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# Synthesis of Antimitotic Polyalkoxyphenyl Derivatives of Combretastatin Using Plant Allylpolyalkoxybenzenes[1]

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Combretastatins A-1, A-2, and A-4 are natural antimitotic compounds that interact with the colchicine binding site of tubulin. A significant effort has been dedicated to the discovery of their synthetic derivatives featuring improved safety−efficacy profiles. In searching for a reliable natural source of building blocks for the synthesis of novel combretastatin analogues, the Apiaceae family of plants including dill and parsley species were of particular interst since they produce diverse allylpolyalkoxybenzenes. These starting materials were converted initially to isoapiol (**2a**), isodillapiol (**2b**), isoallyltetramethoxybenzene (**2c**), and isomyristicin (**2d**). Compounds **2a**−**d** were used to access the corresponding aldehydes (**3a**−**d**). The sequence included a key ozonolysis step conducted in a $CHCl_3$−$CH_3OH$−pyridine system at low temperature (−15 to 0 °C) with controlled addition of $O_3$. This procedure worked well on a preparative scale (ca. 100 g). Subsequent synthetic steps included either Wittig reaction of the resulting aldehydes or their conversion to carboxylic acid intermediates to yield a series of novel polyalkoxyaryl derivatives of combretastatins including both olefinic and the respective *ortho*-substituted five-membered aza-heterocyclic analogues. Compounds **5*Z***, **6*Z***, **7*Z***, **8*Z***, **9*Z***, **10*Z***, and **11*Z*** exhibited high antiproliferative effects in a sea urchin embryo assay.

Combretastatins A-1, A-2, and A-4 (Figure 1; CA1, CA2, CA4) are natural antimitotic compounds isolated initially from the bark of *Combretum caffrum* Kuntze (Combretaceae) in 1982.[2] These molecules are tubulin polymerization inhibitors that interact at the colchicine binding site.[3,4] The phosphorylated prodrugs CA4 disodium phosphate (CA4P, Zybrestat) and combretastatin A-1 phosphate (Oxi4503) are currently undergoing clinical evaluation as antitumor vascular targeting agents.[5,6] However, after CA4P administration, side effects have been observed, particularly regarding the cardiovascular system.[7] A significant effort has been dedicated to the discovery of synthetic combretastatins featuring potencies similar to the parent molecules but with better safety−efficacy profiles.[8,9] Combretastatin analogues display homology with the A and C rings of colchicine and are generally described as a tilted biaryl system connected by a hydrocarbon linker (bridge) of variable length (i.e., the A and B rings of combretastatins, Figure 1). The bridge furnishes a *cis*-configuration of the biaryl template necessary for efficient interaction of a molecule with the colchicine binding site of tubulin.[10,11] Notably, five-membered heterocycles were reported to provide a nonisomerizable and metabolically stable isosteric replacement for the *cis*-styrene. In particular, 1,2-substituted isoxazolines, oxadiazolines, and isoxazole derivatives (**I**) were reported to be more active than the respective 3,5-substituted analogues (**II**) (Figure 1).[12,13]

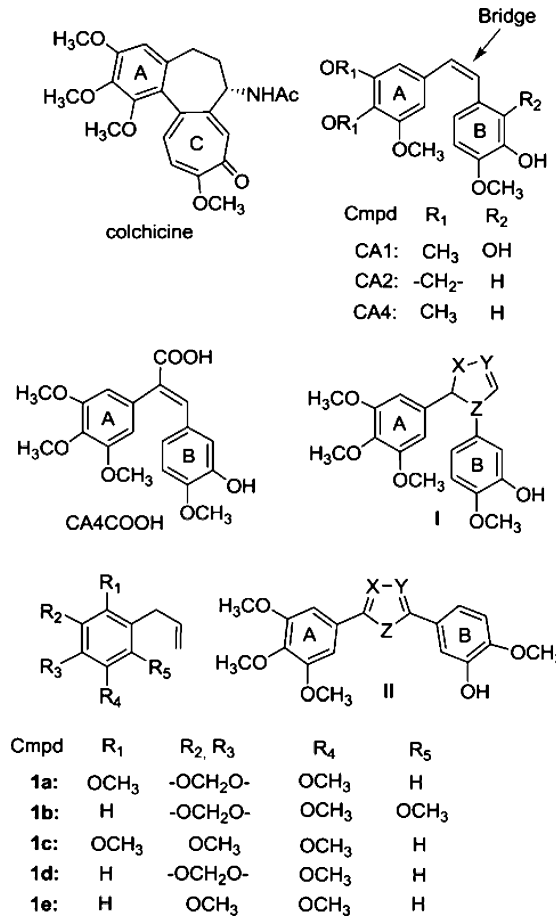


**Figure 1**

Examples of synthetic modifications of ring B with diverse pharmacophores (e.g., OH, $NH_2$, F) are quite abundant in the literature.[8,9] At the same time, structure−activity relationship (SAR) studies of substituents on ring A have been conducted to a lesser extent, although several resultant derivatives were reported to be potent tubulin binders. This is presumably due to the lack of the necessary building blocks substituted with more than three alkoxy groups. In a representative example, a CA4 analogue modified with the *ortho*-$NH_2$ group in ring A exhibited a comparable activity to the parent molecule.[14] It was assumed that similar modification of ring A with an additional $OCH_3$ functionality could yield potent antimitotic agents. Moreover, the tetraalkoxybenzene pharmacophore is featured in several natural products with reported antiproliferative activity, including Cactaceae tetrahydroisoquinolines[15] and flavonoids and isoflavonoids.[16]

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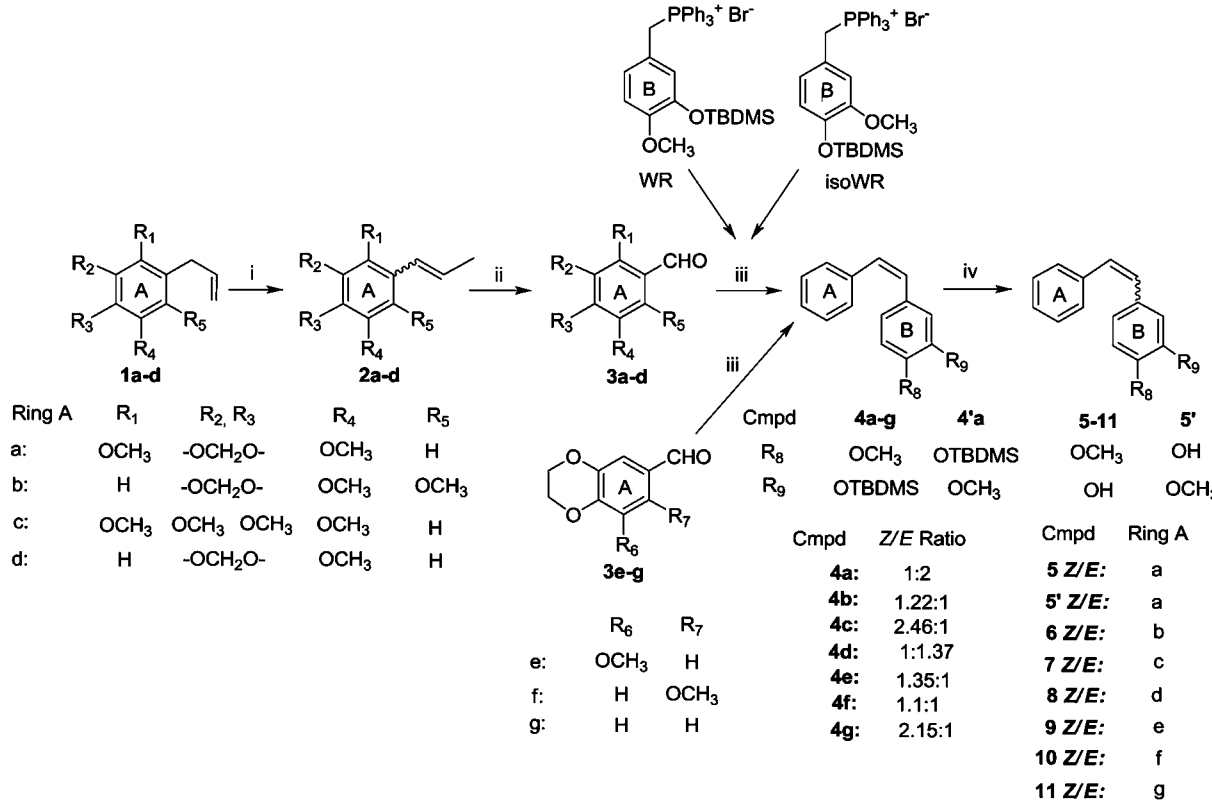
**Scheme 1.** Synthesis of Combretastatin Analogues from Allylpolyalkoxybenzenes[a]




[a] Reagents and conditions: (i) KOH, 100 °C, 40 min; (ii) $O_3$, $CHCl_3$−MeOH−pyridine (80:20:3 v/v), −15 °C, 1−2 h; (iii) *n*-BuLi, rt, 10 h; (iv) TBAF·$3H_2O$, THF, rt, 1 h. WR = Wittig reagent.

In searching for a reliable natural source of building blocks for combretastatin analogues, the Apiaceae family of plants became of interest. These species have been reported to contain significant amounts of pharmacologically active allyl polyalkoxybenzenes, namely, apiol (**1a**), dillapiol (**1b**), allyltetramethoxybenzene (**1c**), myristicin (**1d**), and elemicin (**1e**) (Figure 1).[17] The distribution of allylalkoxybenzenes varies greatly between species, plant organs, and geographic regions of collection.[18]

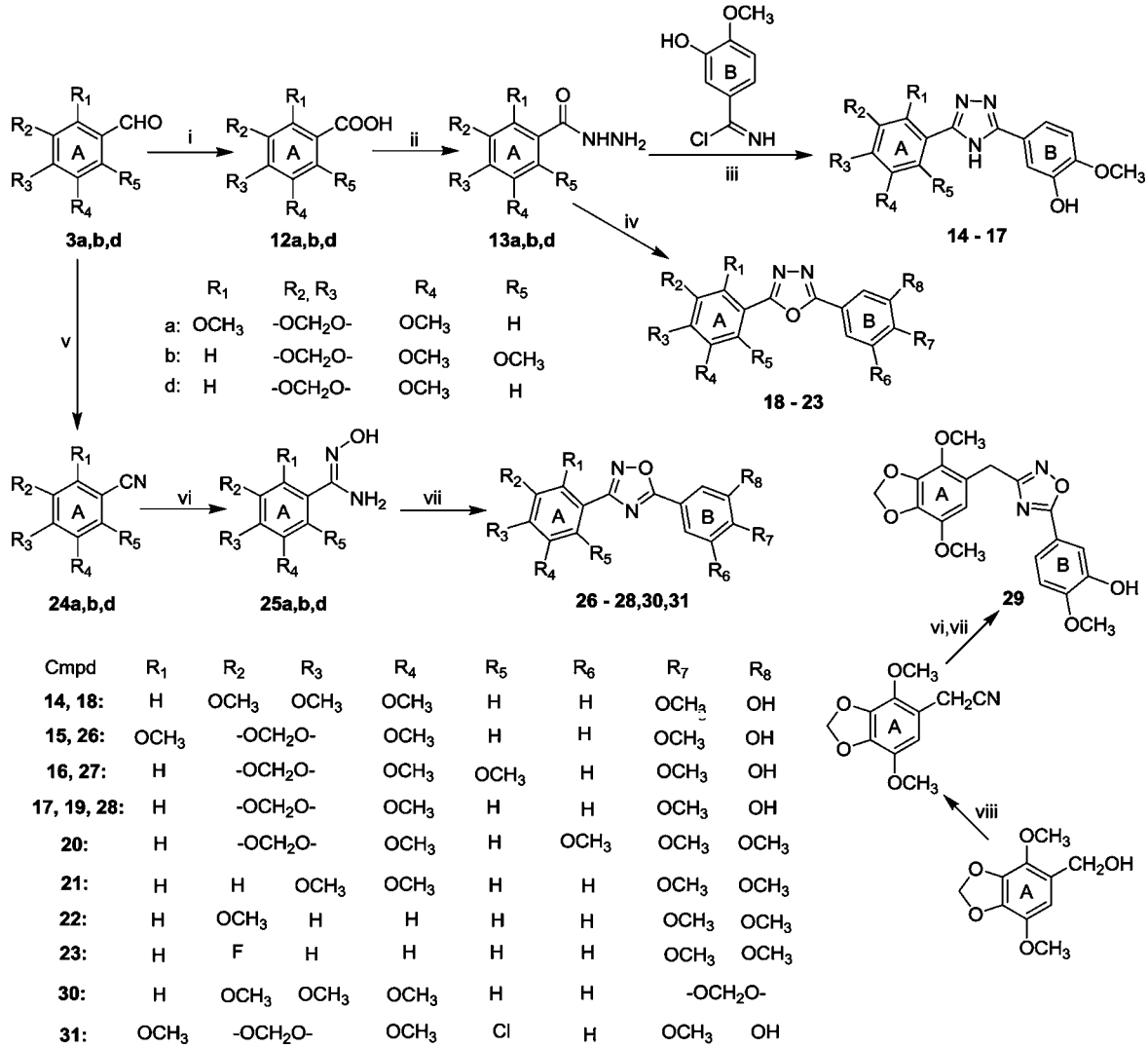
It was discovered that seeds of parsley, *Petroselinum sativum* Hoffm., cultivated in Russia, and dill, *Anethum graveolens* L., grown in India, are both versatile sources of allylpolyoxybenzenes that can be isolated by supercritical $CO_2$ extraction followed by high-efficiency large-scale distillation (up to 40 kg of allylbenzenes).[1a,19]

Multiple SAR studies of combretastatin analogues converged on the 3-hydroxy-4-methoxyphenyl group as the optimal substituent for the ring B (e.g., CA2, CA4, Figure 1).[8,9] This moiety was incorporated into test molecules while varying the nature of both ring A and the bridge. Compounds featuring a 1,3,4-oxadiazole linker displayed good steric overlap with the isovanillin moiety of combretastatins as reported earlier.[20] Introduction of 3,5-disubstituted 1,2,4-oxadiazole[21] and 2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoline[13] linkers into combretastatin derivatives yielded agents selective against specific cancer cell lines. Analogues featuring the triazole core moiety also displayed potent inhibition of tubulin polymerization and cytotoxicity against cancer cell lines including multi-drug-resistant cells.[22] Considering evidence from the earlier in-house studies as well as these literature data, a short synthetic protocol was developed to access a series of new polyalkoxyaryl derivatives of combretastatins. These molecules included the respective *ortho*-substituted five-membered analogues that feature the relevant spatial orientations of rings A and B. The starting materials used for the synthesis of combretastatin analogues were isoapiol (**2a**), isodillapiol (**2b**), isoallyltetramethoxybenzene (**2c**), and isomyristicin (**2d**) (Scheme 1). The resulting molecules were evaluated in vivo using a sea urchin embryo assay.[23]

## Results and Discussion

In the initial approach toward the respective aldehydes of apiol, dillapiol, tetramethoxybenzene, and myristicin (**3a**−**d**, Scheme 1), a published procedure describing ozonolysis of the respective styrene precursors in acetic acid was followed.[24] However, yields of the targeted molecules did not exceed 20−40% versus the reported 75−80% values. In order to improve both purity and yields of the targeted molecules **3a**−**d**, the literature protocol was amended. Accordingly, the reaction was conducted in the solvent system $CHCl_3$−$CH_3OH$−pyridine (4:1:1) at low temperatures (−15 to 0 °C). Addition of pyridine was found to be critical to the reaction outcome, and presumably this facilitates conversion of the intermediate molozonide into aldehydes **3a**−**d**. In addition, excess of $O_3$ led to significant side reactions. These included oxidation of the aldehyde group into the respective carboxylic acid, Bayer−Villiger rearrangement to the corresponding phenols, and their further oxidation to afford a biaryl system. In order to carefully control the amount of $O_3$, the ozonolysis step was conducted using a custom-designed apparatus (Science and Technology Park, St. Petersburg State Polytechnic University, Russia), equipped with an IR detector, allowing for the accurate allotment of the reagent. The targeted polyalkoxybenzoic acids (**12a**,**b**,**d**) were synthesized in high yields (80−90%) from the aldehyde precursors using the urea−hydrogen peroxide complex in water. Polyalkoxybenzonitriles **24a**,**b**,**d** were prepared in >90% yields via oxidation of aldehydes by molecular iodine (molar ratio 1:1.1) in aqueous $NH_4OH$, as described recently.[25] A combination of the specialized equipment and optimized protocols described above allowed for preparation of the targeted aldehydes in yields of 60−85% on a 100 g scale (Scheme 1, step ii).

**Scheme 2.** Synthesis of Heterocyclic Combretastatin Analogues from Allylpolyalkoxybenzenes[a]




[a] Reagents and conditions: (i) $CO(NH_2)_2 \cdot H_2O_2$, $CH_3OH$, reflux, 1.5 h; (ii) (1) $SOCl_2$, MeOH, reflux, 3 h; (2) 100% $NH_2NH_2 \cdot H_2O$, MeOH, reflux, 6 h; (iii) MeOH−MeONa, reflux, 10 h; (iv) ArCOCl, pyr, rt, 12 h; (v) $I_2$−$NH_4OH$(28%)−$H_2O$, rt, 16 h; (vi) $NH_2OH \cdot H_2O$, EtOH, reflux, 12 h; (vii) 3-OH, 4-$OCH_3$−$C_6H_3COOH$, CDI, DMF, 120−125 °C, 3 h; (viii) (1) $SOCl_2$, $C_6H_6$, 48−50 °C, 2.5 h; (2) KCN, $CH_3CN$, 50 °C, 10 h. Compounds **14**, **18**, **21**−**23**, and **29**−**31** were synthesized from the corresponding commercial aldehydes, acids, and nitriles using the same procedures.

Polymethoxy analogues of combretastatin were synthesized conveniently via Wittig reaction from aldehydes **3a**−**d** (Scheme 1), as reported for the synthesis of CA4.[26] *n*-BuLi was a base of choice to ensure the preferential formation of a *cis*-alkene at −78 °C.[27] Combined yields of the silylated derivatives **4a**−**g** and **4′a** obtained as a mixture of *Z-/E*-isomers were in the 70−85% range. These compounds were separated by column chromatography and subsequently converted to the targeted molecules **5*Z***, **5′*Z***, **6**−**11*Z*** and **5*E***, **5′*E***, **6**−**11*E*** (Scheme 2) with TBAF·$3H_2O$ in THF (85−90% yields). Notably, attempts to separate *E*- and *Z*-isomers as their respective phenols were unsuccessful under a variety of conditions. Chemical identity of the individual isomers was confirmed unequivocally by $^1$H NMR spectroscopy. Specifically, *J* values for each *Z/E* pair were ca. 12 and 16 Hz, respectively. A detailed analysis of the NMR data was conducted for the *Z-/E*-isomers of myristicin derivatives **4d** and **8** (Figures S1 and S2, Supporting Information). For the pair **4e** and **9**, chemical shifts for the *Z*- and *E*-isomers overlapped. In order to assign chemical structures to the individual compounds, we used the respective vicinal constants of a strong-field $^{13}$C satellite (Figure S3, Supporting Information).

The respective five-membered aza-heterocyclic analogues of combretastatins were conveniently prepared from the respective carboxylic acid (**12**) or nitrile (**24**) precursors (Scheme 2). Synthetic reactions leading to the 1,3,4-triazole (**14**−**17**)[28] and 1,3,4-oxadiazole (**18**−**23**)[29] derivatives involved preparation of the intermediate hydrazides (**13**). The respective 1,2,4-oxadiazole molecules **26**−**28**, **30**, and **31** were accessed from **24** via this modified procedure.[21] A similar heterocyclization step was followed in the synthesis of **29** (Scheme 2).

Synthetic derivatives of combretastatin synthesized as described above (Schemes 1 and 2) were further evaluated for their antiproliferative and tubulin-destabilizing activity using a phenotypic sea urchin embryo assay.[23] This in vivo assay allows for the robust and reliable identification of compounds targeting tubulin including their antiproliferative, antimitotic, and cytotoxic effects. It features (i) a fertilized egg test for antimitotic activity as displayed by cleavage alteration/arrest and (ii) behavioral monitoring of a free-swimming blastula treated immediately after hatching (9−12 h after fertilization). Lack of forward movement, settlement to the bottom of the culture vessel, and rapid spinning around the animal−vegetal axis of the embryo suggest a tubulin-destabilizing effect caused by a molecule.[30] The results are presented in Table 1 (see also Table S1, Supporting Information). Notably, the starting materials inclusive of apiol, dillapiol,[31] and myristicin on their own had no effect on sea urchin embryo cleavage up to 80−100 $\mu$M. Isoapiol

**Table 1.** Effects of Polyalkoxybenzene Analogues of Combretastatins on Sea Urchin Embryos

| | | | EC, $\mu$M[a] | | |
|---|---|---|---|---|---|
| compound | mp, °C | yield, % | cleavage alteration | cleavage arrest | embryo spinning |
| **2a** | 56.5[b] | | 2 | 8 | >10 |
| **2b** | 44[c] | | 20 | 80 | >100 |
| **2d** | 42.5[c] | | >5 | >5 | >5 |
| CA4P[d] | | | 0.005 | 0.01 | 1 |
| CA4[e] | 116[e] | | 0.002 | 0.01 | 0.05 |
| CA4COOH[g] | 237−239[g] | | >11.2 | >11.2 | >11.2 |
| **5*Z*** | 23−26 | 99 | 0.02 | 0.1 | 1 |
| **5*E*** | 140−145 | 63 | 0.5 | 4 | 5 |
| **5′*E*** | 145−147 | 66 | >4 | >4 | >5 |
| **6*Z*** | oil | 79 | 0.01 | 0.2 | 0.5 |
| **6*E*** | 88−90 | 96 | 0.1 | 4 | 5 |
| **7*Z*** | 80−82 | 98 | 0.02 | 0.1 | 1 |
| **7*E*** | 97−101 | 99 | 0.1 | 1 | 5 |
| **8*Z***, CA2 | oil | 92 | 0.002 | 0.01 | 0.05 |
| **8*E*** | 137−141 | 62 | 0.02 | 0.1 | 1 |
| **9*Z*** | 82−85 | 91 | 0.002 | 0.01 | 0.05 |
| **9*E*** | 96−98 | 98 | 0.02 | 0.1 | 2.00 |
| **10*Z*** | 78−83 | 99 | 0.02 | 0.2 | 1 |
| **10*E*** | 87−93 | 99 | 0.1 | 2 | >5 |
| **11*Z*** | oil | 80 | 0.02 | 0.5 | 1 |
| **11*E*** | 97−99 | 96 | 0.1 | 1 | 2 |
| **14** | 125 | 64 | 4 | >4 | >4 |
| **15** | 192−194 | 48 | >4 | >4 | >4 |
| **16** | 218−220 | 26 | 4 | >4 | >4 |
| **17** | 192−195 | 67 | 2 | >4 | >5 |
| **18** | 222−225 | 18 | >4 | >4 | >4 |
| **19** | 235−238 | 12 | 0.5 | 2 | >5 |
| **20** | 175−178 | 78 | 0.5 | 2 | >5 |
| **21**[h] | 176−178 | 76 | 0.5 | 10 | 5 |
| **22** | 155−157 | 41 | 0.05 | 4 | 2 |
| **23** | 153−155 | 40 | 1 | >4 | >5 |
| **26** | 164−168 | 18 | >4 | >4 | >4 |
| **27** | 168−172 | 29 | >4 | >4 | >4 |
| **28** | 180−183 | 32 | 4 | >4 | >4 |
| **29** | 168−170 | 12 | 4 | >4 | >4 |
| **30** | 178−180 | 39 | >4 | >4 | >4 |
| **31** | 143−146 | 18 | >4 | >4 | >5 |

[a] The sea urchin embryo assay was conducted as described in ref 23. Duplicate measurements showed no differences in effective threshold concentration (EC) values. [b] Ref 40. [c] Ref 39. [d] Obtained from OXiGENE. [e] Synthesized according to ref 26c; mp value ref 26c. [g] Synthesized from 3,4,5-trimethoxyphenylacetic acid and isovanillin according to ref 38. [h] Synthesized according to ref 49.

(**2a**) and isodillapiol (**2b**) displayed non-tubulin antiproliferative activity, whereas isomyristicin (**2c**) was inactive up to 5 $\mu$M. Tests of **2c** at higher concentrations were not successful due to its low solubility.

It has been reported that CA4 is considerably more cytotoxic and more effective as a tubulin polymerization inhibitor than CA2.[3,26c,32] According to the literature data, CA4 and CA4P showed similar cytotoxicity against a panel of cancer cell lines.[5,11] CA2 exhibited a more pronounced cytotoxic effect than its phosphorylated derivative CA2P.[33] In the sea urchin embryo assay, CA4P was somewhat less effective than CA4 (Table 1). This effect could be attributed to a time-dependent conversion of prodrug CA4P into active molecule CA4 mediated by intracellular phosphatases.

As evidenced from Table 1, compounds **5**−**9**, **10*Z***, **11**, **21**, and **22** displayed significant cleavage alteration, arrest, and embryo spinning, suggesting their tubulin-destabilizing activity. It was assumed that the less potent compounds **10*E***, **19**, and **20** were tubulin destabilizers as well, due to the tuberculose shape of the arrested eggs in the assay, although these molecules did not induce embryo spinning.[20,23,34] Agents **10*E***, **19**, and **20** were not tested at concentrations of >5 $\mu$M due to their limited solubility in DMSO and/or seawater.

Literature data suggest that the presence of three methoxy substituents in the A ring of combretastatins promotes the antitubulin activity of a compound, while a methylenedioxy group decreases such activity.[3,11,33] Compounds CA4 and CA2 (**8*Z***) showed similar effects in the sea urchin embryo test. Azole derivatives featuring a myristicin moiety (**17**, **19**, **20**, and **28**) were consistently more potent than other derivatives within the same structural class.

Numerous studies have confirmed that the *cis*-orientation of the aromatic substituents in combretastatin analogues is important for their antimitotic activity. The corresponding *trans*-isomers were reported to be significantly less potent or inactive.[3,8−11,32,35] In agreement with these observations, *cis*-stilbenes were consistently more active than their corresponding *trans*-isomers (Table 1; compare *Z-/E*-isomers in **5**−**11**). Notably, the *trans*-isomer of CA2 (**8*E***) still displayed good potency in the sea urchin embryo assay. This was comparable with the reported cytotoxicity of **8*E*** against murine leukemia cells and in vitro inhibition of tubulin polymerization.[3] For *Z*-isomers **5**−**8** the antimitotic activity decreased in the following order: CA4 = myristicin derivative CA2 (**8*Z***) > dillapiol derivative (**6*Z***) > apiol derivative (**5*Z***) = tetramethoxybenzene derivative (**7*Z***). Replacement of the methylenedioxy moiety in **8*Z*** with an ethylenedioxy group (**9*Z***) did not have any significant effect on the compound's potency. A comparative study of ethylenedioxy derivatives **9**−**11** further confirmed the importance of the 5-methoxy substituent in ring A, as both the respective 6-methoxy (**10*Z*** and **10*E***) and unsubstituted (**11*Z*** and **11*E***) analogues were less active. A substitution of the *p*-OMe group with a *p*-OH (Table 1, **5′*E***) moiety dramatically reduced the antiproliferative effect of the resulting molecule.[3,10] Nitro and amino derivatives of combretastatins endowed with the *p*-OH group completely lacked cytotoxicity and tubulin-depolymerizing activity.[36] In the series reported, a related replacement also yielded inactive molecule **5′*E*** (compared to **5*E***), the analogue of isocombretastatin A-4 derived from vanillin.[37] A carboxylic group at the olefin bridge was not tolerated (Figure 1, Table 1), as in CA4COOH, synthesized from 3,4,5-trimethoxyphenylacetic acid and isovanillin.[38] A similar observation was made for the CA4 analogue, whereby introduction of the COOH group into the bridge dramatically decreased the cytotoxicity of the resulting compound.[35]

A replacement of the olefin bridge with respective aromatic isosteres including the 1,3,4-triazoles **14**−**17**, 1,3,4-oxadiazoles **18**−**23**, and 1,2,4-oxadiazoles **26**−**31** caused a dramatic drop in antimitotic activity of the respective derivatives, with the 1,3,4-oxadiazole derivatives **19**−**22** being the only notable exceptions. These molecules did affect embryo cleavage alteration. However their effect on either cleavage arrest or spinning was modest at best. Agents **28** and **29** yielded cleavage alterations only at the maximal tested concentration (4 $\mu$M). Compound **27** applied after hatching at a concentration of 2−4 $\mu$M caused developmental abnormalities; specifically it inhibited growth of the skeletal spiculae. A CA2 analogue (**19**) and its respective derivative (**20**), featuring three methoxy groups in the ring B, were determined to be ca. 250 times less potent than CA2. Unfortunately, poor solubility of these compounds in DMSO and/or seawater precluded the accurate testing of their potency at higher concentrations. Molecule **23** showed weak antimitotic activity with an EC of 1 $\mu$M. Agents **15**, **18**, **26**, **27**, **30**, and **31** failed to alter embryo development at the maximal tested concentration (4 $\mu$M).

In conclusion, a variety of ring A moieties derived from apiol (**5**), dillapiol (**6**), tetramethoxybenzene (**7**), and myristicin (**8**), including the 5-methoxy-2,3-ethylenedioxy (**9**), 6-methoxy-2,3-ethylenedioxy (**10**), and 2,3-ethylenedioxy (**11**) analogues, yielded active compounds. A typical range of antiproliferative potencies for these molecules in the sea urchin embryo assay was 0.002−0.1 $\mu$M (Table 1; **5**−**11**). The difference in threshold concentrations varied from 5−25 times for cleavage alteration to 10−40 times for cleavage arrest. The most active compounds, **8*Z*** (CA2) and

**9*Z***, contained 5-methoxymethylenedioxy and 5-methoxyethylenedioxy substituents, respectively.

## Experimental Section

**General Experimental Procedures.** NMR spectra were collected on a Bruker DR-500 instrument [working frequencies of 500.13 MHz ($^1$H) and 75.47 ($^{13}$C)]. Mass spectra were obtained on a Finnigan MAT/INCOS 50 instrument (70 eV) using direct probe injection. Elemental analysis was accomplished with the automated Perkin-Elmer 2400 CHN microanalyzer. Ozonolysis was conducted using a custom-designed apparatus (Science and Technology Park, St. Petersburg State Polytechnic University, Russia) equipped with an IR detector of $O_3$ concentration (Japan) and an automated shut-down circuit. The device allowed for the controlled generation of ozone, with a maximal capacity of 10 g of $O_3$ per hour from $O_2$.

**Isolation of Plant Allylpolyalkoxybenzenes.** [1a] Liquid $CO_2$ extraction of parsley and dill seeds was carried out earlier by Company Karavan Ltd. (Krasnodar, Russia). Allylpolymethoxybenzenes **1a**−**d** with 98−99% purity were obtained by high-efficiency distillation using a pilot plant device at N.D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russia). The seed essential oils of parsley varieties cultivated in Russia contained 70−75% of **1a** (var. Sakharnaya), 21% of **1c** (var. Slavyanovskaya), and 40−46% of **1d** (var. Astra). Indian dill seeds were purchased from Vremya & Co. (St. Petersburg, Russia). The dill seed essential oil contained 30−33% of **1b**.

**General Procedure 1 for the Synthesis of Styrenes 2a−d.** These were prepared according to a published procedure.[1a,39,40] A mixture of an allylbenzene (**1a**−**d**) (0.25 mol), freshly recrystallized tetrabutylammonium bromide (2.5 g, 0.0075 mol), and powdered KOH (10 g, 0.18 mol) was heated for 40 min on a water bath. The reaction mixture was cooled to rt and extracted with $Et_2O$ (2 × 250 mL), and the combined organic extracts were washed with $H_2O$ (2 × 150 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The solid residue was recrystallized from petroleum ether to furnish 85−90% overall yields of targeted molecules as a mixture of *trans*- (ca. 80−85%) and *cis*-isomers (15−20%).

**General Procedure 2 for the Synthesis of Aldehydes 3a−d.** $O_3$ (6.24 g, 0.13 mol) was bubbled through a styrene (**2a**−**d**) (0.1 mol) in a mixture of $CHCl_3$−MeOH−pyridine (240:60:9 mL) for 1−2 h at −15 °C. The resulting solution was kept for an additional 3 h at 0 °C and concentrated in vacuo at 20 °C. The residue was treated with 150 mL of $H_2O$, and the pH of the slurry was adjusted to ca. 3 with concentrated HCl. The resulting solid was filtered, washed with 3 × 70 mL of $H_2O$, and dried to afford the desired aldehyde (60−80%).

**2,5-Dimethoxy-3,4-methylenedioxybenzaldehyde (Apiol Aldehyde, 3a).** Reaction of 175 g (787 mmol) of crude isoapiol **2a** furnished **3a** (111 g, 529 mmol, 67% yield) as an off-white solid: mp 102 °C (lit.[41] 102 °C); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 10.12 (1H, s, CHO), 7.00 (1H, s, H-6), 6.20 (2H, s, $OCH_2O$), 3.99 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$).

**2,3-Dimethoxy-4,5-methylenedioxybenzaldehyde (Dillapiol Aldehyde, 3b):** 16.8 g, 79.9 mmol, 80% yield; off-white solid; mp 75−77 °C (lit.[41] 75 °C); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 10.08 (1H, s, CHO), 6.85 (1H, s, H-6), 6.13 (2H, s, $OCH_2O$), 3.98 (3H, s, $OCH_3$), 3.87 (3H, s, $OCH_3$).

**2,3,4,5-Tetramethoxybenzaldehyde (3c):** 66.8 g, 295 mmol, 70% yield; off-white solid; bp 124−129/1−2 mmHg, mp 35−36 °C (EtOH) (lit.[42] 37−39 °C) (lit.[43] 115−125 °C/2 mmHg); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.19 (1H, s, CHO), 7.03 (1H, s, H-6), 3.90 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$), 3.81 (3H, s, $OCH_3$).

**3-Methoxy-4,5-methylenedioxybenzaldehyde (Myristicin Aldehyde) (3d):** 11 g, 61.06 mmol, 61% yield; off-white solid; mp 133−135 °C (lit.[39] 132.5 °C); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.78 (1H, s, CHO), 7.26 (1H, s, H-Ph), 7.05 (1H, s, H-Ph), 6.12 (2H, s, $OCH_2O$), 3.95 (3H, s, $OCH_3$-3).

**General Procedure 3 for the Synthesis of Combretastatin OTBDMS Analogues 4a−g and 4′a.** These were synthesized according to a published procedure.[26] A solution of WR (2.136 g, 3.6 mmol) in 15 mL of dry THF at −78 °C under Ar was treated with *n*-BuLi (3.78 mmol, 1.5 mL of a 2.5 M solution in hexane). The mixture was stirred for 30 min, and an aldehyde (**3a**−**g**) (3.0 mmol) in 7 mL of dry THF was added. The reaction mixture was stirred for 10 h at ambient temperature, treated with 20 mL of $H_2O$, and extracted with 2 × 50 mL of EtOAc. The organic layers were combined, dried over $Na_2SO_4$, concentrated in vacuo, and separated using column chromatography (silica gel, mesh 5/40, 100 g), eluted with hexane−EtOAc mixtures (9:1 to 4:1 gradient), affording 70−85% yields.

**General Procedure 4 for the Synthesis of Combretastatin Analogues 5−11.** A solution of TBAF·3$H_2O$ (0.525 mmol) in 1 mL of dry THF was added to the solution of a stilbene (**4a**−**g**) (0.35 mmol) in 2 mL of the same solvent, and the reaction mixture was stirred for 1 h at rt, treated with 20 mL of $H_2O$, and extracted with 2 × 40 mL of $Et_2O$. The organic extracts were combined, washed with 2 × 20 mL of $H_2O$, dried over $Na_2SO_4$, and concentrated in vacuo to afford the desired compounds in 85−99% yields.

**Apiol Acid (12a).** Aqueous NaOH (1.6 mL of 6 M solution) was added to a stirred solution of the urea−hydrogen peroxide complex (1:1) (6 g, 63.4 mmol) and aldehyde **3a** (0.9 g, 4.28 mmol) in 20 mL of $CH_3OH$ at rt. The reaction mixture was stirred at reflux for 1 h followed by the addition of the urea−hydrogen peroxide complex (1.5 g, 15.85 mmol) and reflux for 30 min. The reaction mixture was brought to rt, and the pH was adjusted to 3 with 18% aqueous HCl. The precipitate was filtered, washed with 2 × 50 mL of ice water, and dried to afford **12a** (0.85 g, 3.76 mmol, 88% yield) as an off-white solid: mp 174 °C (lit.[39] mp 175.5 °C).

**Dillapiol Acid (12b).** This was prepared as described for **12a** (1.83 g, 8.1 mmol, 87% yield): off-white solid; mp 151 °C (lit.[41] mp 151−152 °C).

**Myristicin Acid (12d).** This was prepared as described for **12a**. Aqueous NaOH (1.7 mL of 6M) was added dropwise to a stirred solution of the urea−hydrogen peroxide complex (1:1) (6 g) and myristicin aldehyde (0.9 g, 5 mmol) in 20 mL of MeOH at rt. The resulting mixture was stirred at 66 °C for 1 h, cooled, treated with 1.5 g of the urea−hydrogen peroxide complex (1:1), and reheated at 66 °C for an additional 30 min. The pH of the reaction mixture was adjusted to 3 with 18% HCl, and the resulting precipitate was collected, washed with ice water (2 × 50 mL), and dried to afford **12d** (0.8 g, 4.07 mmol, 81.6% yield) as an off-white solid: mp 212 °C (lit.[39] mp 211 °C).

**General Procedure 5 for the Synthesis of Polyalkoxybenzoic Acid Methyl Esters.** A mixture of acid **12** (5 mmol) and $SOCl_2$ (6 mmol) in 10 mL of MeOH was refluxed for 3 h and concentrated in vacuo, and 100 mL of $CH_2Cl_2$ added. The organic extract was treated with saturated aqueous $NaHCO_3$ (5 mL) to neutral pH and water (3 × 5 mL), dried over $Na_2SO_4$, and concentrated in vacuo to yield the desired methyl esters.

**General Procedure 6 for the Synthesis of Polyalkoxybenzoic Acid Hydrazides (13a,b,d).** These were prepared as described in the literature.[44] A mixture of the methyl ester of **12** (5 mmol) and 100% $NH_2NH_2·H_2O$ (25 mmol) in 5 mL of MeOH was refluxed for 6 h, concentrated in vacuo, with the residue treated with ice water (5 mL), and filtered. The filtrate was washed with 3 × 2 mL of ice water and dried to afford the desired hydrazide.

**3-Hydroxy-4-methoxybenzenecarboximidoyl Chloride.** This was synthesized according to the published procedure.[45] Dry HCl was bubbled through a suspension of 3-hydroxy-4-methoxybenzonitrile (1.86 g, 12.5 mmol) and absolute MeOH (0.58 g, 0.73 mL, 18 mmol) in 20 mL of dry $Et_2O$ at 0 °C for 10 min. The reaction mixture was sealed and stirred for 6 days at +5 °C and for an additional 10 h at 0 to +4 °C and triturated with $Et_2O$. The solid residue was washed with 3 × 5 mL of dry $Et_2O$ and dried in vacuo at 2 mmHg over $P_2O_5$ to furnish the imidoyl chloride (2.585 g, 13.9 mmol, 95% yield) as a greenish powder. This was used in the next step without further purification.

**General Procedure 7 for the Synthesis of 3,5-Diaryl-1,2,4-triazoles (14−17).** A mixture of hydrazide **13** (2 mmol) and 3-hydroxy-4-methoxybenzenecarboximidoyl chloride (3 mmol) in a flame-dried flask was treated with 3 mL of absolute MeOH and MeONa (3 mL of a 1 M solution in absolute MeOH) and stirred for 10−15 h at 45 °C (monitoring the disappearance of the starting hydrazide by TLC), refluxed for 10 h, treated with AcOH to neutral pH, and concentrated. The residue was redissolved in MeOH, treated with silica gel (3 g), and concentrated in vacuo at rt, followed by chromatographic purification (silica gel, 35 g, mesh 5/40) with a benzene−EtOAc gradient (9:1 to 1:1).

**General Procedure 8 for the Synthesis of 2,5-Diaryl-1,3,4-oxadiazoles (18−23).** A solution of hydrazide **13** (2 mmol) in 4 mL of dry pyridine at −20 °C was treated with a solution of aroyl chloride (prepared in situ by refluxing 2.2 mmol of acid and 1 mL of $SOCl_2$ for

2 h) in 1.5−2 mL of dry $CH_2Cl_2$. The resulting mixture was stirred for 12 h at rt and concentrated in vacuo. The residue was treated with 2 × 10 mL of $H_2O$ and filtered. The filtrate was washed with $H_2O$ followed by 5% aqueous $NH_3$ and 10% aqueous HCl to adjust the pH to neutral and dried to afford the targeted diacylhydrazines as grayish crystals in 81−92% yield. The resulting diacylhydrazine was used in the next step[29] without further purification. Specifically, a suspension of diacylhydrazine in 15 mL of dry $CH_2Cl_2$ was treated with TsCl (2.2 mmol) and $Et_3N$ (2.5 mmol); the resulting mixture was stirred overnight at rt and concentrated in vacuo. The residue was treated with water, and the solid was collected, washed with $H_2O$ followed by 5% aqueous $NH_3$ and 10% aqueous HCl, and dried. The resulting product was deacetylated by treating the crystals with a mixture of $Et_3N$ (0.5 mL), $H_2O$ (0.5 mL), and MeOH (2 mL) for 24 h at rt. The reaction mixture was concentrated in vacuo, and the solid residue obtained was treated with $H_2O$ followed by 5% of aqueous $NH_3$ and 10% aqueous HCl, and dried. It was then redissolved in EtOAc and purified by flash chromatography (silica gel, 36 g, mesh 5/40), using a benzene−EtOAc gradient (19:1 to 1:1) as solvent.

**General Procedure 9 for the Synthesis of Polyalkoxybenzoic Acid Nitriles (24a,b,d).** A literature procedure was followed.[25] A solution of aldehyde **3** (42.04 g, 0.2 M) in THF (300 mL) was treated with $I_2$ (56.85 g, 0.224 mol) in 28% aqueous $NH_4OH$ (1800 mL). The reaction mixture was stirred overnight and extracted with $CHCl_3$ (3 × 300 mL), and the combined organic layers were washed with water (300 mL), 10% aqueous $Na_2S_2O_3$ (300 mL), and brine (200 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting residue was recrystallized from EtOH to afford the respective nitriles in 65−90% yields.

**2,5-Dimethoxy-3,4-methylenedioxybenzonitrile (24a):** 3.7 g, 17.86 mmol, 89% yield; off-white solid; mp 134−135 °C (lit.[46] 135.5 °C); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.71 (1H, s, H-6), 6.07 (2H, s, $OCH_2O$), 4.07 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$); EIMS *m*/*z* 207 $[M]^+$ (100), 192 (95), 162 (17), 134 (20); *anal*. C 58.06, H 4.47, N 6.69%, calcd for $C_{10}H_9NO_4$, C 57.97, H 4.38, N 6.76%.

**2,3-Dimethoxy-4,5-methylenedioxybenzonitrile (24b):** 24.2 g, 116.8 mmol, 91% yield; off-white solid; mp 92−94 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.64 (1H, s, H-6), 6.03 (2H, s, $OCH_2O$), 4.03 (3H, s, $OCH_3$), 3.95 (3H, s, $OCH_3$); EIMS *m*/*z* 207 $[M]^+$ (100), 192 (93), 162 (13), 134 (15); *anal*. C 57.89, H 4.44, N 6.70%, calcd for $C_{10}H_9NO_4$, C 57.97, H 4.38, N 6.76%.

**3-Methoxy-4,5-methylenedioxybenzonitrile (24d).** For the marginally soluble myristicin aldehyde, the amount of solvents was increased by 15% to the overall volume of 345 mL of THF and 2070 mL of aqueous $NH_4OH$ (28%). A reaction of myristicin aldehyde (57.6 g, mol) and $I_2$ (100.8 g, mol) in 3200 mL of 28% aqueous $NH_3$ and THF (480 mL) furnished 55 g of a crude mixture containing **24d** (88%) and unreacted aldehyde (12%). This was further oxidized with $KMnO_4$ (6 g per 60 mL of $H_2O$) in acetone (150 mL) at reflux for 4 h. Concentration of the residue followed by its recrystallization from EtOH afforded myristicin acid (**12d**) (4.5 g, 22.9 mmol, 7% yield; mp 212 °C; lit.[39] mp 211 °C) and the targeted nitrile **24d** (37 g, 208.9 mmol, 65% yield) as an off-white solid: mp 162−164 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.86 (1H, d, $J$ = 1.4 Hz, H-6), 6.80 (1H, d, $J$ = 1.4 Hz, H-2), 6.08 (2H, s, $OCH_2O$), 3.92 (3H, s, $OCH_3$); EIMS *m*/*z* 177 $[M]^+$ (100), 176 (77), 162 (15), 132 (42), 104 (26); *anal*. C 61.12, H 4.05, N 7.83%, calcd for $C_9H_7NO_3$, C 61.02, H 3.98, N 7.91%.

**2,5-Dimethoxy-3,4-methylenedioxybenzyl Chloride.** Neat $SOCl_2$ (47 mL, 644 mmol) was added dropwise to a stirred solution of 2,5-dimethoxy-3,4-methylenedioxybenzyl alcohol[47] (66.5 g, 313 mmol) in dry benzene (150 mL) at 10 °C. The resulting mixture was warmed to 48−50 °C, stirred for 2.5 h, and concentrated in vacuo. The resulting crude benzyl chloride (68 g, 294.8 mmol, 94% yield) was used for the synthesis of nitrile without further purification.

**2,5-Dimethoxy-3,4-methylenedioxyphenylacetonitrile.** A solution of crude 2,5-dimethoxy-3,4-methylenedioxybenzyl chloride (68 g, 0.28 mol) in acetonitrile (300 mL) was treated with dibenzo-18-crown-6 (1.4 g, 3.9 mmol) followed by dried KCN (42 g, 0.645 M). The reaction mixture was stirred for 10 h at 50 °C, concentrated in vacuo, and treated with water (180 mL). The solid residue was filtered and recrystallized from alcohol to yield a nitrile (57.5 g, 259.9 mmol, 88.2%) as an off-white solid: mp 96−98 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.50 (1H, s, H-6), 5.99 (2H, s, $OCH_2O$), 3.97 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$), 3.61 (2H, s, $CH_2$); EIMS *m*/*z* 221 $[M]^+$ (72), 206 (80), 176 (5), 166 (5), 148 (11); *anal*. C 59.64, H 4.97, N 6.25%, calcd for $C_{11}H_{11}NO_4$, C 59.73, H 5.01, N 6.33%.

**General Procedure 10 for the Synthesis of Myristicin, Apiol, and Dillapiol Amidoximes (25a,b,d).** Aqueous $NH_2OH \cdot H_2O$ (5 mL, 20 mmol) was added to a solution of nitrile **24** (10 mmol) in 20 mL of EtOH. The reaction mixture was brought to reflux, treated portionwise with solid $NaHCO_3$ (20 mmol), refluxed for 12 h, and concentrated in vacuo. The residue was recrystallized from EtOH to furnish the targeted amidoximes (65−75% yields, 85−90% purity), which were used for the next step without further purification.

**General Procedure 11 for the Synthesis of 3,5-Diaryl-1,2,4-oxadiazoles (26−31).** These were synthesized by a modified procedure.[21] Solid CDI (3.6 mmol) was added to a stirred suspension of crude amidoxime **25** (3 mmol) in 5 mL of dry MeCN. The resulting mixture was stirred for 1 h at rt until the amidoxime was dissolved completely. 3-Hydroxy-4-methoxybenzoic acid (3 mmol) was added at once, and the mixture was stirred for 12 h and concentrated in vacuo. The solid residue was redissolved in 5 mL of dry DMF, with the resulting solution stirred for 3 h at 120−125 °C. Solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, EtOAc−petroleum ether, 1:4).

**Biological Evaluation Using a Sea Urchin Embryo Assay.** Adult sea urchins, *Paracentrotus lividus* L. (Echinidae), were collected from the Mediterranean Sea on the Cyprus coast in March−May and October−December, 2009, and kept in an aerated seawater tank. Gametes were obtained by intracoelomic injection of 0.5 M KCl. Eggs were washed with filtered seawater and fertilized by adding drops of diluted sperm. Embryos were cultured at room temperature under gentle agitation with a motor-driven plastic paddle (60 rpm) in filtered seawater. The embryos were observed with a Biolam light microscope (LOMO, St. Petersburg, Russia). For treatment with the test compounds, 5 mL aliquots of embryo suspension were transferred to six-well plates and incubated as a monolayer at a concentration up to 2000 embryos/mL. Stock solutions of compounds were prepared either in 95% EtOH at 5 mM or in DMSO at 5−20 mM concentrations followed by a 10-fold dilution with 95% EtOH. This procedure enhanced solubility of the test compounds in the salt-containing medium (seawater), as evidenced by microscopic examination of the samples. The maximal tolerated concentrations of DMSO and EtOH in the in vivo assay were determined to be 0.05% and 1%, respectively. Higher concentrations of either DMSO (≥0.1%) or EtOH (>1%) caused nonspecific alteration and retardation of the sea urchin embryo development independent of the treatment stage. CA4P (OXiGENE) was prepared as 5 mM in distilled water. The antiproliferative activity was assessed by exposing fertilized eggs (10−25 min after fertilization, 45−60 min before the first mitotic cycle completion) to 2-fold decreasing concentrations of the compound. For the *Z*-/*E*-isomers, compound stock solutions and treated embryo samples were protected from light. Cleavage alteration and arrest were clearly detected 2.5−6 h after fertilization. The effects were estimated quantitatively as an effective threshold concentration, EC, resulting in cleavage alteration and embryo death before hatching or full mitotic arrest. For tubulin-destabilizing activity, the compounds were tested on free-swimming blastulae just after hatching (9−12 h after fertilization), which originated from the same embryo culture. Embryo spinning was observed after 0.5−20 h of treatment, depending on the nature and concentration of the compound. Both spinning and lack of forward movement were interpreted to be the result of the tubulin-destabilizing activity of a molecule according to previous studies.[23,30]

Compound substructure searching in the sea urchin embryo screening database is available free on line.[48]

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**Supporting Information Available:** Experimental details regarding selected syntheses, analytical data, and effects on sea urchin embryo development. This material is available free of charge via the Internet at http://pubs.acs.org.

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