (4 Å). Diethyl ether was distilled immediately before use from Na/benzophenone under a slight positive atmosphere of N_2. When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2. Melting points

Scheme 5. Synthesis of Triazoles **10A−L**[a]



[a] Reagents and conditions: (a) toluene, 90 °C; (b) H_2, $Pd(OH)_2$/C 10%, MeOH, r.t.

Table 1. Approximate IC_{50} Values of the Unpurified Compounds Synthesized[a]

	approximate IC_{50} (nM)	
	5	10
A	>1000	630 ± 70
B	>1000	28 ± 11 (4.7 ± 0.7)
C	>10000	126 ± 38
D	>10000	257 ± 250
E	>1000	>1
F	>10000	192 ± 23
G	>10000	2.2 ± 1.0 (1.9 ± 2.0)
H	>10000	ns
Hbis	255 ± 160	ns
I	415 ± 109	72 ± 6
J	>10000	366 ± 80
K	n.s.	41 ± 22
L	406 ± 280	7.5 ± 2.0 (12.2 ± 1.2)
M	>1000	ns
N	>1000	ns
O	>1000	ns
CA-4	3.0 ± 0.3	

[a] Number in parenthesis corresponds to calculated IC_{50} values of the purified compounds; ns = not synthesized.

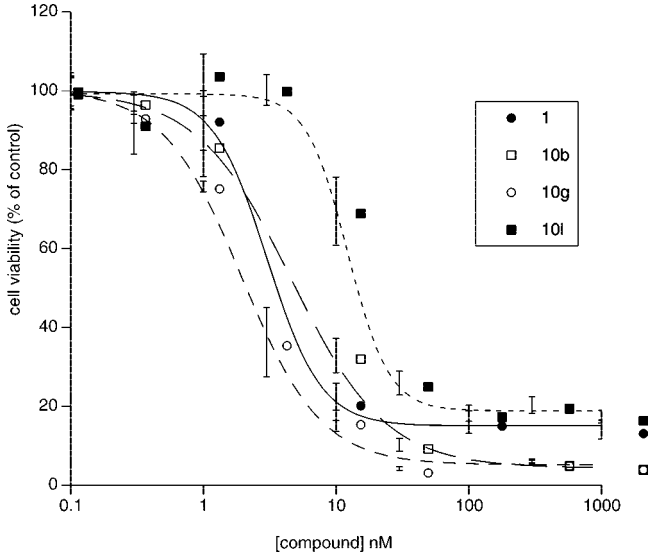


Figure 4. Dose−response curves of the characterized purified products. Values represent mean + SEM of at least 8 determinations from two separate experiments. Please see text for IC_{50} values.

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). NMR spectra were recorded with a JEOL ECP 300 MHz spectrometer, and the δ values are in parts per million. The HPLC purity and the mass spectra of each compound were performed using a LC-ESI-MS "on line" (Thermo Finnigan LCQ Deca XP-*plus* Ion Trap Mass Spectrometer instrument from Thermo Finnigan, San Josè, CA) equipped with an electrospray ion source (ESI) connected to a Surveyor HPLC system by a splitting of 50%. The MS spectra were acquired in positive or negative ion mode (mass scan range was *m*/*z* 50−800, source voltage, 5.30 kV; source current, 80 uA; capillary temperature, 350 °C; capillary voltage, −21 V (negative mode) 17 V (positive mode); tube lens offset, −50 V (negative mode) 30 V (positive mode); sheath gas flow (N2), 60 au), while UV spectra were collected at 254 nm. Xcalibur system manager data acquisition software was used for the interpretation of the data acquired. The solution of each compound was prepared in methanol at the concentration of 0.2 mg/mL, and the injection volume was 10 μL. 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 × 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$. All the azides were synthesized by diazotation−azidation protocol[7] of the corresponding amines and were stored at −20 °C. Compound **6** was synthesized as reported in literature.[20]

[2-Oxo-2-(3,4,5-trimethoxyphenyl)ethyl](diphenyl)2-pyridinylphosphonium bromide (4). To a cooled (0 °C) solution of the corresponding acetophenone **2** (2 g, 9.5 mmol, 1 equiv) in diethyl ether (90 mL), bromine (1.82 g, 1.2 equiv; 11.4 mmol), dissolved in diethyl ether (60 mL) was added dropwise. After 10 min, the reaction mixture was worked up, and the organic layer was washed with water (×1) and brine (×1). The organic layer was dried over sodium sulfate. Filtration and evaporation of the solvent gave a crude product that was used directly for the next step. The bromine derivative was dissolved in dry toluene (30 mL), and diphenyl-2-pyridyl-phosphine (2.49 g, 9.5 mmol) dissolved in dry toluene (25 mL) was added dropwise. The resulting solution was stirred at room temperature overnight. The precipitate was collected by filtration. After the precipitate was with toluene, it was dried under vacuum to afford **4** as a orange solid (3.96 g; 86%). mp: 201.1−201.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (d, J = 4.7 Hz, 1H), 8.30−8.21 (m, 2H), 8.01−7.50 (m, 11H), 7.46 (s, 2H), 6.46 (d, J = 12.6 Hz, 2H), 3.88 (s, 6H), 3.77 (s, 3H). MS (ESI): *m*/*z* 472 $(M)^+$.

2-[Diphenyl(2-pyridinyl)phosphoranylidene]-1-(3,4,5-trimethoxyphenyl)-1-ethanone (5). To the phosponium salt **4** (3.1 g; 6.5 mmol; 1 equiv) dissolved in CH_2Cl_2 (30 mL), $NaHCO_3$ (600 mg, 7.1 eq; 1.1 equiv.) dissolved in water (10 mL) was added. The resulting two-phase solution was vigorously stirred at room temperature for 1 h. Then the reaction was worked up by dilution with CH_2Cl_2, and the organic layer was washed with water (×2). The aqueous layer was further washed with CH_2Cl_2 (×1), and the combined organic extracts

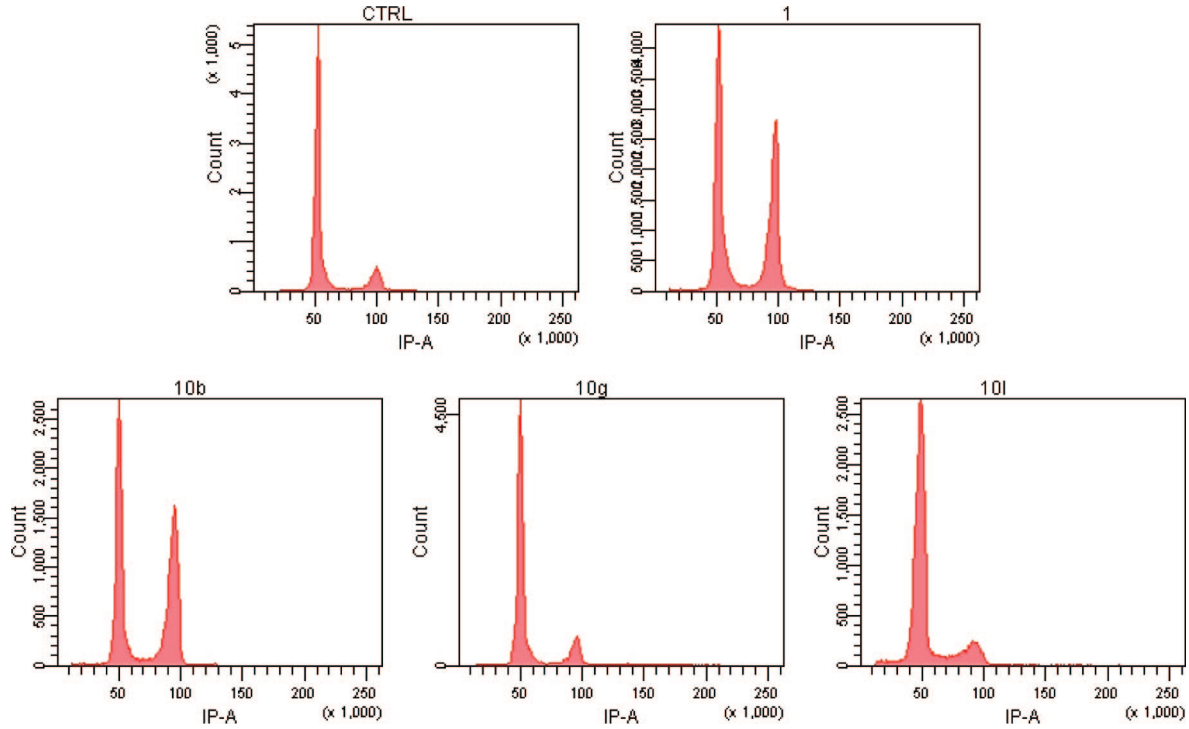


Figure 5. FACS analysis of the characterized purified products. Data is representative of at least 6 cytofluorimeter analysis in two experimental days.

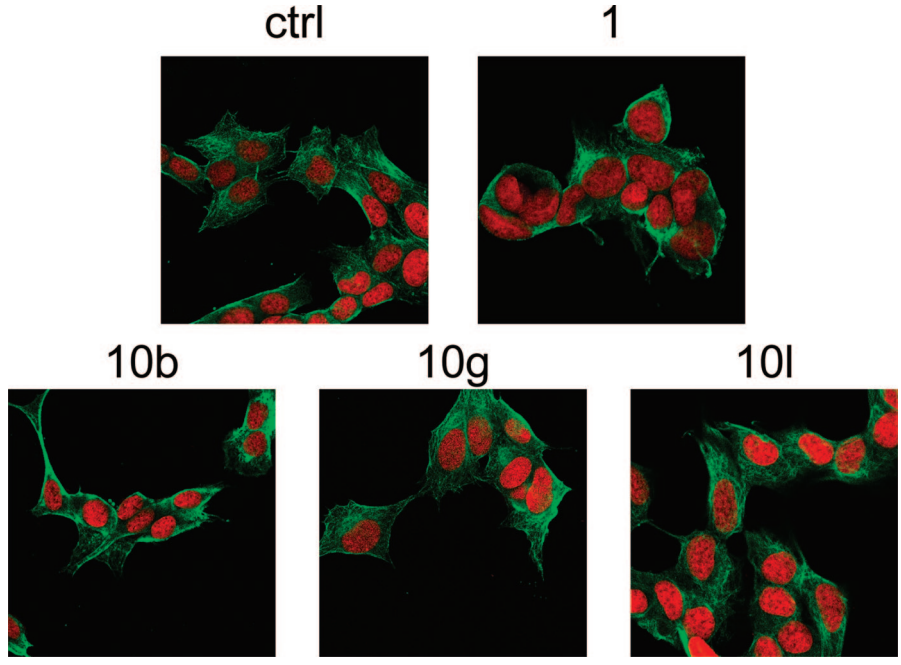


Figure 6. Confocal microscopy of cells treated for 8 h with the indicated compounds at the IC_{50} values (see text). Cells were stained with an antitubulin antibody and nuclei were stained with DRAQ5. Pictures are representative of at least 3 separate experiments.

were washed with brine (×1). After it was dried over sodium sulfate and the solvent was evaporated, crude **5** was obtained as a brownish solid (2.17 g, 85%) and was enough pure to be used directly for the following step. mp: 171.3−172.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, J = 4.6 Hz, 1H), 8.23 (t, J = 6.9 Hz, 1H), 7.90−7.70 (m, 5H), 7.60 - 7.35 (m, 7H), 4.36 (d, J = 24.2 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 184.4 (d, J = 2.3 Hz), 152.7, 151.8 (d, J = 123.2 Hz), 150.3 (d, J = 18.4 Hz), 139.5, 136.6 (d, J = 8.6 Hz), 136.5 (d, J = 8.6 Hz), 133.3 (d, J = 9.8 Hz), 132.1 (d, J = 2.3 Hz), 130.5 (d, J = 24.2 Hz), 128.8 (d, J = 12.1 Hz), 126.4 (d, J = 91.5 Hz), 125.4 (d, J = 2.8 Hz), 104.2, 60.9, 56.3, 49.5 (d, J = 110.3 Hz). MS (ESI): m/z 472 $(M + H)^+$.

{2-[3-(Benzyloxy)-4-methoxyphenyl]-2-oxoethyl}(diphenyl)3-pyridinylphosphonium Bromide (8). To a cooled (0 °C) solution of the corresponding acetophenone **6** (5.0 g, 20.5 mmol, 1 equiv) in ethanol (50 mL), bromine (3,27 g, 1 equiv.; 20.5 mmol), dissolved in ethanol (50 mL), was added dropwise. After 15 min, the off-white precipitate was collected by filtration, and the crude product (5.25 g) was useddirectly for the next step. The bromine derivative was

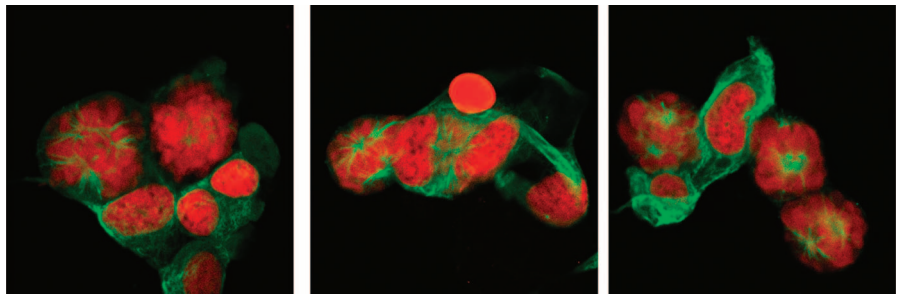


Figure 7. Atypical appearance of cells treated with **10G** for 16 h. Approximately 30% of cells appeared with morphologies similar to those depicted above (multinucleated and with aberrant mitotic spindles). Cells were stained with an antitubulin antibody and with nuclei were stained with DRAQ5. Pictures are representative of atypical cells from all experiments performed ($n = 3$). This morphology was observable, albeit to a smaller extent, in cells treated with **10L** and was not observable in cells treated with **1** or **10B**.

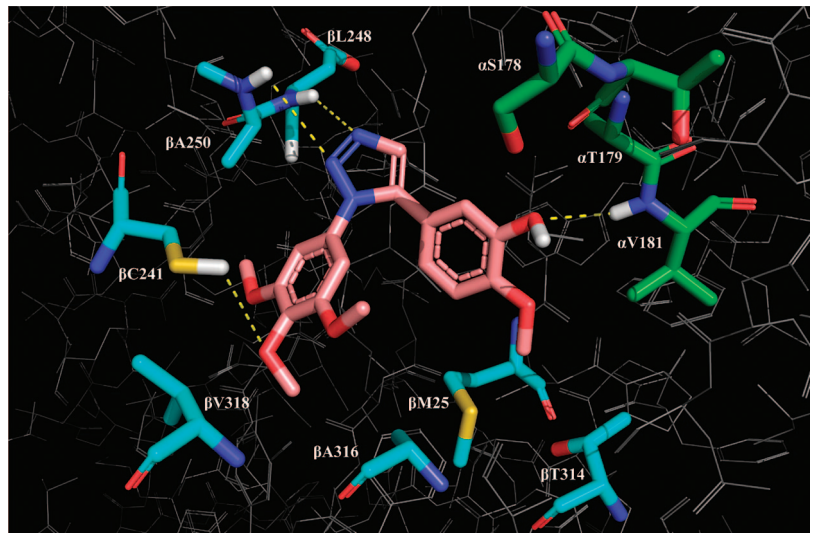


Figure 8. Structure of **10B** docked into the colchicines binding site of tubulin.

dissolved in dry toluene (50 mL), and diphenyl-2-pyridyl-phosphine (4.26 g, 1 equiv., 16.2 mmol), dissolved in dry toluene (30 mL), was added dropwise. The resulting solution was stirred at room temperature overnight. The precipitate was collected by filtration. After the precipitate was washed with toluene, it was dried under vacuum to afford **8** as an off-white solid (9.6 g; 90%). mp: 91.8−93.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, $J = 3.8$ Hz, 1H), 8.39 (br t $J = 6.6$ Hz, 1H), 8.25 (dd, $J = 8.5/1.9$ Hz, 1H), 8.05−7.98 (m, 4H), 7.80−7.47 (m, 10H), 7.35−7.10 (m, 4H), 6.99 (d, $J = 8.5$ Hz, 1H), 6.32 (d, $J = 12.3$ Hz, 2H), 5,24 (s, 2H), 3.91 (s, 3H). MS (ESI): m/z 518 $(M)^+$.

1-[3-(Benzyloxy)-4-methoxyphenyl]-2-[diphenyl(3-pyridinyl)phosphoranylidene]-1-ethanone (9). To the phosponium salt **8** (12.0 g; 23.2 mmol; 1 equiv) dissolved in CH_2Cl_2 (100 mL), $NaHCO_3$ (2.14 g, 1.1 equiv.; 25.5 mmol) dissolved in water (30 mL) was added. The resulting two-phase solution was vigorously stirred at room temperature for 30 min. Then the reaction was worked up by dilution with CH_2Cl_2, and the organic layer was washed with water (×2). The aqueous layer was further washed with CH_2Cl_2 (×1), and the combined organic extracts were washed with brine (×1). After the mixture was dried over sodium sulfate and the solvent was evaporated, crude **9** was obtained as a yellowish solid (7.14 g, 61%) and was pure enough to be used directly for the following step. mp: 178.5−179.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, $J = 4.6$ Hz, 1H), 8.22 (t, $J = 6.87$ Hz, 1H), 7.79−7.10 (m, 19H), 6.83 (d, $J = 8.5$ Hz, 1H), 5.13 (s, 2H), 4.30 (br s, 1H), 3.86 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 183.4, 161.0, 149.5 (d, $J = 120.5$ Hz), 150.3 (d, $J = 18.4$ Hz), 147.5, 137.4, 136.6 (d, $J = 10.3$ Hz), 133.3 (d, $J = 9.2$ Hz), 132.27 (2C), 130.5 (d, $J = 24.7$ Hz), 128.8 (d, $J = 12.1$ Hz), 128.5, 127.8, 127.7, 126.9 (d, $J = 90.8$ Hz), 125.4, 120.6, 112.5, 110.7, 71.0, 56.2, 48.8 (d, $J = 110.5$ Hz). MS (ESI): m/z 519 $(M + H)^+$.

General Procedure for the Parallel Synthesis of the Series 5 Compounds. In a cap-screw vial, a solution of the corresponding azide (1.1 equiv) and the corresponding α-keto phosphorus ylides (100 mg; 1 equiv) in dry toluene (2 mL) was heated at 90 °C for 3 days. The solvent was evaporated, and the residue was dissolved with THF (0.5 mL) and water (0.5 mL). Then, diphenyl-2-pyridyl-phosphine (0.5 equiv) was added, and the resulting solution was stirred at room temperature for 1 h. The reaction was diluted with EtOAc, washed with HCl 2 N (×6), and dried over sodium sulfate. Filtration and evaporation of the solvent yield the corresponding 1,5-diarylsubstituted 1,2,3-triazole.

General Procedure for the Parallel Synthesis of the Series 10 Compounds. In a cap-screw vial, a solution of the corresponding azide (1.1 equiv) and of the corresponding α-keto phosphorus ylides (100 mg; 1 equiv) in dry toluene (2 mL) was heated at 90 °C for 3 days. The solvent was evaporated, and the residue was dissolved with THF (0.5 mL) and water (0.5 mL). Then, diphenyl-2-pyridyl-phosphine

(0.5 equiv) was added, and the resulting solution was stirred at room temperature for 1 h. The reaction was diluted with EtOAc, washed with HCl (2 N; ×6) and dried over sodium sulfate. Filtration and evaporation of the solvent yield the protected 1,5-diarylsubstituted 1,2,3-triazole. The compounds were dissolved in MeOH, and palladium hydroxide on carbon was added. The round-bottomed flask was equipped with a balloon of hydrogen gas, and the mixture was stirred at room temperature. After 24 h, the reaction mixture was filtered through a pad of Celite. The filtrate was evaporated, and the residue was directly used for the biological tests.

1-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5A). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.38 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.62 (s, 6H). MS (ESI) m/z 342 $(M + H)^+$. IR (neat) 2939, 1585, 1514, 1230, 1126 cm^{-1}.

1,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 6.57 (s, 2H), 6.42 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70 (s, 6H), 3.66 (s, 3H). MS (ESI): m/z 402 $(M + H)^+$. IR (neat): 2937, 1596, 1505, 1463, 1417, 1229, 1122 cm^{-1}.

1-[4-(Trifluoromethoxy)Phenyl]-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 6.35 (s, 2H), 3.83 (s, 3H), 3.65 (s, 6H). MS (ESI): m/z 396 $(M + H)^+$. IR (neat): 2941, 1585, 1498, 1205, 1123 cm^{-1}.

1-(1,3-Benzodioxol-5-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5D). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 6.78 (br s, 3H), 6.37 (s, 2H), 5.97 (s, 2H), 3.78 (s, 3H), 3.65 (s, 6H). MS (ESI): m/z 356 $(M + H)^+$. IR (neat): 2930, 1590, 1500, 1454, 1417, 1229, 1125 cm^{-1}.

1-(4-Phenoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5E). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.36−7.29 (m, 4H), 7.13 (t, J = 7.9 Hz, 1H), 7.03−6.96 (m, 4H), 6.40 (s, 2H), 3.84 (s, 3H), 3.68 (s, 6H). MS (ESI): m/z 404 $(M + H)^+$. IR (neat): 2958, 1585, 1507, 1227 cm^{-1}.

1-(3,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5F). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 6.91 (s, 1H), 6.82 (br s, 2H), 6.38 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.63 (s, 6H). MS (ESI): m/z 372 $(M + H)^+$. IR (neat): 2836, 1585, 1515, 1463, 1234, 1123 cm^{-1}.

1-(3,5-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5G). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 6.47 (br s, 2H), 6.41 (s, 2H), 3.79 (s, 3H), 3.67 (s, 6H), 3.65 (s, 6H). MS (ESI): m/z 372 $(M + H)^+$. IR (neat): 1599, 1504, 1264, 1157, 1018 cm^{-1}.

1-(4-Methoxy-3-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 2.7 Hz, 1H), 7.81 (s, 1H), 7.52 (dd, J = 9.1/2.5 Hz, 1H), 7.13 (d, J = 9.1 Hz, 1H), 6.41 (s, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 3.71 (s, 6H). MS (ESI): m/z 387 $(M + H)^+$. IR (neat): 2939, 1585, 1536, 1498, 1349, 1126 cm^{-1}.

2-Methoxy-5-[5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenol (5I). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.07 (d, J = 2.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 8.2/2.2 Hz, 1H), 6.42 (s, 2H), 6.38 (br s, -OH), 3.91 (s, 3H), 3.84 (s, 3H), 3.68 (s, 6H). MS (ESI): m/z 358 $(M + H)^+$, 356 $(M - H)^-$. IR (neat): 3200, 2940, 1585, 1498, 1259, 1115 cm^{-1}.

1-(3-Fluoro-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5J). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.13 (dd, J = 8.8 /2.2 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.95 (br t, 1H), 6.36 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.65 (s, 6H). MS (ESI): m/z 360 $(M + H)^+$. IR (neat): 2998, 1584, 1518, 1275, 1120 cm^{-1}.

1-(2-Naphthyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5L). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.86 − 7.75 (m, 4H), 7.51−7.48 (br t, 2H), 7.34 (dd, J = 8.5/2.2 Hz, 1H), 6.39 (s, 2H), 3.78 (s, 3H), 3.51 (s, 6H). MS (ESI): m/z 362 $(M + H)^+$. IR (neat): 3005, 2995, 1583, 1496, 1460, 1275, 1125 cm^{-1}.

1-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5M). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.41 (m, 2H), 7.31 (m, 2H), 6.36 (s, 2H), 3.83 (s, 3H), 3.67 (s, 6H). MS (ESI): m/z 346 $(M + H)^+$. IR (neat): 2980, 1585, 1496, 1348, 1125 cm^{-1}.

1-Phenyl-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.44−7.32 (m, 5H), 6.36 (s, 2H), 3.81 (s, 3H), 3.62 (s, 6H). MS (ESI): m/z 312 $(M + H)^+$. IR (neat) 2995, 1580, 1493, 1120 cm^{-1}.

1-[3-Methoxy-5-(trifluoromethoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (5O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.19 (br s, 1H), 7.16 (br s, 1H), 7.10 (br s, 1H), 6.38 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.66 (s, 6H). MS (ESI): m/z 410 $(M + H)^+$. IR (neat): 2985, 1595, 1510, 1260, 1153 cm^{-1}.

2-Methoxy-5-[5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]aniline (5Hbis). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 6.77−6.75 (m, 2H), 6.63 (dd, J = 8.5/2.4 Hz, 1H), 6.44 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.68 (s, 6H). MS (ESI): m/z 357 $(M + H)^+$. IR (neat): 3354, 1619, 1586, 1517, 1497, 1233 1126 cm^{-1}.

2-Methoxy-5-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-5-yl]phenol (10A). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.28−7.24 (m, 2H), 6.92 (br d, 2H), 6.78 (br d, 2H), 6.70 (br *d*, J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H). MS (ESI): m/z 298 $(M + H)^+$, 296 $(M - H)^-$. IR (neat): 3141, 1578, 1516, 1499, 1258, 1018 cm^{-1}.

2-Methoxy-5-[1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl]phenol (10B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 6.87 (d, J = 2.2 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 8.5/2.2 Hz, 1H), 6.57 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.71 (s, 6H). MS (ESI): m/z 358 $(M + H)^+$, 356 $(M - H)^-$. IR (neat): 3230, 1597, 1507, 1463, 1415, 1275, 1126 cm^{-1}.

2-Methoxy-5-{1-[4-(trifluoromethoxy)phenyl]-1*H*-1,2,3-triazol-5-yl}phenol (10C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.82 (d + s overlapped 2H), 6.68 (dd, J = 8.2/ 2.2 Hz, 1H), 3.89 (s, 3H). MS (ESI): m/z 352 $(M + H)^+$, 350 $(M - H)^-$. IR (neat): 3150, 1615, 1597, 1454, 1275, 1166 cm^{-1}.

5-[1-(1,3-Benzodioxol-5-yl)-1*H*-1,2,3-triazol-5-yl]-2-methoxyphenol (10D). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 6.82−6.75 (m, 5H), 6.73 (dd, J = 8.2/1.9 Hz, 1H), 6.04

(s, 2H), 3.89 (s, 3H). MS (ESI): *m/z* 312 $(M + H)^+$, 310 $(M - H)^-$. IR (neat): 3270, 1581, 1503, 1452, 1232 cm^{-1}.

2-Methoxy-5-[1-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-5-yl]phenol (10E). ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.40−7.25 (m, 5H), 7.15 (br t, 1H), 7.06−6.99 (m, 4H), 6.82 (br s, 1H), 6.73 (dd, $J = 8.0/1.9$ Hz, 1H), 3.89 (s, 3H). MS (ESI): *m/z* 360 $(M + H)^+$, 358 $(M - H)^-$. IR (neat): 3211, 1585, 1507, 1227 cm^{-1}.

5-[1-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl]-2-methoxyphenol (10F). ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 6.92 (s, 1H), 6.87−6.76 (m, 4H), 6.68 (d, $J = 8.0$ Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H). MS (ESI): *m/z* 328 $(M + H)^+$, 326 $(M - H)^-$. IR (neat) 3240, 1560, 1510, 1460, 1233 cm^{-1}.

5-[1-(3,5-Dimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl]-2-methoxyphenol (10G). ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 6.84 (d, $J = 2.2$ Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 6.74 (dd, $J = 8.2/2.2$ Hz, 1H), 6.50 (br s, 3H), 3.89 (s, 3H), 3.72 (s, 6H). MS (ESI): *m/z* 328 $(M + H)^+$, 326 $(M - H)^-$. IR (neat): 3118, 1598, 1514, 1450, 1253, 1132 cm^{-1}.

5-[5-(3-Hydroxy-4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-2-methoxyphenol (10I). ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.22 (br s, 1H), 6.95 (br s, 1H), 6.89−6.68 (m, 4H), 3.91 (s, 3H), 3.86 (s, 3H). MS (ESI): *m/z* 314 $(M + H)^+$, 312 $(M - H)^-$. IR (neat): 3380, 1601, 1505, 1439, 1269, 1127 cm^{-1}.

5-[1-(3-Fluoro-4-methoxyphenyl)-1*H*-1,2,3-triazol-5-yl]-2-methoxyphenol (10J). ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.12 (m, 2H), 6.97 (br t, 1H), 6.79 (s + d overlapped, 2H), 6.68 (d, $J = 7.8$ Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H). MS (ESI): *m/z* 316 $(M + H)^+$, 314 $(M - H)^-$. IR (neat): 3200, 1518, 1501, 1277, 1264, 1016 cm^{-1}.

2-Methoxy-5-[1-(1-naphthyl)-1H-1,2,3-triazol-5-yl]phenol (10K). ^1H NMR (300 MHz, $CDCl_3$): δ 8.0−7.90 (m, 3H), 7.53−7.42 (m, 4H), 7.32 (d, $J = 8.5$ Hz, 1H), 6.73 (d, $J = 1.9$ Hz, 1H), 6.61−6.55 (m, 2H), 3.77 (s, 3H). MS (ESI): *m/z* 318 $(M + H)^+$, 316 $(M - H)^-$. IR (neat): 3076, 1581, 1506, 1444, 1275 cm^{-1}.

2-Methoxy-5-[1-(2-naphthyl)-1*H*-1,2,3-triazol-5-yl]phenol (10L). ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, $J = 1.9$ Hz, 1H), 7.89−7.84 (m, 3H), 7.57−7.50 (m, 2H), 7.36 (dd, $J = 8.8/1.9$ Hz, 1H), 6.85 (d, $J = 1.9$ Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), 6.70 (dd, $J = 8.2/1.9$ Hz, 1H), 5.64 (br s, −OH), 3.87 (s, 3H). MS (ESI): *m/z* 318 $(M + H)^+$, 316 $(M - H)^-$. IR (neat): 3213, 1597, 1502, 1443, 1247, 1144 cm^{-1}.

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Supporting Information Available. Materials and Methods for the biological section, molecular modeling procedure and binding mode of colchicines, combretastatin A-4, **10A**, **10F**, **10G**, **10H**, **10I**, **10J**, and **10L**, and HPLC data for all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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