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Synthesis and evaluation of diaryl sulfides and diaryl selenide compounds for antitubulin and cytotoxic activity

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ABSTRACT

We have devised a procedure for the synthesis of analogs of combretastatin A-4 (CA-4) containing sulfur and selenium atoms as spacer groups between the aromatic rings. CA-4 is well known for its potent activity as an inhibitor of tubulin polymerization, and its prodrugs combretastatin A-4 phosphate (CA-4P) and combretastatin A-1 phosphate (CA-1P) are being investigated as antitumor agents that cause tumor vascular collapse in addition to their activity as cytotoxic compounds. Here we report the preparation of two sulfur analogs and one selenium analog of CA-4. All synthesized compounds, as well as several synthetic intermediates, were evaluated for inhibition of tubulin polymerization and for cytotoxic activity in human cancer cells. Compounds **3** and **4** were active at nM concentration against MCF-7 breast cancer cells. As inhibitors of tubulin polymerization, both **3** and **4** were more active than CA-4 itself. In addition, **4** was the most active of these agents against 786, HT-29 and PC-3 cancer cells. Molecular modeling binding studies are also reported for compounds **1**, **3**, **4** and CA-4 to tubulin within the colchicine site.

An important chemotherapeutic target is the tubulin/microtubule system, since microtubules, the primary component of the mitotic spindle, are essential for cell replication. The tubulin/microtubule equilibrium is disrupted and fails to function in the presence of compounds that interact with either tubulin or microtubules, which are formed by the polymerization of α,β-tubulin heterodimers.[1]

The natural product combretastatin A-4 (CA-4; Fig. 1) was isolated from the bark of the African tree *Combretum caffrum* (Combretaceae). In spite of its low molar mass and structural simplicity, the compound is one of the most powerful inhibitors of tubulin polymerization. CA-4 binds to the colchicine site of tubulin,[2] and the compound is an exceptionally potent inhibitor of the binding of radiolabeled colchicine to tubulin. Its prodrug combretastatin A-4 phosphate (Zybrestatin™) and related compounds, such as combretastatin A-1 phosphate (OXi4503) and AVE8062A, are considerably more water soluble than the parent agents and are under clinical trials for the treatment of cancer. [3,4]

Extensive work has been dedicated to elucidate the structure–activity relationships (SAR) of CA-4 and its analogs.[5] Most substituent modifications of the trimethoxybenzene ring A result in large reductions in activity, while ring B is more tolerant of structural modifications, particularly at position C-3′ (Fig. 1).[6] Several studies have focused on obtaining analogs with different spacer groups between the aromatic rings of CA-4, replacing the double bond. Active analogs include compounds containing an ethane group,[7] ethane-1,2-dione,[8] a ketone known as phenstatin,[9] and α,β-unsaturated carbonyls.[10]

Studies carried out by Barbosa and coauthors resulted in the preparation of sulfide **1** (Fig. 1), sulfoxide and sulfone derivatives.[11]

Studies with tubulin were performed with these compounds and showed that sulfide **1** inhibited polymerization with an IC_{50} of 1.2 μM, while the oxidized derivatives were inactive. The activity of sulfide **1** is very similar to that of CA-4 (IC_{50} of 1.1 μM) and better than that of colchicine (IC_{50} of 3.2 μM).[11] In other work by our research group, we explored the effect of changing the attachment position of the sulfur atom to ring A, and we found that this modification led to a major loss in activity.[12]

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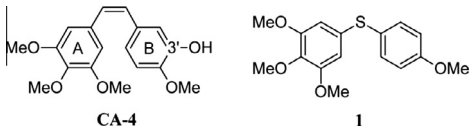
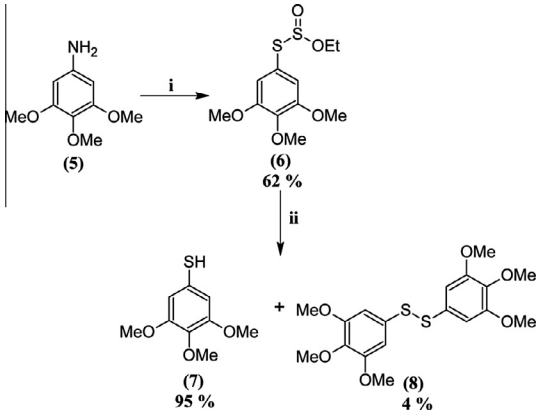


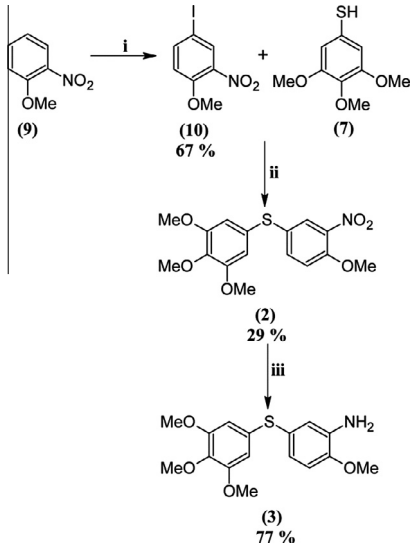
Figure 1. Structures of CA-4 and sulfide **1**.

Here we report the synthesis of additional CA-4 analogs containing sulfur (**2** and **3**) as a spacer group between the aromatic rings and an additional substituent on ring B. We also report the first example of selenium (**4**) as a spacer group. Other than the altered spacer group, compound **4** is structurally identical to compound **1**. The reason for preparing this organoselenium compound is the fact that such compounds can exhibit many biological activities, such as antioxidant, antitumor, antibacterial and antifungal properties.[13]

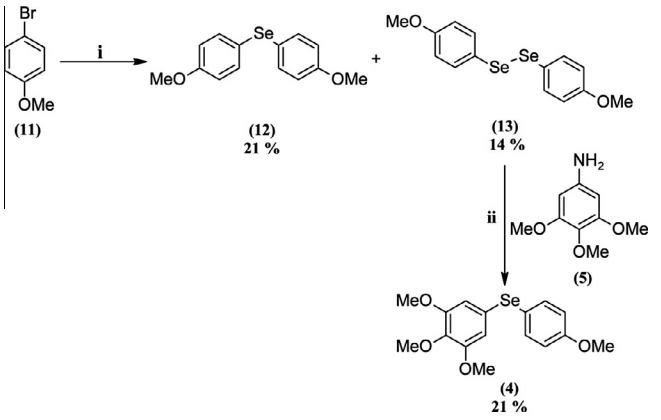
The synthesis of the sulfur analogs was started from amine **5** (commercial). Sulfide **7** was prepared by the Leuckart reaction,[14] which led to xanthate **6**, followed by basic hydrolysis with NaOH. This last step also generated a small amount of disulfide **8**[15] (Scheme 1).



Scheme 1. Synthesis of **7**. Reagents and conditions: (i) (1) $NaNO_2$, $HCl_{(concd)}$, H_2O, 0 °C, 10 min, (2) $EtOCS_2K$, 50–55 °C, 40 min; (ii) EtOH, NaOH, 65 °C, 1.5 h.



Scheme 2. Synthesis of **2** and **3**. Reagents and conditions: (i) NIS, $H_2SO_{4(concd)}$, 0 °C→rt, 20 min; (ii) neocuproine, CuI, *t*-NaOBu, toluene, Δ, N_2, 17 h; (iii) $SnCl_2$, HCl (36%), AcOH, rt, 2 h.



Scheme 3. Reagents and conditions: (i) (1) Mg, THF (dry), Δ, N_2, 1 h, (2) Se, Δ, N_2, 3 h; (ii) (1) $NaNO_2$, $H_2SO_{4(aq)}$ 6%, 0 °C, 1 h (diazonium salt formation), (2) $NaBH_4$, $THF_{(aq)}$, 0 °C, 10 min, (3) diazonium salt of amine **5**, 0 °C→rt, 17 h.

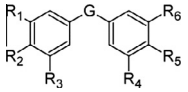
As shown in Scheme 2, compound **10** was prepared through the reaction of commercially available **9** with *N*-iodosuccinimide (NIS) in H_2SO_4. This reaction selectively yielded only one isomer.[16] The coupling of intermediates **7** (Scheme 1) and **10** was catalyzed by the neocuproine–Cu^+ complex[17] to obtain **2**. The preparation of amine **3** was achieved by reduction of **2** with $SnCl_2$ in an acid medium.[18]

In order to prepare target selenide **4** (Scheme 3), we started with the synthesis of **12** by forming the Grignard reagent from bromide **11** (commercial), followed by the addition of elemental selenium.[19] This procedure, as with the sulfur analogs (Scheme 1), resulted in the formation of diaryl selenide **12** and the diaryl diselenide **13**, except that in this case the proportion of the latter was greater. Compound **13** was then reduced with $NaBH_4$ to produce the required selenol nucleophile[20] to attack the diazonium salt produced by amine **5**[21] to yield desired final product **4**.

The effects of compounds **2**, **3**, **4**, **8**, **12** and **13** on the growth of four human tumor cell lines and on tubulin polymerization and the binding of [^{3}H]colchicine to tubulin are presented in Tables 1 and 2. Studies with CA-4 and compound **1** are also shown in Table 1 and with doxorubicin (DOX) in Table 2.

Among the sulfur analogs, the diaryl disulfide **8**, with two trimethoxybenzene rings, showed moderate activity as an inhibitor of tubulin polymerization but only minimal inhibition of colchicine binding to tubulin. In contrast, the diaryl sulfides **2**, and especially **3**, both, like CA-4, with a single *para*-methoxy group in ring B, along with a nitrogen-containing substituent at the *meta*-position in ring B (cf. the OH group in CA-4), were strong inhibitors of tubulin assembly. Compound **3** was also almost as potent an inhibitor of colchicine binding as CA-4, demonstrating that the *meta*-amino group is superior to the *meta*-nitro group in enhancing the ability of these sulfides to interact with tubulin. Based on our previous study with compound **1** (data shown in Table 1), the *meta*-amino group, but not the *meta*-nitro group, increases activity relative to the unsubstituted compound. We also note that *cis*-stilbene analogs of CA-4 with *meta*-substituents in ring B replacing the hydroxyl group in the natural product had relative activities similar to those we found with the sulfides.[22] Thus, in the study by Pinney et al., CA-4 inhibited tubulinassembly with an IC_{50} of 1.2 μM, while the nitro and amino analogs had IC_{50}'s of 1.8 and 1.2 μM, respectively, with the amino but not the nitro analog equivalent to CA-4 as an inhibitor of colchicine binding.[22] With respect to the selenium derivatives, compound **12** showed the least antitubulin activity. In contrast, diaryldiselenide **13** strongly inhibited tubulin assembly, but it was less active an inhibitor of colchicine binding, perhaps because of the absence of a trimethoxy system in ring A

Table 1
Compound effects on tubulin polymerization, the binding of colchicine to tubulin, and the growth of MCF-7 human breast cancer cells

	Tubulin polymerization IC_{50}[c] (μM) ± SD	Inhibition of binding of colchicine, % inhibition ± SD		MCF-7 IC_{50}[d] (μM) ± SD
		5 μM inhibitor	1 μM inhibitor	
(CA-4)[a] 5-G = *cis*-CH=CH, $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = H$, $R_6 = OH$	1.1 ± 0.1	99 ± 0.06	90 ± 1	0.006 ± 0.003
(**1**)[b] 5-G = S, $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = R_6 = H$	1.2 ± 0.1	89 ± 1	56 ± 7	0.016 ± 0.005
(**2**) 5-G = S, $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = H$, $R_6 = NO_2$	2.8 ± 0.3	58 ± 0.9	-	1 ± 0[e]
(**3**) 5-G = S, $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = H$, $R_6 = NH_2$	0.74 ± 0.04	95 ± 0.1	74 ± 0.5	0.008 ± 0.003
(**4**) 5-G = Se, $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = R_6 = H$	0.62 ± 0.08	94 ± 1	74 ± 1	0.010 ± 0[e]
(**8**) 5-G = S_2, R_1-$R_6 = OCH_3$	5.4 ± 0.4	9.0 ± 1	—	>10
(**12**) 5-G = Se, $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = R_5 = OCH_3$	>20	—	—	>10
(**13**) 5-G = Se_2, $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = R_5 = OCH_3$	1.7 ± 0.06	34 ± 0.2	—	>10

[a] IC_{50} for inhibition of tubulin assembly and % inhibition of binding of colchicine for CA-4 were obtained contemporaneously with the values for all compounds except **1**.
[b] IC_{50} for inhibition of tubulin assembly and % inhibition of colchicine binding as reported in the literature.[11]
[c] IC_{50} is the concentration inhibiting the extent of tubulin polymerization by 50% after 20 min at 30 °C.
[d] IC_{50} is the concentration inhibiting 50% of cell growth after a 96 h incubation at 37 °C.
[e] SD = 0 indicates that there were obtained the same value was obtained in all experiments.

Table 2
Cytotoxic activity against human cancer cell lines 786, HT-29 and PC-3

Compounds	IC_{50}[a] (μM ± SD)		
	786 (kidney)	HT-29 (colon)	PC-3 (prostate)
2	1.71 ± 0.29	0.63 ± 0.02	0.20 ± 0.26
3	1.24 ± 0.16	1.31 ± 0.33	0.53 ± 0.13
4	0.68 ± 0.09	0.28 ± 0.08	0.08 ± 0.003
8	111.67 ± 26.30	76.54 ± 19.05	6.75 ± 0.89
12	N.T.[b]	210.42 ± 36.21	8.80 ± 1.70
13	20.69 ± 4.49	59.51 ± 10.29	1.99 ± 0.37
CA-4	5.0 ± 0.2	1.0 ± 0.1	1.0 ± 0[d]
DOX[c]	0.33 ± 0.03	0.44 ± 0.03	0.63 ± 0.15

[a] IC_{50} is the concentration inhibiting 50% of cell growth after a 48 h incubation at 37 °C.
[b] N.T.—not tested.
[c] Doxorubicin—positive control, as a known cytotoxic agent.
[d] SD = 0 indicates that there were obtained the same value was obtained in all experiments.

and the absence of a hydrophilic group at position C3′ in ring B.[23] The selenium derivative **4**, a close analog of the active sulfide **1**, was the most active of all tested samples including CA-4 as an inhibitor of tubulin polymerization. As an inhibitor of colchicine binding, however, compound **4** was slightly less active than CA-4 and equivalent to compound **3**.

To evaluate atomic-level contacts between the inhibitors and colchicine binding site residues that might rationalize differences in the potencies of **1**, **3**, **4**, and CA-4, molecular docking studies were performed. To initiate the studies, a previously reported pharmacophore for colchicine site inhibitors[24] was used to identify key features shared by **1**, **3**, **4**, CA-4, and colchicine (Fig. 2).

Following, common pharmacophore features were used to orient the compounds in the colchicine receptor pocket using their best pharmacophoric alignments with the conformation of colchicine as it co-crystallizes with tubulin (PDB code 1SAO[25]). Next, **1**, **3**, **4**, and CA-4 were energy refined in the colchicine binding site using constrained minimizations. The refined compound binding modes were then evaluated using the program Hydropathic INTeractions (HINT),[24] which scores both favorable and unfavorable intermolecular, atom–atom contacts. The results from the HINT analyses were used to guide manual adjustment (rotational, torsional, and translational) to provide hydropathically feasible binding models for all compounds. Figure 3 shows the superimposed binding modes of **1**, **3**, and **4**, and CA-4; colchicine is also included for reference purposes. In general, colchicine site binding for all compounds is dominated by interactions with hydrophobic residues in the receptor pocket. The hydrophobic collapse that occurs between the small molecules and the receptor is then reinforced by the formation of key hydrogen bonds. Overall, compounds **1**, **3**, **4**, and CA-4 occupy steric space in the receptor that is similar to that of colchicine (i.e., as it binds in co-crystal 1SA0). Specifically: (**1**) all of the compounds' trimethoxphenyl (i.e., A ring) components and substituents are located in close proximity, with the oxygen atoms of the *para*-methoxy substituents of **1**, **3**, **4**, CA-4, and colchicine all engaging in a hydrogen bond with the side chain thiol of receptor site residue β-Cys 241 (Fig. 3), and (**2**) all of the compounds engage in a hydrogen bond with the backbone amide nitrogen of receptor site residue α-Val 181. For **1**, **3**, and **4**, the hydrogen bond is mediated by the oxygen atom of the B ring *para*-methoxy substituent, for CA-4 it is mediated by the oxygen atom of the ring B *meta*-hydroxyl substituent, and for colchicine it is mediated by the ring B carbonyl oxygen (Fig. 3).

However, there are subtle differences in the compounds binding modes that provide hypotheses for rationalizing the % colchicine binding site inhibition data shown in Table 1. For example, compared with the binding modes of **3** and CA-4, the binding mode of **1** lacks a hydrogen bond donor substituent required to mimic the hydrogen bond formed between the ring B *meta*-aniline and -hydroxyl subsitutents of **3** and CA-4, respectively, and the backbone amide carbonyl of receptor site residue α-Thr179. Hence, as shown in Table 1, **1** would be expected to be a weaker colchicine binding site inhibitor than **3** and CA-4. In another example, a structure-based hypothesis rationalizing the lower potency of

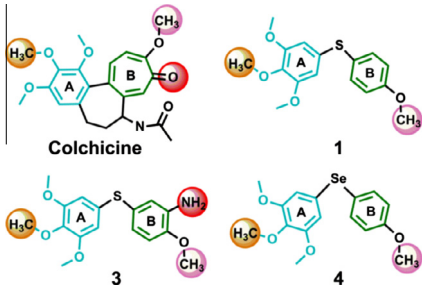


Figure 2. Pharmacophore requirements for colchicine site binding.[24] Orange and pink spheres indicate hydrophobic points; red spheres indicate polar points. Cyan and green indicate key hydrophobic-aromatic components that form the core scaffold for colchicine site binding. Aromatic rings are labeled A and B to provide points of reference to the structures in Table 1 and Figure 1.

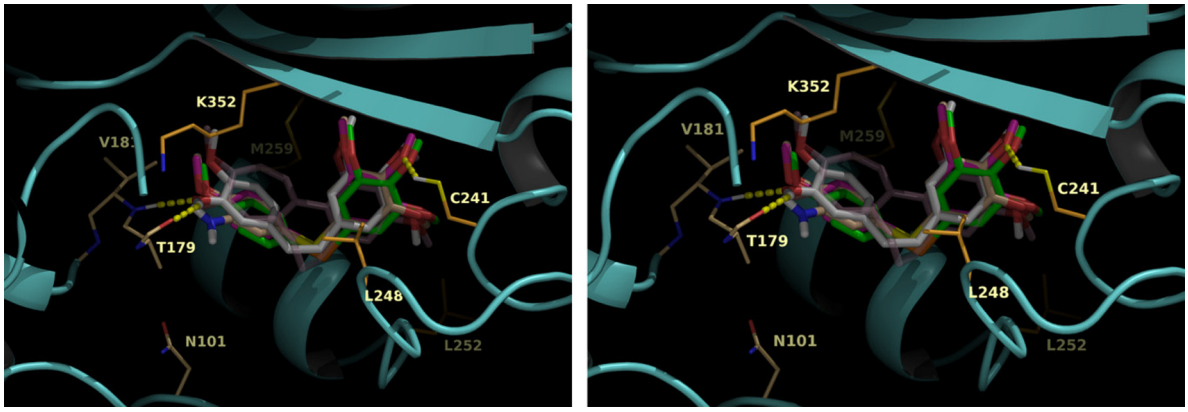


Figure 3. Docked models of **1**, **3**, **4**, and CA-4 in the colchicine binding site. The figure is designed to be looked at using the cross-eye stereo technique. A larger 2D image is provided in the Supplementary data. Tubulin is rendered in light blue ribbon, with select amino acid side-chains rendered in thin stick. The carbon atoms of α-subunit residues are tan; β-subunit carbons are orange. Compounds **1**, **3**, **4**, CA-4, and colchicine are depicted in thicker stick ,with carbons colored magenta, wheat, green, white, and light pink (semi-transparent), respectively. Hydrogen bonds are shown in yellow dashed lines.

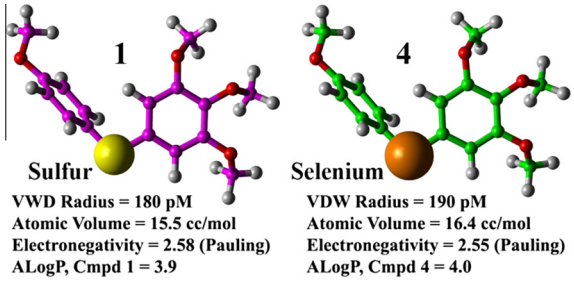


Figure 4. Comparison of physiochemical properties of the sulfur atom in compound **1** and the selenium atom in compound **4**,[26] and *A*log*P* values for the two compounds using the Ghose and Crippen method.[27] Compound **1** carbons are magenta; compound **4** carbons are green. The sulfur and selenium atoms of **1** and **4** are shown in CPK to punctuate the difference in size. VWD = van der Waals.

compound **1** versus compound **4** is based on differences in the angle and hydrophobicity of a thioether verses a selenoether (Fig. 4). Specifically, the angle of the thioether linking rings A and B in **1** is 104.35°, while the angle of the corresponding selenoether of **4** is 101.19°. The sharper angle of the selenoether allows for 'colchicine-like' depth of binding in the receptor site (Fig. 3), where the larger atomic size, volume, and increased hydrophobic character (i.e., lower electronegativity and more diffuse electron cloud) of the selenium atom (vs a sulfur atom) (Fig. 4), results in increased receptor occupancy versus compound **1**. Interestingly, the colchicine-like depth of binding observed for compound **4** forms the basis for rationalizing why it is equipotent to **3** with respect to colchicine binding site inhibition. In particular, while the aniline nitrogen of **3** can form an additional hydrogen bond with the backbone amide carbonyl of residue α-Thr179, it, like **1**, adopts a shallower binding conformation than **4** due to its thioether linker (Fig. 3). The shallower binding mode is similar to that of CA-4 (Fig. 3). Therefore, it is hypothesized that, although **4** engages in one less hydrogen bond than **3**, it is equipotent to **3** due to enhanced steric and hydrophobic occupancy of the receptor.

The new compounds were compared with CA-4 as cytotoxic agents in MCF-7 human breast cancer cells (Table 1). Somewhat surprisingly, compounds **2**, **8**, **12** and **13** were inactive. In contrast, the sulfide amino analog **3** and the diaryl selenide **4** had activity comparable to that of CA-4 and the activity we reported previously for compound **1**.[11] Using different cell lines, Pinney et al. found that the CA-4 analog with the *meta*-amino substituent was about 100-fold more cytotoxic than the CA-4 analog with the *meta*-nitro substituent.[22]

The analysis with three other human cancer cell lines (Table 2) was done in comparison with doxorubicin (DOX) and CA-4. The diaryl selinide **4** was the most active among the new compounds against the three lines, and sulfides **2** and **3** were almost equally active. Isosteric replacement of sulfur by selenium has been reported to potentialize analogs since selenium compounds can induce apoptosis of tumor cells.[28] This selective activity may be associated with the selenium acting as redox catalyst center, modulating the intracellular redox balance.[29] All three compounds were more active than DOX against at least one of the cell lines. Compounds **8**, **12** and **13** were significantly less active than the other compounds tested in these studies.

In comparison with our previously described compound **1**,[11] we found that the addition of a *meta*-amino group in the B ring enhanced activity, and, again in comparison with **1**, superior activity was obtained when a selenium atom replaced the sulfur atom as the bridge between the two aryl rings. Molecular modeling studiesprovided structure-based hypotheses rationalizing the improved potencies of **3** and **4** versus **1**. Specifically, the models indicated that the increased potency observed when the sulfur atom bridge of **1** was replaced by a selenium atom (i.e., **4**) resulted from both a deeper, more 'colchicine-like,' binding conformation and increased compound hydrophobicity. Moreover, for **3**, colchicine site inhibition was improved by the incorporation of a *meta*-position aniline moiety on ring B because it engages in a hydrogen bond with the backbone amide carbonyl of receptor site residue α-Thr179. Based on this information, it would be interesting to generate a derivative of **3** possessing a selenium bridge. Within the limits of the compounds synthesized and examined, two sulfur or two selenium atoms as the spacer group yielded agents with antitubulin activity but not with significant cytotoxic activity. Again, within the limits of the compounds synthesized, we found that a trimethoxybenzene ring was desirable for ring A, while fewer substituents were desirable for ring B for maximal antitubulin and cytotoxic activities. Compounds **3** and **4**, based on their excellent biological properties, merit further consideration as potential anticancer drugs.

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Supplementary data

Supplementary data (synthetic procedures and analytical/spectral data for the synthesized, procedures for the cytotoxicity and tubulin assays, and molecular modeling methods) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.06.009.

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