Novel analogs of 5-hydroxymethyl-2-methoxyphenyl adamantane-1-acetate: synthesis, biotesting, and molecular modeling

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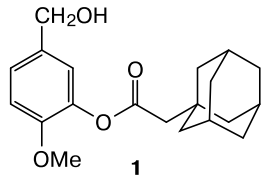
A series of novel analogs of dual-targeted antimitotic agent 5-hydroxymethyl-2-methoxyphenyl adamantane-1-acetate was synthesized. These compounds maintained the cytostatic ability of the lead molecule and induced no depolymerization of microtubules in human lung carcinoma cells A549. The importance of substituent positions in the aromatic ring for interactions with the microtubules was explained using computer molecular modeling.

Key words: adamantane, isovanillin, vanillin, chalcone, microtubules, tubulin, colchicine binding site, molecular docking, lung carcinoma A549.

Antimitotic effect of 5-hydroxymethyl-2-methoxyphenyl adamantane-1-acetate (**1**)[1] on tumor cells is related to the ability of the compound to act upon at least two cellular molecular targets.[2] One of them is unknown and is possibly attributed to receptor tyrosine kinases or retinoid receptors[3] (ligands of the latter bear adamantane-containing substances involved in various phases of clinical tests[4]) and to some other receptor and enzymatic proteins (see published examples[3,5,6]). Another molecular target of molecule **1** is cellular protein tubulin, since this compound stimulates the depolymerization of microtubules (MT) of tumor cells.[1]



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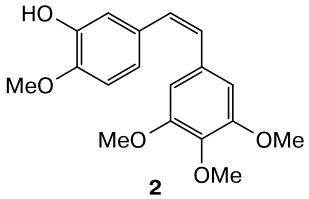

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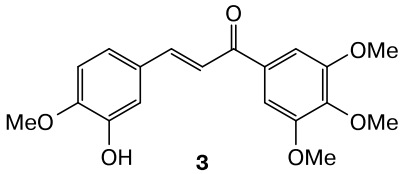


3

This action is typical for many ligands of the colchicine binding site in tubulin, for example, for combrestatin A-4 (**2**), chalcone **3**, and many others.[7—11] However, similar ligands are not characterized by the presence of adamantane as a base structural fragment (see Refs 7—11 and references cited therein).

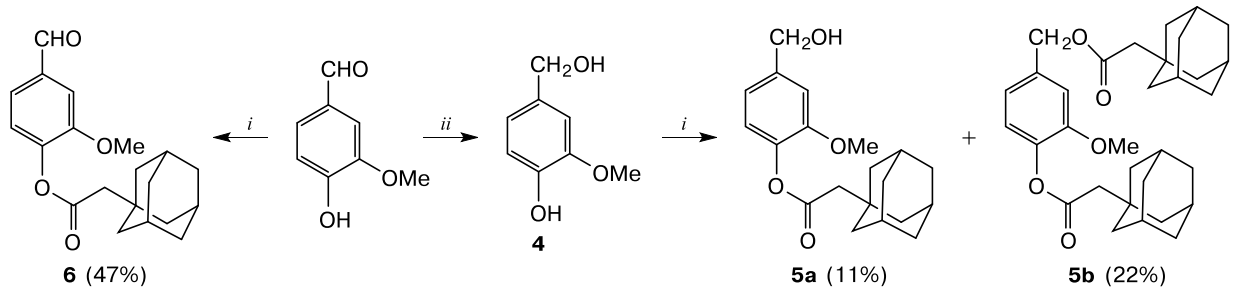
We have previously[2] studied a structure—activity relationship for a series of the derivatives of compound **1** and demonstrated an important role of adamantane and benzylic hydroxyl group for binding with tubulin and the possibility of removal of the carbonyl oxygen atom with retention of the tubulin-directed effect.[2] This work is a continuation of the indicated studies.

Results and Discussion

We carried out the synthesis (Scheme 1) and biotesting of compounds **5a** and **6** in which the isovanillin fragment of molecule **1** is replaced by the vanillin fragment as well as of more farther structural analogs of molecule **1**, namely,

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 549—554, March, 2021.
1066-5285/21/7003-0549

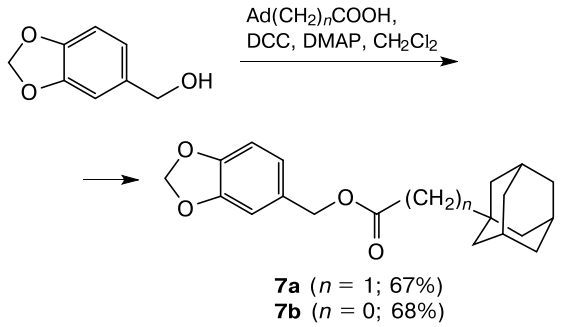
Scheme 1



Reagents and conditions: *i*. $AdCH_2COOH$, DCC, DMAP, CH_2Cl_2; *ii*. $NaBH_4$, MeOH.

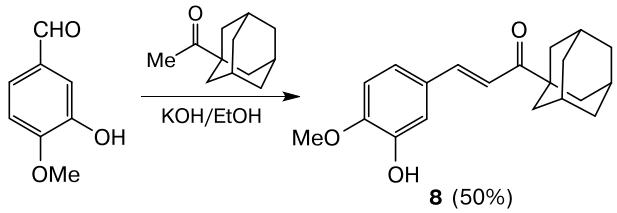
compounds **7a**,**b** and **8** (Schemes 2 and 3). Compound **8** is a combination of the structures of lead **1** and chalcone **3**.[12,13]

Scheme 2



Esters **5a**, **6**, and **7a,b** were synthesized using a standard procedure of Steglich esterification (see Schemes 1 and 2), and bis(ester) **5b** was also isolated by the chromatographic separation of a complicated mixture of products in the first case.

Scheme 3



Target compound **8** was synthesized by the condensation of 3-hydroxy-4-methoxybenzaldehyde and 1-adamant-1-yl ethanone in the presence of the base (see Scheme 3). The signals of two *trans*-protons at the double bond of compound **8** are observed in the ^1H NMR spectrum at δ 7.03 and 7.59 (spin-spin coupling constant is 15.5 Hz), and the signal of the carbonyl carbon atom is observed in the ^{13}C NMR spectrum at δ 203.92.

The influence of synthesized compounds **5a,b**, **6**, **7a,b**, and **8** on the MT network and morphology of human lung carcinoma cells A549 was studied by immunofluorescence microscopy according to earlier described procedures[14—16] (Table 1 and Fig. 1, *a*—*d*).

Table 1. Biotesting results for compounds **5a,b**, **6**, **7a,b**, and **8**

Compound	Concentration /μmol L^{-1}	Effect on microtubules (MT) and morphology of cells A549
5a	100	MT within normal, termination of cell growth, their contraction, elongation rounding of many cells and loss of adhesion
5b	100	MT within normal, termination of cell growth, their contraction, elongation rounding of many cells and loss of adhesion
6	100	MT within normal, cell contraction
7a	10	MT within normal, cell contraction
	100	MT within normal, termination of cell growth, their contraction and elongation
7b	10	MT within normal, cell contraction
	100	MT within normal, termination of cell growth, their strong contraction and elongation
8	100	MT within normal, termination of cell growth, their strong contraction and elongation

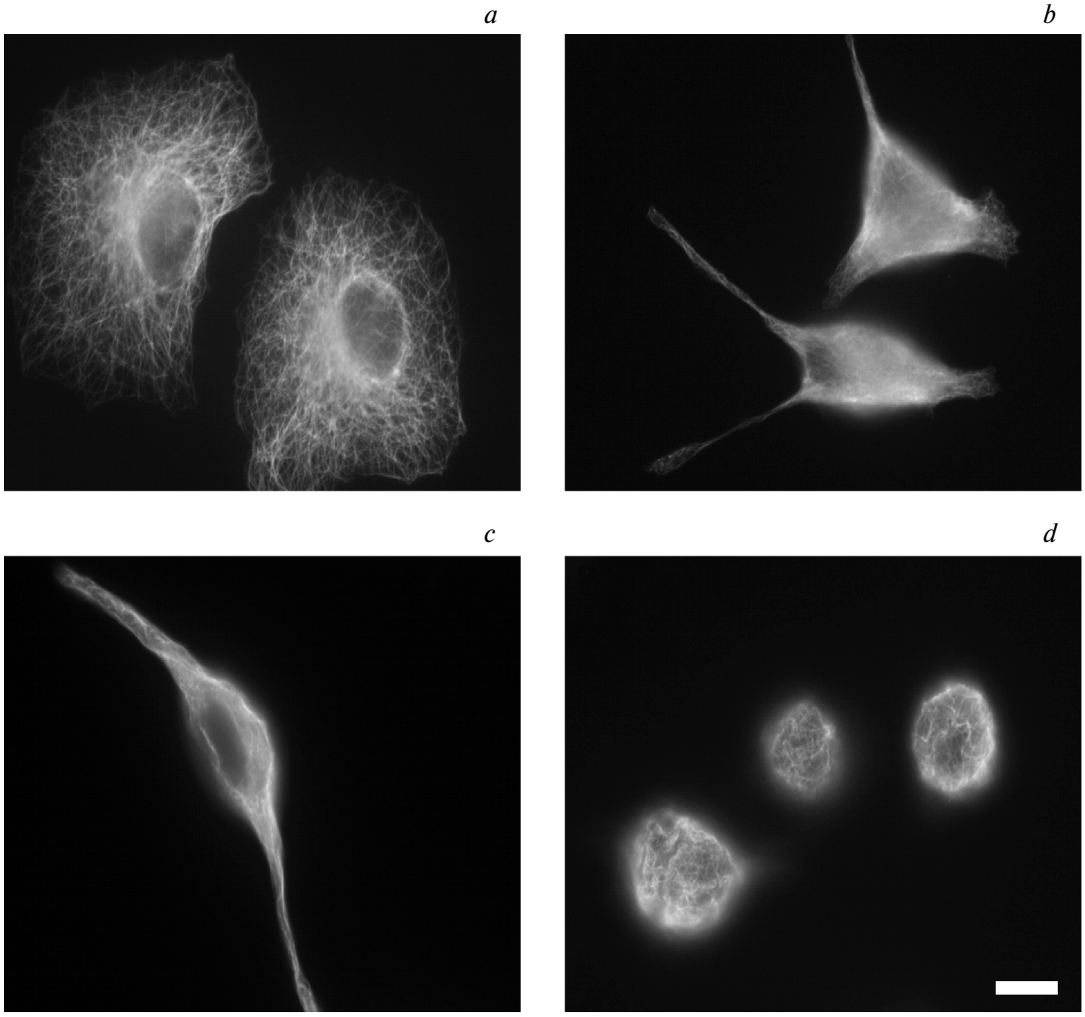


Fig. 1. Immunofluorescence microscopy of cells A549 treated with a 0.5% solution of DMSO (MT within normal) (*a*) and with solutions ($C = 100$ μmol L^{-1}) of compound **8** (MT within normal, cell contraction) (*b*), compound **5a** (MT within normal, cell elongation) (*c*), and compound **5b** (MT within normal, cell rounding) (*d*). Scale 10 μm.

As can be seen from Table 1, the vanillin analogs of the lead compound do not stimulate MT depolymerization even at a high concentration of 100 μmol L^{-1}. Nevertheless, compounds **5a,b**, **7a,b**, and **8** (but nor aldehyde **6**) terminate the cell growth and change their morphology (see Fig. 1, *c*, *d*). The incapability of compound **5a** of inducing MT depolymerization indicates an important role of the relative arrangement of substituents in the aromatic ring of lead compound **1**. This fact can be explained from the data of computer molecular modeling using the three-dimensional model of the colchicine site of tubulin in a complex with combrestatin A-4 (**2**) (PDB ID: 5LYJ). For the most favorable variant of arrangement of the structures of compounds **1** and **5a** in the protein (Fig. 2), their benzylic hydroxyl groups participate in the formation of hydrogen bonds with the carbonyl oxygen atoms of the amino acid residues Tyr202(β) (for compound **5a**) and Val315(β) and Asn350(β) (for compound **1**). However, the positions of the adamantane and aryl moieties of the ligands differ sharply, and the arrangement of lead compound **1** is closer to that for combrestatin A-4 (see Fig. 2). This can be a reason for the loss of the tubulin-directed effect of compound **5a**.

The results of testing substances **7a**,**b** and **8** demonstrate that more significant deviations from the structure of the lead molecule also result in the loss of the ability of the ligands to bind with tubulin. Note that since compound **8** is the Michael acceptor, its pronounced cytotoxic effect can be a consequence of nonspecific interactions with cellular proteins.[17] However, this does not exclude the possibility of specific binding of compound **8** with the molecular target different from tubulin. According to the biotesting data, all studied compounds do not induce apoptosis of cells A549.

Thus, the biotesting results for novel analogs of the multitarget antimitotic agent 5-hydroxymethyl-2-me-

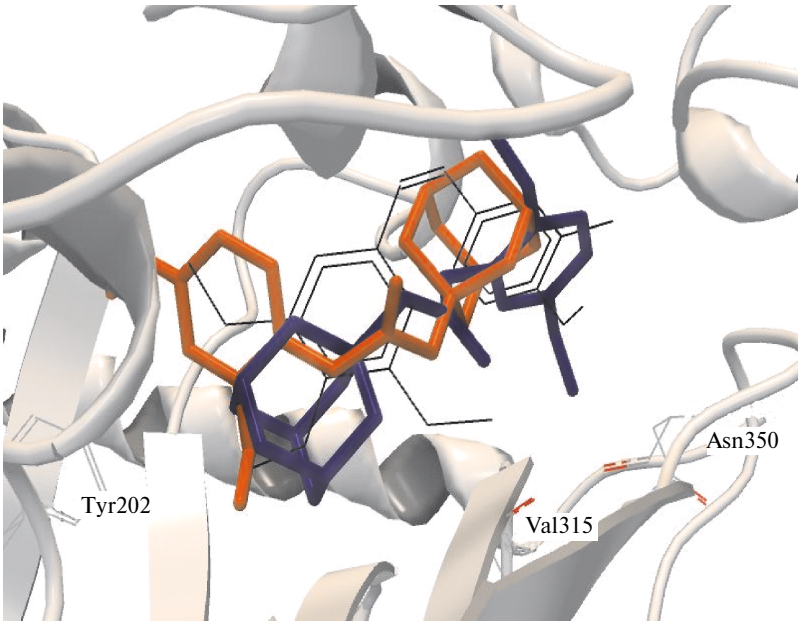


Fig. 2. Arrangement of ligands **1** (blue) and **5a** (orange) in the colchicine site of tubulin (position of combrestatin A-4 (**2**) is shown for comparison by thin black lines, and hydrogen atoms are omitted).
Note. Figure 2 is available in full color on the web page of the journal (http://link.springer.com/journal/11172/volumes-and-issues).

thoxyphenyl adamatane-1-acetate (**1**) indicate that the mutual arrangement of substituents in the aromatic ring of this compound plays an important role in the manifestation of the antitubulin effect. The adamantane analog of chalcone **3**, (2*E*)-3-(3-hydroxy-4-methoxyphenyl) adamantyl-1-prop-2-en-1-one, loses the ability to stimulate MT depolymerization, which is characteristic of compounds **1** and **3**, but retains the cytotoxic effect toward cancer cells of carcinoma A549.

Experimental

The three-dimensional model of the colchicine binding site in α,β-tubulin (PDB ID: 5LYJ) was used for molecular docking of molecules **1** and **5a**. The charges were assigned to protein atoms by the Kollman method using the AutoDock Tools 1.5.6 program. The 2D model of compound **5a** was transformed into the 3D model, and the geometries were submitted to a conformational MMFF Amber ff14SB optimization using Gasteiger charges using the USCF Chimera 1.13.1 program.[18] The docking procedure was performed using the AutoDock Vina 1.1.2 program[19] (grid box 20.25×20.25×21.0 Å, grid center size x = 20.558 Å, y = 69.278 Å, z = 45.414 Å; exhaustiveness 20). Ligand—protein complexes with the best values of the estimate functions calculated using this program were selected.

All solvents were purified according to standard procedures. The reaction course was monitored by thin-layer chromatography on the ALUGRAM Xtra G/UV254 plates. Chromatography was carried out on columns packed with silica gel Macherey–Nagel (0.063—0.2 mm). ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 400-MR spectrometer (400 and 100 MHz, respectively) at 28 °C. Chemical shifts are presented relative to the residual signal of $CDCl_3$: δ_H = 7.24, δ_C = 77.0. The MALDI-TOF mass spectrum was detected on a Bruker Autoflex II instrument in the reflectron mode (acceleration voltage 20 kV). Elemental analysis of compound **5b** was conducted on a Carlo-Erba CHN analyzer, and that of compound **8** was carried out on a MicroCube Elementar analyzer. The following commercially available initial reagents were used: 4-hydroxy-3-methoxybenzaldehyde, *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-*N*,*N*-dimethylaminopyridine (DMAP), and 1-adamantanecarboxylic and 1-adamantaneacetic acids (Sigma—Aldrich). 4-(Hydroxymethyl)-2-methoxyphenol (**2**) was synthesized by the reduction of 4-hydroxy-3-methoxybenzaldehyde with sodium boron hydride in methanol.

General procedure of the Steglich esterification. 1-Adamantanecarboxylic or 1-adamantaneacetic acid was dissolved in CH_2Cl_2 (5—10 mL), and an equivalent amount of alcohol, an equivalent amount of DCC, and a catalytic amount of DMAP (0.05 g) were added. The mixture was stirred at ~20 °C for 6 h, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), and the solution was kept at 4 °C for 1 h. The precipitate was filtered off and washed with cold ethyl acetate, and the solvent was removed under reduced pressure. The residue was chromatographed (eluent is indicated for each compound).

4-Hydroxymethyl-2-methoxyphenyl adamantane-1-acetate (5a) and **4-[2-(adamantan-1-yl)acetoxy]-3-methoxybenzyl-2-(adamantan-1-yl)acetate (5b)** were synthesized according to the general procedure from 1-adamantaneacetic acid (0.106 g, 0.545 mmol) and 4-(hydroxymethyl)-2-methoxyphenol (0.086 g, 0.545 mmol). An ethyl acetate—petroleum ether mixture (40—70 °C, gradient 1 : 7—1 : 5) served as the eluent for chromatography. Compound **5b** eluted first: yield 0.060 g (22%), colorless oily liquid; then compound **5a** eluted: yield 0.020 g (11%), colorless waxy substance.

Compound 5a. ^{1}H NMR ($CDCl_3$), δ: 1.66—1.77 (m, 12 H, H_{Ad}); 2.02 (m, 3 H, H_{Ad}); 2.33 (s, 2 H, AdC$\underline{H}_2$); 3.85 (s, 3 H, OCH_3); 4.68 (s, 2 H, C$\underline{H}_2$OH); 6.91 (dd, 1 H, C(5)H, *J* = 1.65 Hz, *J* = 8.07 Hz); 6.99—7.01 (m, 1 H, C(6)H); 7.02 (d, 1 H, C(3)H, *J* = 1.65 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.7, 33.1, 36.8, 42.3, 48.6 (Ad$\underline{C}H_2$); 55.7 (O$\underline{C}H_3$); 65.1 ($\underline{C}H_2$OH); 111.0 (C(3)); 118.9 (C(5)); 122.9 (C(6)); 139.1 (C(4)); 139.7 (C(1)); 151.2 (C(2)); 169.7 (C=O). Found (%): C, 72.65; H, 7.89. $C_{20}H_{26}O_4$. Calculated (%): C, 72.70; H, 7.93.

Compound 5b. ^{1}H NMR ($CDCl_3$), δ: 1.62—1.63 (m, 9 H, H_{Ad}); 1.67—1.73 (m, 8 H, H_{Ad}); 1.76—1.77 (m, 7 H, H_{Ad}); 1.97 (m, 3 H, H_{Ad}); 2.02 (m, 3 H, H_{Ad}); 2.13 (s, 2 H, AdC$\underline{H}_2$); 2.33 (s, 2 H, AdC$\underline{H}_2$); 3.83 (s, 3 H, OCH_3); 5.08 (s, 2 H, C$\underline{H}_2$O); 6.94 (dd, 1 H, C(5)H, *J* = 1.7 Hz, *J* = 8.0 Hz); 6.98 (d, 1 H, C(3)H, *J* = 1.7 Hz); 7.01 (d, 1 H, C(6)H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.5, 28.6, 32.9, 33.1, 36.7, 36.8, 42.2, 42.4, 48.5 (Ad$\underline{C}H_2$); 48.9 (Ad$\underline{C}H_2$); 55.7 (O$\underline{C}H_3$); 65.4 ($\underline{C}H_2$O); 112.4 (C(3)); 120.5 (C(6)); 122.9 (C(5)); 134.9 (C(4)); 139.5 (C(1)); 151.1 (C(2)); 169.5 (C=O); 171.5 (C=O). MS (MALDI-TOF): found *m/z* 506 $[M]^+$, 529 $[M + Na]^+$, 545 $[M + K]^+$; calculated for $C_{32}H_{42}O_5$ 506.

4-Formyl-2-methoxyphenyl-adamantane-1-acetate (6) was synthesized according to the general procedure from 1-adamantaneacetic acid (0.128 g, 0.66 mmol) and 3-methoxy-4-hydroxybenzaldehyde (0.100 g, 0.66 mmol). Ethyl acetate—petroleum ether (40—70 °C, 1 : 7) served as the eluent for chromatography. The yield was 0.101 g (47%), white powder, m.p. 90 °C. ^{1}H NMR ($CDCl_3$), δ: 1.66—1.77 (m, 12 H, HAd); 2.02 (m, 3 H, HAd); 2.35 (s, 2 H, $AdCH_2$); 3.90 (s, 3 H, OCH_3); 7.20 (d, 1 H, C(6) H, *J* = 7.9 Hz); 7.47 (dd, 1 H, C(5)H, *J* = 1.8 Hz, *J* = 7.9 Hz); 7.50 (d, 1 H, C(3)H, *J* = 1.7 Hz); 9.94 (s, 1 H, C(O)H). ^{13}C NMR ($CDCl_3$), δ: 28.6, 33.1, 36.7, 42.2, 48.4 (Ad$\underline{C}H_2$); 55.8 (O$\underline{C}H_3$); 110.7 (C(3)); 123.5 (C(6)); 124.6 (C(5)); 135.0 (C(4)); 145.0 (C(1)); 151.9 (C(2)); 168.9 (C=O), 191.0 (C(O)H). MS (MALDI-TOF): found *m/z* 351 $[M + Na]^+$, 367 $[M + K]^+$; calculated for $C_{20}H_{24}O_4$ 328.4.

1,3-Benzodioxol-5-ylmethyl adamantane-1-acetate (7a) was synthesized using the general procedure from 1-adamantaneacetic acid (0.1 g, 0.51 mmol) and 1,3-benzodioxol-5-ylmethanol (0.078 g, 0.51 mmol). Ethyl acetate—petroleum ether (40—70 °C, 1 : 10) served as the eluent for chromatography. The yield was 0.112 g (67%), pale yellow oily liquid. ^{1}H NMR ($CDCl_3$), δ: 1.58—1.68 (m, 12 H, H_{Ad}); 1.93 (s, 3 H, H_{Ad}); 2.07 (s, 2 H, AdC$\underline{H}_2$); 4.97 (s, 2 H, ArC$\underline{H}_2$); 5.93 (s, 2 H, OC$\underline{H}_2$O); 6.75 (d, 1 H, C(5)H, *J* = 7.66 Hz); 6.82 (dd, 2 H, C(2)H, C(6)H, *J* = 1.73 Hz, *J* = 8.81 Hz). ^{13}C NMR ($CDCl_3$), δ: 29.0, 33.2, 37.1, 42.8 ($C(1)_{Ad}$)); 49.3 (Ad$\underline{C}H_2$); 66.2 (Ar$\underline{C}H_2$); 101.5 (O$\underline{C}H_2$O); 108.6 (C(2)); 109.5 (C(5)); 122.6 (C(6)); 130.4 (C(1)); 147.9 (C(4)); 148.1 (C(3)); 172.0 (C=O). MS (MALDI-TOF): found *m/z* 328 $[M]^+$, 351 $[M + Na]^+$, 367 $[M + K]^+$; calculated for $C_{20}H_{24}O_4$ 328.4.

1,3-Benzodioxol-5-ylmethyl adamantane-1-carboxylate (7b) was synthesized according to the general procedure from 1-adamantaneacetic acid (0.1 g, 0.56 mmol) and 1,3-benzodioxol-5-ylmethanol (0.085 g, 0.56 mmol). Ethyl acetate—petroleum ether (40—70 °C, 1 : 10) served as the eluent for chromatography. The yield was 0.120 g (68%), white solid, m.p. 74—75 °C ^{1}H NMR ($CDCl_3$), δ: 1.65—1.72 (m, 6 H, H_{Ad}); 1.88 (d, 6 H, H_{Ad}, *J* = 2.89 Hz); 1.99 (s, 3 H, H_{Ad}); 4.97 (s, 2 H, ArC$\underline{H}_2$); 5.94 (s, 2 H, OC$\underline{H}_2$O); 6.76 (dd, 1 H, C(5)H, *J* = 0.58 Hz, *J* = 7.22 Hz); 6.79 (dd, 2 H, C(2)H, C(6)H, *J* = 1.59 Hz, *J* = 8.53 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.3, 36.9, 39.2, 41.2 ($C(1)_{Ad}$)); 66.2 (Ar$\underline{C}H_2$); 101.5 (O$\underline{C}H_2$O); 108.6 (C(2)); 109.9 (C(5)); 122.0 (C(6)); 130.7 (C(1)); 147.7 (C(4)); 148.1 (C(3)); 177.8 (C=O). MS (MALDI-TOF): found *m/z* 314 $[M]^+$, 337 $[M + Na]^+$, 353 $[M + K]^+$; C calculated for $C_{19}H_{22}O_4$ 314.4.

(2*E*)-3-(3-Hydroxy-4-methoxyphenyl) adamantane-1-prop-2-en-1-one (8). Sodium hydroxide (0.029 g, 0.728 mmol) was added with stirring to a solution of 1-adamant-1-yl ethanone (0.1 g, 0.56 mmol) in ethanol (5 mL). 3-Hydroxy-4-methoxybenzaldehyde (0.085 g, 0.56 mmol) was added to the mixture, and the reaction mixture was stirred at ~20 °C for 24 h. The solvent was evaporated under reduced pressure. The residue was chromatographed. Ethyl acetate—petroleum ether (40—70 °C, gradient 1 : 7—1 : 5) served as the eluent for chromatography. The yield was 0.088 g (50%), white crystals, m.p. 142 °C. ^{1}H NMR ($CDCl_3$), δ: 1.72—1.81 (m, 6 H, H_{Ad}); 1.88 (d, 6 H, H_{Ad}, *J* = 2.8 Hz); 2.09 (m, 3 H, H_{Ad}); 3.94 (s, 3 H, OC$\underline{H}_3$); 5.67 (m, 1 H, OH); 6.84 (d, 1 H, *J* = 8.2 Hz); 7.03 (d, 1 H, CH=C$\underline{H}$—C(O), *J* = 15.5 Hz); 7.06 (dd, 1 H, *J* = 2.0 Hz, *J* = 8.2 Hz); 7.23 (d, 1 H, *J* = 2.0 Hz); 7.59 (d, 1 H, C$\underline{H}$=CH—C(O), *J* = 15.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.0, 36.6, 38.2, 45.4 ($C(1)_{Ad}$); 56.0 (OCH_3); 110.4, 112.7 (OCH_2O); 118.6, 122.5 (CH=$\underline{C}$HC(O)); 128.7, 142.6 ($\underline{C}$H=CHC(O)); 145.7, 148.4, 203.9 (C=O). Found (%): C, 76.82; H, 7.71. $C_{20}H_{24}O_3$. Calculated (%): C, 76.89; H, 7.74.

Morphology of cells and microtubules was studied on lung carcinoma cells A549 (CCL-185™) by immunofluorescence microscopy. The cells were cultivated on small cover glasses, incubated for 24 h together with the tested compounds in a concentration of 10 or 100 μmol L^{-1} at 37 °C and 5% CO_2 (0.5% DMSO was used as the negative control).The fixed cells were stained using primary mouse monoclonal antibodies to α-tubulin (Sigma, USA) followed by incubation with secondary goat antibodies against mouse immunoglobulins fluorescently labeled with AlexaFlour488 (Molecular Probes, USA). The cells were analyzed with a Nikon Diaphot 300 microscope (Nikon GmbH, Germany) equipped with a SenSys camera (Photometrics, Germany). The procedure was described in detail.[14—16]

This work was financially supported by the Russian Science Foundation (Project No. 19-13-00084). The synthesis and biotesting of compound **7a** were performed in terms of state assignment AAAA-A16-116032250004-2. The authors are grateful to the German Academic Exchange Service.

This paper does not contain description of studies on animals or humans.

The authors declare no competing interests.

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Received October 27, 2020;
in revised form December 21, 2020;
accepted January 13, 2021