Polyalkoxybenzenes from plant raw materials
4*. Parsley and dill seed extracts in the synthesis of polyalkoxy-3,5-diaryl-1,2,4-oxadiazoles with antiproliferative activity

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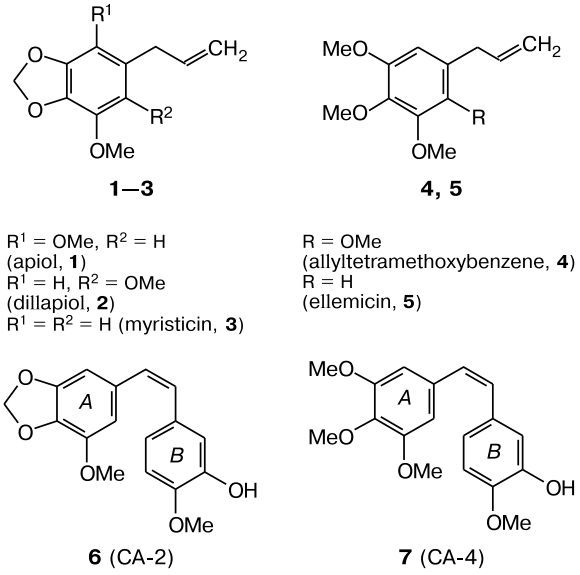
Polyalkoxy-5-(4-hydroxyphenyl)-3-phenyl-1,2,4-oxadiazoles were prepared from allylpolyalkoxybenzenes, the main metabolites of parsley and dill seeds. Due to the spatial arrangement of the aryl substituents provided by 1,2,4-oxadiozole fragment, these compounds can be considered as structural analogs of natural antimitotic combretastatins. The antimitotic activity of the synthesized compounds was evaluated *in vivo* using sea urchin embryo test.

Key words: apiol, dillapiol, myristicin, combretastatin, oxadiazoles, antimitotic activity, sea urchin embryo.

Various pharmacologically active allylpolyalkoxybenzenes **1—5** are the main metabolites of *Umbelliferae* plants.[2,3] The protocol for their isolation from the parsley and dill seeds using liquid CO_2 extraction followed by high-efficient distillation has been developed previously.[3] Allylpolyalkoxybenzenes could be successively applied in synthesis of the analogs of the natural antimitotic compounds with polyalkoxybenzene fragments, *e.i.*, combretastatins.[1,4—6] Combretastatins A-2 (CA-2, **6**) and A-4 (CA-4, **7**) isolated from the bark of a South African plant *Combretum caffrum*[7] possess a strong antimitotic activity owing to inhibition of tubulin polimerization and alteration of mitotic spindle structure and function.[8,9] In combretastatin molecule, two aromatic rings, the *A* ring and the *B* ring, are linked by ethylene bridge thus arranged at a certain distance and dihedral angle. The bridge furnishes a *cis*-configuration of the stilbene template necessary for efficient interaction with tubulin.[5,6,8] Phosphorylated water-soluble derivative CA-4 prodrug currently undergoes clinical evaluation as antitumor agent.[10,11]



1—3

R^1 = OMe, R^2 = H (apiol, **1**)
R^1 = H, R^2 = OMe (dillapiol, **2**)
R^1 = R^2 = H (myristicin, **3**)

4, 5

R = OMe (allyltetramethoxybenzene, **4**)
R = H (ellemicin, **5**)

6 (CA-2)

7 (CA-4)

A numerous modern studies in medicinal chemistry are devoted to the design of novel synthetic analogs of combretastatin, which possess the configuration stability and strong antimitotic effect along with minimal side effects and ability to overcome multi-drug resistance.[5,6] The availability of raw materials and simplicity of synthetic procedures are also important.

Modification of the *B* ring of combretastatins by introduction of different substituents, *e.g.*, NH_2, F, is widely known.[5,6] Various derivatives bearing different linkers that stabilize the *cis*-configuration of the stilbene template were reported. Besides, five-membered heterocycles, including

* For Part 3, see Ref. 1.

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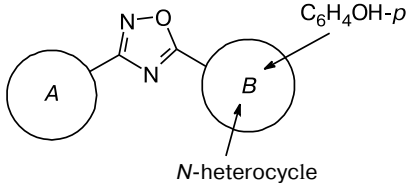
readily available 1,2,4-oxadiazolines[12] and 1,2,4-oxadiazoles[1] are regarded as bioisosteric non-isomerizable and metabolically stable substitute for the double bond in *cis*-stilbene. Recently, combretastatin derivatives with only two alkoxy groups in the *A* ring, *p*-hydroxyphenyl or *N*-heterocyclic moiety as the *B* ring, and 1,2,4-oxadiazole fragment as the bridge were synthesized.[13] Among these compounds, derivatives with a pronounced cytotoxicity against human cancer cell lines were identified.[13] However, the biological activity of the compounds bearing more than three methoxy groups in the *A* ring have been less studied due probably to low availability of the corresponding starting benzaldehydes. At the same time, these structures are of interest owing to noticeable antiproliferative activity exhibited by a number of natural compounds with tetraalkoxy moiety, for example, tetrahydroisoquinolines of *Cactaceae*,[14] flavonoids, and isoflavonoids.[15—17]



The aim of the present work is the synthesis of novel combretastatin analogs with optimal for the antimitotic activity number of alkoxy groups in the *A* and *B* rings, necessary spatial orientation of which provided by the 1,2,4-oxadiazole binding block. The *A* ring was designed on the base of tri- and tetraalkoxy benzenes of plant origin, while *p*-hydroxyphenyl or six-membered *N*-heterocycles were used as the *B* ring. Moreover, for a more detailed study of the structure—activity relationship, we synthesized compounds with 3,4-methylenedioxyphenyl moiety as the *A* ring, which presented also in the structures of the number of secondary plant metabolites.[18]

Results and Discussion

Synthetic approach to heterocyclic combretastatin analogs on the base of tri- and tetraalkoxy benzenes is given on Scheme 1. Reaction of aldehydes **8** with iodine in nearly equimolar ratio in aqueous ammonia[19] resulted in polyalkoxybenzonitriles **9**, which were used for the synthesis of intermediate compounds, amidoximes **10**. Target 3,5-diaryl-1,2,4-oxadiazoles **11—19** (Table 1) were synthesized at heating of equimolar amounts of amidoxime **10** and the corresponding acid in the presence of carbonyldiimidazole.

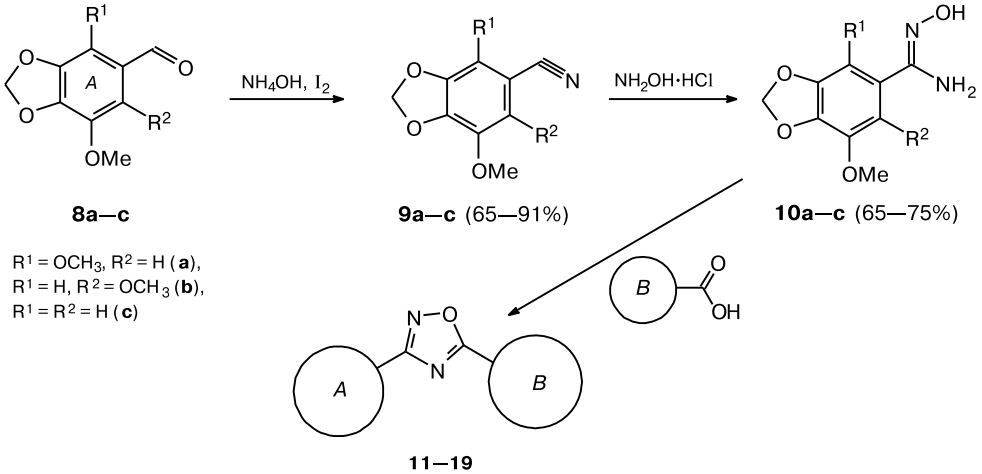
Combretastatin analogs **20—35** bearing 3,4-methylenedioxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, or 4-pyridyl moieties as the *A* ring (see Table 1 and Experimental) were synthesized similar to compounds **11—19**.

Biological study. Sea urchin embryos are widely used as a model for identification of compound with antiproliferative activity.[20,21] Recently we developed a simple and effective phenotypic sea urchin embryo assay, which serves for both the identification of the substances arresting cell division and study the mechanism of antimitotic activity.[22] The effective concentrations (EC) of the substances resulting in the alteration of sea urchin embryo cleavage are comparable with the IC_{50} for mammalian and human tumor cell lines.[22,23] The results of sea urchin embryo assay for the compounds synthesized are summarized in Table 1.

It was found that compound **17** with myristicin fragment affected sea urchin embryo cleavage at concentration of 4 μmol L^{-1}. At the same time, no antimitotic activity up to 4 μmol L^{-1} were found for 1,2,4-oxadiazole combretastatin analogs **11** and **14**, derivatives of apiol and dillapiol, respectively, prepared by introduction of the additional methoxy group in the *A* ring.

Replacement of the isovaniline moiety in the *B* ring by *p*-hydroxyphenyl group (apiol **12** derivative) was found to

Scheme 1



8a—c

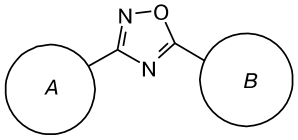
$R^1 = OCH_3$, $R^2 = H$ (**a**),
$R^1 = H$, $R^2 = OCH_3$ (**b**),
$R^1 = R^2 = H$ (**c**)

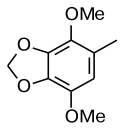
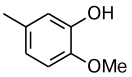
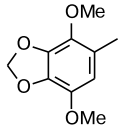
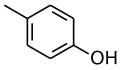
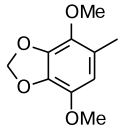
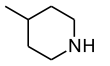
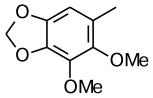
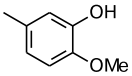
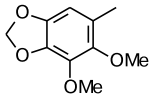
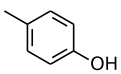
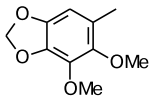
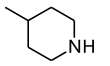
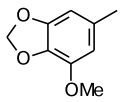
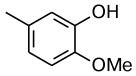
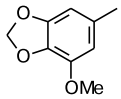
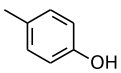
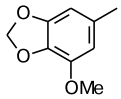
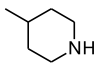
9a—c (65—91%)

10a—c (65—75%)

11—19

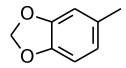
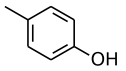
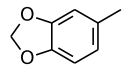
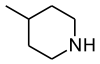
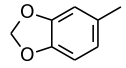
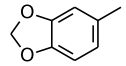
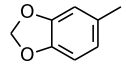
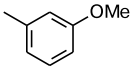
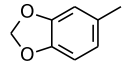
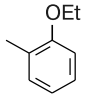
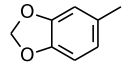
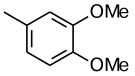
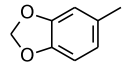
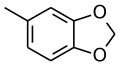
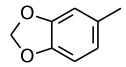
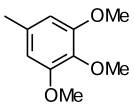
Table 1. Structure, yields, melting points, ^{1}H NMR spectral data (DMSO-d_6), and biological activity of combretastatin analogs **11—35**



Compound	*A*	*B*	Yield (%)	M.p./°C	^{1}H NMR, δ (*J*/Hz)	EC* /μmol L^{-1}
11			18	164—168	3.87 (s, 3 H, OMe); 3.89 (s, 6 H, 2 OMe); 6.16 (s, 2 H, OCH_2O); 7.16 (d, 1 H, H(5′), Ar, *J* = 8.5); 7.17 (s, 1 H, H(6), Ar); 7.55 (d, 1 H, H(2′), Ar, *J* = 2.15); 7.63 (dd, 1 H, H(6′), Ar, J_1 = 2.15, J_2 = 8.5); 9.71 (s, 1 H, OH)	>4
12			43	255—256	3.87 (s, 3 H, OMe); 3.88 (s, 3 H, OMe); 6.16 (s, 2 H, OCH_2O); 7.00 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.7); 7.19 (s, 1 H, H(6), Ar); 8.01 (d, 2 H, H(2′), H(6′), Ar, *J* = 7.0); 10.52 (s, 1 H, OH)	>4
13			18	107—108	1.61—1.70 (m, 2 H, H_a(3′), H_a(5′)); 1.98 (d, 2 H, H_e(3′), H_e(5′), *J* = 11.5); 2.57—2.63 (m, 2 H, H_a(2′), H_a(6′)); 2.98 (d, 2 H, H_e(2′), H_e(6′), *J* = 12.4); 3.16 (m, 1 H, H(4′)); 3.38 (s, 6 H, 2 OMe); 6.14 (s, 2 H, OCH_2O); 7.08 (s, 1 H, H(6), Ar)	>4
14			29	168—172	3.79 (s, 3 H, OMe); 3.89 (s, 3 H, OMe); 3.99 (s, 3 H, OMe); 6.13 (s, 2 H, OCH_2O); 7.09 (s, 1 H, H(6), Ar); 7.16 (d, 1 H, H(5′), Ar, *J* = 8.5); 7.55 (d, 1 H, H(2′), Ar, *J* = 2.15); 7.63 (dd, 1 H, H(6′), Ar, J_1 = 2.15, J_2 = 8.5); 9.71 (s, 1 H, OH)	>4
15			59	230—231	3.79 (s, 3 H, OMe); 4.00 (s, 3 H, OMe); 6.12 (s, 2 H, OCH_2O); 6.99 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.7); 7.10 (s, 1 H, H(6), Ar); 8.00 (d, 2 H, H(2′), H(6′), Ar, *J* = 8.7); 10.51 (s, 1 H, OH)	1
16			24	100—101	1.62—1.68 (m, 2 H, H_a(3′), H_a(5′)); 1.98 (d, 2 H, H_e(3′), H_e(5′), *J* = 12.1); 2.57—2.63 (m, 2 H, H_a(2′), H_a(6′)); 2.95—3.00 (m, 2 H, H_e(2′), H_e(6′)); 3.15 (m, 1 H, H(4′)); 3.75 (s, 1 H, OMe); 3.98 (s, 3 H, OMe); 6.11 (s, 2 H, OCH_2O); 7.00 (s, 1 H, H(6), Ar)	>4
17			32	180—183	3.89 (s, 3 H, OMe); 3.94 (s, 3 H, OMe); 6.13 (s, 2 H, OCH_2O); 7.16 (d, 1 H, H(5′), Ar, *J* = 8.5); 7.22 (d, 1 H, H(2) or H(6), Ar, *J* = 1.4); 7.34 (d, 1 H, H(2) or H(6), Ar, *J* = 1.4); 7.56 (d, 1 H, H(2′), Ar, *J* = 2.15); 7.63 (dd, 1 H, H(6′), Ar, J_1 = 2.15, J_2 = 8.5); 9.71 (s, 1 H, OH)	4
18			11	205—206	3.93 (s, 3 H, OMe); 6.13 (s, 2 H, OCH_2O); 7.00 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.7); 7.22 (d, 1 H, H(6), Ar, *J* = 0.95); 7.33 (d, 1 H, H(2), Ar, *J* = 0.95); 8.02 (d, 2 H, H(2′), H(6′), Ar, *J* = 8.7); 10.53 (s, 1 H, OH)	2
19			21	104—105	1.62—1.71 (m, 2 H, H_a(3′), H_a(5′)); 1.97 (d, 2 H, H_e(3′), H_e(5′); *J* = 11.8), 2.61 (т, 2 H, H_a(2′), H_a(6′), *J* = 12.5); 2.99 (d, 2 H, H_e(2′), H_e(6′), *J* = 12.5); 3.18 (m, 1 H, H(4′)); 3.90 (s, 3 H, OMe); 6.12 (s, 2 H, OCH_2O); 7.15 (d, 1 H, H(6), Ar, *J* = 1.4); 7.26 (d, 1 H, H(2), Ar, *J* = 1.4)	>4

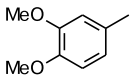
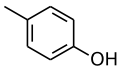
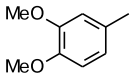
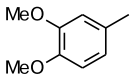
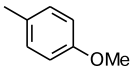
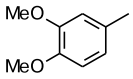
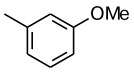
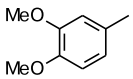
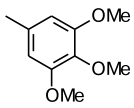
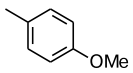
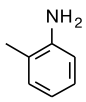
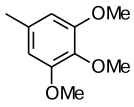
(*to be continued*)

Table 1 (*continued*)

Compound	*A*	*B*	Yield (%)	M.p./°C	^{1}H NMR, δ (*J*/Hz)	EC* /μmol L^{-1}
20			15	204—206	6.16 (s, 2 H, OCH_2O); 6.99 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.7); 7.12 (d, 1 H, H(5), Ar, *J* = 8.1); 7.50 (d, 1 H, H(2), Ar, *J* = 1.7); 7.64 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 8.01 (d, 2 H, H(2′), H(6′), Ar, *J* = 8.7); 10.54 (s, 1 H, OH)	0.5
21			35	96—97	1.61—1.70 (m, 2 H, H_a(3′), H_a(5′)); 1.96 (d, 2 H, H_e(3′), H_e(5′); *J* = 12.8); 2.57—2.63 (m, 2 H, H_a(2′), H_a(6′)); 2.98 (m, 2 H, H_e(2′), H_e(6′)); 3.12—3.19 (m, 1 H, H(4′)); 6.15 (s, 2 H, OCH_2O); 7.19 (d, 1 H, H(5), Ar, *J* = 8.1); 7.44 (d, 1 H, H(2), Ar, *J* = 1.7); 7.57 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1)	>4
22			31	207—208	6.15 (s, 2 H, OCH_2O); 7.12 (d, 1 H, H(5), Ar, *J* = 8.1); 7.53 (d, 1 H, H(2), Ar, *J* = 1.7); 7.67 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 8.07 (d, 2 H, H(3′), H(5′), Py, *J* = 5.5); 8.90 (d, 2 H, H(2′), H(6′), Py, *J* = 5.5)	5
23			41	199—200	6.18 (s, 2 H, OCH_2O); 7.16 (d, 1 H, H(5), Ar, *J* = 8.1); 7.56 (d, 1 H, H(2), Ar, *J* = 1.7); 7.70 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 8.94 (dd, 1 H, H(5′), pyrazine, J_1 = 1.4, J_2 = 2.4); 8.98 (d, 1 H, H(6′), pyrazine, *J* = 2.4); 9.49 (d, 1 H, H(3′), pyrazine, *J* = 1.4)	5
24			71	122—123	3.89 (s, 3 H, OMe); 6.17 (s, 2 H, OCH_2O); 7.13 (d, 1 H, H(5), Ar, *J* = 8.1), 7.31 (ddd, 1 H, H(5′), Ar, J_1 = 1.1, J_2 = 2.5, J_3 = 7.8); 7.53 (d, 1 H, H(2), Ar, *J* = 1.7); 7.58 (t, 1 H, H(4′), Ar, *J* = 7.8); 7.64 (dd, 1 H, H(2′), Ar, J_1 = 1.1, J_2 = 2.5); 7.67 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 7.75 (dt, 1 H, H(6′), Ar, J_1 = 1.1, J_2 = 7.8)	>4
25			41	119—120	1.41 (t, 3 H, $MeCH_2O$, *J* = 7.0); 4.23 (q, 2 H, $MeCH_2O$, *J* = 7.0); 6.17 (s, 2 H, OCH_2O); 7.13 (d, 1 H, H(5), Ar, *J* = 8.1); 7.16 (t, 1 H, H(5′), Ar, *J* = 7.7); 7.30 (d, 1 H, H(3′), Ar, *J* = 8.4); 7.52 (d, 1 H, H(2), Ar, *J* = 1.7); 7.64—7.68 (m, 2 H, H(4′), H(6), Ar); 8.06 (dd, 1 H, H(6′), Ar, J_1 = 1.8, J_2 = 7.7)	>4
26			52	192—193	3.88 (s, 3 H, OMe); 3.90 (s, 3 H, OMe); 6.16 (s, 2 H, OCH_2O); 7.12 (d, 1 H, H(2), Ar, *J* = 8.1,); 7.22 (d, 1 H, H(5′), Ar, *J* = 8.4); 7.52 (d, 1 H, H(2), Ar, *J* = 1.7); 7.63 (d, 1 H, H(2′), Ar, *J* = 2.0); 7.66 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 7.78 (dd, 1 H, H(6′), Ar, J_1 = 2.0, J_2 = 8.4)	>4
27			35	207—209	6.16 (s, 2 H, OCH_2O); 6.21 (s, 2 H, OCH_2O); 7.12 (d, 1 H, H(5), Ar, *J* = 8.1); 7.18 (d, 1 H, H(5′), Ar, *J* = 8.1); 7.51 (d, 1 H, H(2), Ar, *J* = 1.7); 7.63 (d, 1 H, H(2′), Ar, *J* = 1.7); 7.64 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.1); 7.76 (dd, 1 H, H(6′), Ar, J_1 = 1.7, J_2 = 8.1)	>4
28			61	150—151	3.78 (s, 3 H, OMe); 3.92 (s, 6 H, 2 OMe); 6.16 (s, 2 H, OCH_2O); 7.12 (d, 1 H, H(5), Ar, *J* = 8.1); 7.42 (s, 2 H, H(2′), H(6′), Ar); 7.53 (d, 1 H, H(2), Ar, *J* = 1.7); 7.67 (dd, 1 H, H(6), J_1 = 1.7, J_2 = 8.1)	>4

(*to be continued*)

Table 1 (*continued*)

Compound	*A*	*B*	Yield (%)	M.p./°C	^{1}H NMR, δ (*J*/Hz)	EC* /μmol L^{-1}
29			15	189—191	3.84 (s, 3 H, OMe); 3.85 (s, 3 H, OMe); 7.00 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.7); 7.15 (d, 1 H, H(5), Ar, *J* = 8.4); 7.55 (d, 1 H, H(2), Ar, *J* = 2.0); 7.67 (dd, 1 H, H(6), Ar, J_1 = 2.0, J_2 = 8.4); 8.03 (d, 2 H, H(2′), H(6′), Ar, *J* = 8.4); 10.54 (s, 1 H, OH)	>4
30			23	82—84	1.59—1.75 (m, 2 H, H_a(3′), H_a(5′)); 1.98 (d, 2 H, H_e(3′), H_e(5′), *J* = 11.8); 2.61 (t, 2 H, H_a(2′), H_a(6′), *J* = 11.8); 2.99 (d, 2 H, H_e(2′), H_e(6′), *J* = 11.8); 3.17 (m, 1 H, H(4′)); 3.83 (s, 6 H, 2 OMe); 7.12 (d, 1 H, H(5), Ar, *J* = 8.4); 7.46 (d, 1 H, H(2), Ar, *J* = 1.9); 7.59 (dd, 1 H, H(6), Ar, J_1 = 1.9, J_2 = 8.4)	>4
31			35	155—157	3.85 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 3.89 (s, 3 H, OMe); 7.15 (d, 1 H, H(5), Ar, *J* = 8.4); 7.19 (d, 2 H, H(3′), H(5′), Ar, *J* = 8.9); 7.55 (d, 1 H, H(2), Ar, *J* = 2.0); 7.68 (dd, 1 H, H(6), Ar, J_1 = 2.0, J_2 = 8.4); 8.13 (d, 2 H, H(2′), H(6′), Ar, *J* = 8.9)	>4
32			65	110—112	3.85 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 3.89 (s, 3 H, OMe); 7.17 (d, 1 H, H(5), Ar, *J* = 8.4); 7.31 (dd, 1 H, H(4′), Ar, J_1 = 2.3, J_2 = 8.3); 7.57 (s, 1 H, H(2), Ar), 7.59 (т, 1 H, H(5′), Ar, *J* = 8.1), 7.66 (t, 1 H, H(2′), Ar, *J* = 2.3), 7.70 (dd, 1 H, H(6), Ar, J_1 = 1.7, J_2 = 8.4); 7.77 (d, 1 H, H(6′), Ar, *J* = 7.7)	>4
33			75	165—167	3.79 (s, 3 H, OMe); 3.86 (s, 3 H, OMe); 3.88 (s, 3 H, OMe); 3.93 (s, 6 H, 2 OMe); 7.16 (d, 1 H, H(5), Ar, *J* = 8.4); 7.42 (s, 2 H, H(2′), H(6′), Ar); 7.56 (d, 1 H, H(2), Ar, *J* = 2.0); 7.70 (dd, 1 H, H(6), Ar, J_1 = 2.0, J_2 = 8.4)	>4
34			17	145—146	3.87 (s, 3 H, OMe); 6,69 (t, 1 H, H(5′), Ar, *J* = 8.0); 6.96 (d, 1 H, H(3′), Ar, *J* = 8.4); 6.98 (s, 2 H, NH_2); 7.14 (d, 2 H, H(3), H(5), Ar, *J* = 8.8); 7.32—7.37 (m, 1 H, H(4′), Ar); 7.84 (dd, 1 H, H(6′), Ar, J_1 = 1.5, J_2 = 8.0); 8.09 (d, 2 H, H(2), H(6), Ar, *J* = 8.8)	>4
35			36	169—170	3.81 (s, 3 H, OMe); 3.93 (s, 6 H, 2 OMe); 7.47 (s, 2 H, H(2′), H(6′), Ar); 8.01 (d, 2 H, H(3), H(5), Ar, *J* = 5.4); 8.84 (d, 2 H, H(2), H(6), Ar, *J* = 5.4)	>10

* EC is an effective concentration of the compound resulting in the cleavage alteration of the sea urchin embryos.

be ineffective, while dillapiol and myristicin derivatives, **15** and **18**, respectively, affect the cell cleavage at 1—2 μmol L^{-1}. Methylenedioxy derivative **20** without methoxy groups in the *A* ring was even more active, its EC was 0.5 μmol L^{-1}. Thus, the replacement of the *p*-OMe group by the *p*-OH in the *B* ring of the oxadiazole derivatives increases the antimitotic effect, while in the combretastatins the same modification resulted in the noticeable decrease in activity.[8,24]

Replacement of *p*-hydroxyphenyl moiety (compounds **12**, **15**, **18**, and **20**) by pyperidin-4-yl fragment (compounds **13**, **16**, **19**, and **21**) led to loss of activity, however, the same modification of the *B* ring of the derivatives bearing two dialkoxy fragments in the *A* ring resulted in the increase in cytotoxicity.[13] Piperonyl-containing derivatives **22** and **23** with pyridine and pyridazine as the *B* ring, respectively, exhibited cleavage alteration at 5 μmol L^{-1}. At the same time, according to the published data, replace-

ment of the piperidine moiety by the pyridine ring gave inactive compounds.[13] Probably, this discrepancy in the biological activity of combretastatin derivatives at bioisosteric replacement of the fragments is due to the difference in the cellular mechanisms of action of the compounds. As an example, the results obtained using the sea urchin embryo suggested the non-tubulin antiproliferative activity of compound **20**.

Moving from methylenedioxy derivatives to dimethoxy ones caused the loss of the activity (compounds **29**—**33**). Similar change in the structure of the natural compounds, α-conidendrin, podophyllotoxin, and sikkimotoxin, yielded 10-fold decrease in cytotoxicity.[25]

According to the preliminary tests, 1,2,4-oxadiazole combretastatin derivatives **11**, **14,** and **17**, pyrazine derivative **23**, and compound **35** showed cytotoxicity against U937, MT4, and CEM13 human leukemia cells.

In summary, allylpolyalkoxybenzenes extracted from parsley and dill seeds are easily available starting material for the synthesis of biologically active compounds possessing antiproliferative activity, which could be used later in design of novel antitumor agents.

Experimental

^{1}H and ^{13}C NMR spectra were run on a Bruker DRX-500 instrument at 500.13 and 125.76 MHz, respectively, in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal standard. Mass spectra were recorded on a Finnigan MAT INCOS 50 quadrupole mass spectrometer (direct inlet, ionization potential 70 eV). Elemental analysis was carried out on an automated Perkin—Elmer 2400 CHN microanalyzer. TLC was performed on Merck 60 F_{254} plates. Preparative chromatography was carried out on silica gel Acros 0.035—0.070 mm, 60 A. Melting points were determined at Boetius apparatus and uncorrected.

Synthesis of polyalkoxybenzonitriles 9 (general procedure). A solution of aldehyde **8** (see Ref. 3) (200 mmol) in THF (300 mL) was added to a solution of I_2 (56.85 g, 224 mmol) in 28% aqueous NH_4OH (1800 mL). The resulting mixture was stirred at 20 °C for 12 h and extracted with $CHCl_3$ (3×300 mL). The combined organic layers were washed with water (300 mL), 10% aqueous $Na_2S_2O_3$ (300 mL), and brine, dried with Na_2SO_4, and the solvent was removed *in vacuo*. The residue was recrystallized from EtOH.

2,5-Dimethoxy-3,4-methylenedioxybenzonitrile (9a). Yield 89%, m.p. 134—135 °C (*cf.* Ref. 26: m.p. 135.5 °C). Found (%): C, 58.06; H, 4.47; N, 6.69. $C_{10}H_9NO_4$. Calculated (%): C, 57.97; H, 4.38; N, 6.76. ^{1}H NMR ($CDCl_3$), δ: 3.86 (s, 3 H, OMe); 4.07 (s, 3 H, OMe); 6.07 (s, 2 H, OCH_2O); 6.71 (s, 1 H, Ar). MS, *m/z* (I_{rel} (%)): 207 $[M]^+$ (100), 192 (95), 162 (17), 134 (20).

2,3-Dimethoxy-4,5-methylenedioxybenzonitrile (9b). Yield 91%, m.p. 92—94 °C. Found (%): C, 57.89; H, 4.44; N, 6.70. $C_{10}H_9NO_4$. Calculated (%): C, 57.97; H, 4.38; N, 6.76. ^{1}H NMR ($CDCl_3$), δ: 3.95 (s, 3 H, OMe); 4.03 (s, 3 H, OMe); 6.03 (s, 2 H, OCH_2O); 6.64 (s, 1 H, Ar). MS, *m/z* (I_{rel} (%)): 207 $[M]^+$ (100), 192 (93), 162 (13), 134 (15).

3-Methoxy-4,5-methylenedioxybenzonitrile (9c). When the reaction was carried out with poor soluble myristicin aldehyde, the amounts of THF and NH_4OH were raised by 15% to the mentioned-above procedure. A mixture of aldehyde **8c** (57.6 g, 320 mmol) and I_2 (100.8 g, 397 mmol) in THF (345 mL) and 28% aqueous NH_4OH (3200 mL) was stirred at 20 °C for 30 h. The reaction mixture was worked-up as above to give an inseparable mixture (55 g) of nitrile **9c** (88%) and unreacted aldehyde **8c** (12%). This mixture was further oxidized with $KMnO_4$ (6 g per 60 mL of H_2O) in acetone (150 mL) at reflux for 4 h. Removal of the solvent *in vacuo* and recrystallization of the residue from EtOH afforded myristicin acid (4.5 g, 7%, m.p. 212 °C, *cf.* Ref. 27: m.p. 211 °C) and nitrile **9c** (37 g, 65%), m.p. 162—164 °C. Found (%): C, 61.12; H, 4.05; N, 7.83. $C_9H_7NO_3$. Calculated (%): C, 61.02; H, 3.98; N, 7.91. ^{1}H NMR ($CDCl_3$), δ: 3.92 (s, 3 H, OMe); 6.08 (s, 2 H, OCH_2O); 6.80 (d, 1 H, H(2), Ar, J = 1.4 Hz); 6.86 (d, 1 H, H(6), Ar, J = 1.4 Hz). MS, *m/z* (I_{rel} (%)): 177 $[M]^+$ (100), 176 (77), 162 (15), 132 (42), 104 (26).

Synthesis of amidoximes 10a—d (general procedure). To a solution of nitrile **9** (10 mmol) and $NH_2OH \cdot HCl$ (1.4 g, 20 mmol) in EtOH (20 mL), a solution of $NaHCO_3$ (1.68 g, 20 mmol) in water (5 mL) was added at room temperature with stirring. The reaction mixture was refluxed for 12 h, the solvent was removed *in vacuo*. Recrystallization of the residue from aqueous EtOH afforded amidoximes **10a—d** in 65—75% yields (85—90% purity), which were used on the next step without further purification.

2,5-Dimethoxy-3,4-methylenedioxybenzamidoxime (10a). M.p. 150—152 °C. Found (%): C, 50.18; H, 5.16; N, 11.50. $C_{10}H_{12}N_2O_5$. Calculated (%): C, 50.00; H, 5.04; N, 11.66. ^{1}H NMR (DMSO-d_6), δ: 3.77 (s, 3 H, OMe); 3.80 (s, 3 H, OMe); 5.60 (s, 2 H, NH_2); 6.04 (s, 2 H, OCH_2O); 6.66 (s, 1 H, H(6), Ar); 9.40 (s, 1 H, OH). MS, *m/z* (I_{rel} (%)): 240 $[M]^+$ (13), 223 (16), 209 (6), 208 (32), 207 (52), 193 (30), 192 (46), 68 (49), 66 (84), 59 (100).

2,3-Dimethoxy-4,5-methylenedioxybenzamidoxime (10b). M.p. 147—148 °C. Found (%): C, 50.12; H, 5.12; N, 11.46. $C_{10}H_{12}N_2O_5$. Calculated (%): C, 50.00; H, 5.04; N, 11.66. ^{1}H NMR (DMSO-d_6), δ: 3.69 (s, 3 H, OMe); 3.83 (s, 3 H, OMe); 5.60 (s, 2 H, NH_2); 6.01 (s, 2 H, OCH_2O); 6.62 (s, 1 H, H(6), Ar); 9.41 (s, 1 H, OH). MS, *m/z* (I_{rel} (%)): 240 $[M]^+$ (13), 223 (17), 208 (28), 207 (56), 193 (18), 192 (38), 68 (34), 66 (72), 59 (100).

3-Methoxy-4,5-methylenedioxybenzamidoxime (10c). M.p. 170—171 °C. Found (%): C, 51.58; H, 4.92; N, 13.19. $C_9H_{10}N_2O_4$. Calculated (%): C, 51.43; H, 4.80; N, 13.33. ^{1}H NMR (DMSO-d_6), δ: 3.85 (s, 3 H, OMe); 5.75 (s, 2 H, NH_2); 6.01 (s, 2 H, OCH_2O); 6.89 (s, 1 H, Ar); 6.98 (s, 1 H, Ar); 9.52 (s, 1 H, OH). MS, *m/z* (I_{rel} (%)): 210 $[M]^+$ (31), 193 (35), 179 (8), 178 (22), 77 (53), 65 (90), 63 (100).

3,4-Methylenedioxybenzamidoxime (10d). M.p. 150—152 °C (*cf.* Ref. 28: m.p. 151 °C). ^{1}H NMR (DMSO-d_6), δ: 5.71 (s, 2 H, NH_2); 6.03 (s, 2 H, OCH_2O); 6.90 (d, 1 H, H(5), Ar, J = 8.5 Hz); 7.18 (s, 1 H, H(2), Ar); 7.19 (dd, 1 H, H(6), Ar, J = 1.6 Hz, J = 8.5 Hz); 9.50 (s, 1 H, OH). MS, *m/z* (I_{rel} (%)): 180 $[M]^+$ (26), 163 (32), 149 (7), 148 (19), 77 (50), 65 (91), 63 (100).

3,4-Dimethoxybenzamidoxime (10e). To a solution of 3,4-dimethoxybenzonitrile (5.0 g, 30.6 mmol) and $NH_2OH \cdot HCl$ (4.26 g, 61.3 mmol) in EtOH (150 mL), a solution of NaOH (2.45 g, 61.3 mmol) in water (20 mL) was added at room temperature with stirring. The reaction mixture was refluxed for 14 h, the solvent was removed *in vacuo*, the residue was washed with water (2×20 mL), and recrystallized from 50% aqueous EtOH

(50 mL) to give amidoxime **10e** (4.3 g, 71.5%), m.p. 142—143 °C (*cf.* Ref. 29: m.p. 137 °C). ^{1}H NMR (DMSO-d_6), δ: 3.76 (s, 6 H, 2 OMe); 5.73 (s, 2 H, NH_2); 6.94 (d, 1 H, H(5), Ar, J = 8.4 Hz); 7.23 (dd, 1 H, H(6), Ar, J = 2.0 Hz, J = 8.4 Hz); 7.25 (d, 1 H, H(2), Ar, J = 2.0 Hz); 9.46 (s, 1 H, OH). MS, m/z (I_{rel} (%)): 196 $[M]^+$ (59), 179 (55), 165 (12), 164 (34), 79 (72), 77 (47), 51 (100).

Synthesis of 3,5-diaryl-1,2,4-oxadiazoles 11—35 (general procedure). Carbonyldiimidazole (0.58 g, 3.6 mmol) was added to a stirred suspension of crude amidoxime **10** (3 mmol) in anhydrous MeCN (5 mL) and stirring was continued at room temperature for 1 h until the amidoxime was dissolved completely. Then the corresponding carboxylic acid (3 mmol) was added and stirring was continued for 12 h. The solvent was removed *in vacuo*, the solid residue was dissolved in anhydrous DMF (5 mL), and the solution was stirred at 120—125 °C for 3 h. The solvent was removed *in vacuo*, the target product was isolated by column chromatography (silica gel, elution with ethyl acetate—hexanes, 1 : 4). Yields, melting points, and ^{1}H NMR spectral data of the synthesized combretastatin analogs are given in Table 1.

3-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-5-(3-hydroxy-4-methoxyphenyl)-1,2,4-oxadiazole (11). Found (%): C, 58.12; H, 4.44; N, 7.63. $C_{18}H_{16}N_2O_7$. Calculated (%): C, 58.07; H, 4.33; N, 7.52. MS, m/z (I_{rel} (%)): 372 $[M]^+$ (13), 266 (17), 193 (26), 178 (17), 151 (100).

3-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-5-(4-hydroxyphenyl)-1,2,4-oxadiazole (12). Found (%): C, 59.59; H, 4.07; N, 8.28. $C_{17}H_{14}N_2O_6$. Calculated (%): C, 59.65; H, 4.12; N, 8.18. MS, m/z (I_{rel} (%)): 342 $[M]^+$ (5), 313 (0.5), 297 (1), 221 (5), 193 (32), 178 (11), 121 (100), 119 (10), 109 (10), 93 (25), 77 (10).

3-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (13). Found (%): C, 57.80; H, 5.84; N, 12.51. $C_{16}H_{19}N_3O_5$. Calculated (%): C, 57.65; H, 5.75; N, 12.61. MS, m/z (I_{rel} (%)): 333 $[M]^+$ (2), 251 (5), 226 (11), 225 (100), 223 (14), 208 (7), 207 (8), 109 (11), 83 (24), 82 (54), 68 (17), 55 (5).

3-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-5-(3-hydroxy-4-methoxyphenyl)-1,2,4-oxadiazole (14). Found (%): C, 58.01; H, 4.25; N, 7.49. $C_{18}H_{16}N_2O_7$. Calculated (%): C, 58.07; H, 4.33; N, 7.52. MS, m/z (I_{rel} (%)): 372 $[M]^+$ (41), 266 (29), 193 (82), 178 (17), 151 (100).

3-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-5-(4-hydroxyphenyl)-1,2,4-oxadiazole (15). Found (%): C, 59.55; H, 4.01; N, 8.02. $C_{17}H_{14}N_2O_6$. Calculated (%): C, 59.65; H, 4.12; N, 8.18. MS, m/z (I_{rel} (%)): 342 $[M]^+$ (38.5), 327 (3), 297 (10), 223 (10), 221 (15), 207 (6), 193 (54), 121 (100), 119 (11), 93 (47), 77 (18).

3-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (16). Found (%): C, 57.74; H, 5.78; N, 12.46. $C_{16}H_{19}N_3O_5$. Calculated (%): C, 57.65; H, 5.75; N, 12.61. MS, m/z (I_{rel} (%)): 333 $[M]^+$ (2), 226 (11), 225 (90), 223 (12), 208 (12), 207 (11), 109 (17), 83 (47), 82 (100), 68 (34), 55 (96).

5-(3-Hydroxy-4-methoxyphenyl)-3-(3-methoxy-4,5-methylenedioxyphenyl)-1,2,4-oxadiazole (17). Found (%): C, 59.58; H, 4.23; N, 8.07. $C_{17}H_{14}N_2O_6$. Calculated (%): C, 59.65; H, 4.12; N, 8.18. MS, m/z (I_{rel} (%)): 342 $[M]^+$ (88), 193 (26), 171 (8), 151 (100).

5-(4-Hydroxyphenyl)-3-(3-methoxy-4,5-methylenedioxyphenyl)-1,2,4-oxadiazole (18). Found (%): C, 61.75; H, 3.96; N, 8.90. $C_{16}H_{12}N_2O_5$. Calculated (%): C, 61.54; H, 3.87; N, 8.97. MS, m/z (I_{rel} (%)): 312 $[M]^+$ (79), 297 (1), 193 (89), 177 (6), 156 (17), 148 (30), 121 (100), 119 (18), 93 (41), 77 (18).

3-(3-Methoxy-4,5-methylenedioxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (19). Found (%): C, 59.43; H, 5.74; N, 14.01. $C_{15}H_{17}N_3O_4$. Calculated (%): C, 59.40; H, 5.65; N, 13.85. MS, m/z (I_{rel} (%)): 303 $[M]^+$ (4), 195 (63), 193 (12), 192 (6), 178 (6), 109 (30), 84 (6), 83 (40), 82 (100), 76 (6), 68 (26), 55 (96).

5-(4-Hydroxyphenyl)-3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazole (20). Found (%): C, 63.74; H, 3.51; N, 9.71. $C_{15}H_{10}N_2O_4$. Calculated (%): C, 63.83; H, 3.57; N, 9.92. MS, m/z (I_{rel} (%)): 282 $[M]^+$ (38), 163 (50), 162 (13), 121 (43), 119 (10), 106 (11), 105 (23), 93 (61), 77 (100).

3-(3,4-Methylenedioxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (21). Found (%): C, 61.63; H, 5.65; N, 15.21. $C_{14}H_{15}N_3O_3$. Calculated (%): C, 61.53; H, 5.53; N, 15.38. MS, m/z (I_{rel} (%)): 273 $[M]^+$ (3), 165 (27), 164 (26), 163 (11), 146 (9), 109 (17), 84 (7), 83 (38.5), 82 (100), 81 (59), 77 (13), 68 (40), 55 (95).

3-(3,4-Methylenedioxyphenyl)-5-(pyridin-4-yl)-1,2,4-oxadiazole (22). Found (%): C, 63.04; H, 3.48; N, 15.62. $C_{14}H_9N_3O_3$. Calculated (%): C, 62.92; H, 3.39; N, 15.72. MS, m/z (I_{rel} (%)): 267 $[M]^+$ (100), 266 (12), 163 (66), 162 (22), 146 (9), 133 (21), 106 (20), 78 (34), 77 (25).

3-(3,4-Methylenedioxyphenyl)-5-(pyrazin-2-yl)-1,2,4-oxadiazole (23). Found (%): C, 58.12; H, 2.94; N, 21.04. $C_{13}H_8N_4O_3$. Calculated (%): C, 58.21; H, 3.01; N, 20.89. MS, m/z (I_{rel} (%)): 268 $[M]^+$ (100), 267 (16), 239 (1), 163 (51), 162 (25), 147 (6), 146 (16), 133 (7), 107 (6), 105 (6), 79 (39), 77 (31).

5-(3-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazole (24). Found (%): C, 64.75; H, 3.96; N, 9.60. $C_{16}H_{12}N_2O_4$. Calculated (%): C, 64.86; H, 4.08; N, 9.45. MS, m/z (I_{rel} (%)): 296 $[M]^+$ (100), 163 (87), 162 (27), 147 (18), 135 (50), 133 (12), 107 (25), 77 (65).

5-(2-Ethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazole (25). Found (%): C, 65.95; H, 4.72; N, 8.84. $C_{17}H_{14}N_2O_4$. Calculated (%): C, 65.80; H, 4.55; N, 9.03. MS, m/z (I_{rel} (%)): 310 $[M]^+$ (41), 295 (3), 265 (6), 163 (38), 162 (58), 149 (8), 147 (59), 133 (92), 121 (100), 119 (48), 105 (24), 77 (48).

5-(3,4-Dimethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazole (26). Found (%): C, 62.45; H, 4.22; N, 8.72. $C_{17}H_{14}N_2O_5$. Calculated (%): C, 62.57; H, 4.32; N, 8.58. MS, m/z (I_{rel} (%)): 326 $[M]^+$ (37), 165 (100), 163 (29), 137 (8), 121 (6), 77 (29).

3,5-Bis(3,4-methylenedioxyphenyl)-1,2,4-oxadiazole (27). Found (%): C, 62.12; H, 3.33; N, 8.87. $C_{16}H_{10}N_2O_5$. Calculated (%): C, 61.94; H, 3.25; N, 9.03. MS, m/z (I_{rel} (%)): 310 $[M]^+$ (43), 163 (30), 162 (13), 149 (100), 147 (8), 146 (19), 121 (18), 77 (27).

3-(3,4-Methylenedioxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (28). Found (%): C, 60.80; H, 4.72; N, 7.76. $C_{18}H_{16}N_2O_6$. Calculated (%): C, 60.67; H, 4.53; N, 7.86. MS, m/z (I_{rel} (%)): 356 $[M]^+$ (28), 341 (1), 195 (100), 178 (13), 163 (10), 161 (8), 152 (14), 122 (6), 77(12).

3-(3,4-Dimethoxyphenyl)-5-(4-hydroxyphenyl)-1,2,4-oxadiazole (29). Found (%): C, 64.36; H, 4.67; N, 9.51. $C_{16}H_{14}N_2O_4$. Calculated (%): C, 64.42; H, 4.73; N, 9.39. MS, m/z (I_{rel} (%)): 298 $[M]^+$ (17), 179 (21), 163 (9), 136 (22), 121 (90), 119 (37), 105 (22), 93 (46), 77 (35).

3-(3,4-Dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (30). Found (%): C, 62.43; H, 6.74; N, 14.36. $C_{15}H_{19}N_3O_3$. Calculated (%): C, 62.27; H, 6.62; N, 14.52. MS, m/z (I_{rel} (%)): 289 $[M]^+$ (1), 181 (83), 179 (11), 163 (8), 109 (28), 84 (8), 83 (50), 82 (100), 77 (12), 68 (33), 55 (99).

3-(3,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (31). Found (%): C, 65.29; H, 5.09; N, 8.84. $C_{17}H_{16}N_2O_4$. Calculated (%): C, 65.38; H, 5.16; N, 8.97. MS, m/z (I_{rel} (%)): 312 $[M]^+$ (10), 283 (1), 179 (27), 164 (8), 163 (6), 136 (32), 135 (100), 133 (16), 119 (14), 107 (18), 104 (10), 92 (28), 77 (54).

3-(3,4-Dimethoxyphenyl)-5-(3-methoxyphenyl)-1,2,4-oxadiazole (32). Found (%): C, 65.48; H, 5.17; N, 9.11. $C_{17}H_{16}N_2O_4$. Calculated (%): C, 65.38; H, 5.16; N, 8.97. MS, m/z (I_{rel} (%)): 312 $[M]^+$ (8), 179 (9), 136 (23), 135 (61), 134 (15), 107 (54), 103 (23), 92 (60), 77 (100).

3-(3,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (33). Found (%): C, 61.36; H, 5.49; N, 7.64. $C_{19}H_{20}N_2O_6$. Calculated (%): C, 61.28; H, 5.41; N, 7.52. MS, m/z (I_{rel} (%)): 372 $[M]^+$ (13), 196 (95), 195 (100), 193 (6), 186 (36), 179 (37), 177 (68), 167 (18), 163 (16), 152 (56), 137 (38), 136 (40), 135 (23), 134 (37), 109 (36), 93 (45), 77 (88).

5-(2-Aminophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (34). Found (%): C, 67.48; H, 5.04; N, 15.87. $C_{15}H_{13}N_3O_2$. Calculated (%): C, 67.41; H, 4.90; N, 15.72. MS, m/z (I_{rel} (%)): 267 $[M]^+$ (6), 133 (5), 120 (100), 118 (12), 106 (7), 92 (29), 77 (8).

3-(Pyridin-4-yl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (35). Found (%): C, 61.44; H, 4.88; N, 13.36. $C_{16}H_{15}N_3O_4$. Calculated (%): C, 61.34; H, 4.83; N, 13.41. MS, m/z (I_{rel} (%)): 313 $[M]^+$ (100), 298 (52), 270 (10), 195 (44), 152 (45), 151 (45), 137 (35), 136 (15), 135 (30), 120 (27), 109 (16), 92 (15), 78 (42).

Antimitotic activity of the compounds synthesized tested on the sea urchin embryo.[22] The study was carried out in the biological laboratory of N. K. Kol´tsov Institute of Developmental Biology, Russian Academy of Sciences on Cyprus. Adult sea urchin *Paracentrotus lividus L.* (*Echinidae, Echinodermata*) were collected on the coast and kept in the aerated seawater tank. The gametes were obtained by intracoelomic injection of 0.5 *M* KCl (1—2 mL). Thus obtained eggs were washed with seawater filtered through a nylon filter and fertilized with a few drops of diluted sperm. Embryos (600—2000 eggs per 1 mL) were incubated in the filtered seawater at room temperature (18—23 °C) in six-well plates.

The stock solutions of the tested compounds were prepared in DMSO or 95% EtOH, the maximum concentrations of compounds depend on their solubility. Solubility of compounds in the solvents and seawater were monitored by microscopic examination.

The embryos were treated with solutions of compounds **11**—**35** after 10—15 min of fertilization. An egg suspension (5 mL) was placed to each well and the corresponding volume of solution of the tested compound was added to achieve the desired final concentration. The maximum solvent concentration of the solvent did not exceed the highest tolerated concentration (1% for EtOH and 0.05% for DMSO). In the tests, two-fold decreasing compound concentrations were used. Antimitotic activity was evaluated by the effective (threshold) concentration (EC) resulting cleavage alteration. The embryos development were monitored with a Biolam light microscope (LOMO, St.Petersburg, Russian Federation).

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