CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Synthesis of ethers containing 1,3-dioxolane and *gem*-dichlorocyclopropane fragments

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Abstract

Objectives. *This study aimed to obtain ethers containing gem-dichlorocyclopropane and 1,3-dioxolane fragments and evaluate their cytotoxic properties against HEK293, SH-SY5Y, MCF-7, and A549 cell lines.*

Methods. *The qualitative and quantitative compositions of the reaction masses were determined using mass spectrometry (using a Chromatek-Kristall 5000M device with the 2012 National Institute of Standards and Technology, USA database) and nuclear magnetic resonance spectroscopy (using a Bruker AM-500 device with operating frequencies of 500 and 125 MHz).*

Results. *Ethers containing gem-dichlorocyclopropane and 1,3-dioxolane fragments were synthesized in the presence of a catamine AB catalyst. The structures of the obtained substances were confirmed using gas-liquid chromatography, mass spectrometry, and nuclear magnetic resonance spectroscopy. The cytotoxicity of the esters was studied against HEK293, SH-SY5Y, MCF-7, and A549 cell lines.*

Conclusions. *Ethers containing gem-dichlorocyclopropane and 1,3-dioxolane fragments were obtained in quantitative yields; however, only 4-{[(2,2-dichloro-3-{[(2,2-dichlorocyclopropyl) methoxy]methyl}cyclopropyl)methoxy]methyl}-2,2-dimethyl-1,3-dioxolane exhibited cytotoxic activity against HEK293, SH-SY5Y, MCF-7, and A549 cell lines.*

Keywords: *2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane, carbenation, cell lines, cytotoxicity*

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НАУЧНАЯ СТАТЬЯ

Синтез простых эфиров, содержащих 1,3-диоксолановый и *гем*-дихлорциклопропановый фрагменты

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Аннотация

Цели. *Получить простые эфиры, содержащие гем-дихлорциклопропановый и 1,3-диоксолановый фрагменты и оценить их цитотоксические свойства в отношении клеточных линий HEK293, SH-SY5Y, MCF-7 и A549.*
Методы. *Для определения качественного и количественного состава реакционных масс были использованы следующие методы анализа: газожидкостная хроматография (на аппаратно-программном комплексе «Кристалл 2000»), масс-спектрометрия (на приборе «Хроматэк-Кристалл 5000М» с базой NIST 2012), и спектроскопия ядерного магнитного резонанса (ЯМР-спектроскопия) (на приборе «Bruker AM-500» с рабочими частотами 500 и 125 МГц).*
Результаты. *Синтезированы простые эфиры, содержащие гем-дихлорциклопропановый и 1,3-диоксолановый фрагменты в присутствии катализатора катамина АВ. Строение полученных веществ было подтверждено с помощью газожидкостной хроматографии, масс-спектрометрии и ЯМР-спектроскопии. Для эфиров изучена цитотоксическая активность в отношении клеточных линий HEK293, SH-SY5Y, MCF-7 и A549.*
Выводы. *С количественными выходами получены простые эфиры, содержащие гем-дихлорциклопропановый и 1,3-диоксолановый фрагменты. Установлено, что цитотоксическую активность в отношении клеточных линий HEK293, SH-SY5Y, MCF-7 и A549 среди ряда полученных соединений проявляет только 4-{[(2,2-дихлоро-3-{[(2,2-дихлорциклопропил)метокси]метил}циклопропил)метокси]метил}-2,2-диметил-1,3-диоксолан.*

Ключевые слова: *2,2-диметил-4-оксиметил-1,3-диоксолан, карбенирование, клеточные линии, цитотоксичность*

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INTRODUCTION

Compounds containing cycloacetal and *gem*-dichlorocyclopropane fragments are important intermediate and final products in the pharmaceutical, perfume, and polymer industries and, depending on the structure of the substituents, exhibit a wide spectrum of biological activity [1–10]. For example, 2-{(4R)-4[(benzyloxy)-methyl]-1,3-dioxolan-2-yl}phenol, diisopropyl-(4R-5R)-2-(2-hydroxyphenyl)-1,3-dioxolane-4,5-dicarboxylate, diisopropyl-2-(2-hydroxyphenyl)-1,3-dioxolane-4,5-dicarboxylate, dimethyl 2-(2-hydroxyphenyl)-1,3-dioxolane-4,5-dicarboxylate, and 2-[(4S,5S)-4,5-bis(benzyloxymethyl)-1,3-dioxolane-2-yl] phenol have been shown to exhibit pronounced antibacterial properties against *Staphylococcus aureus* and *Staphylococcus epidermidis* as well as antifungal activity against *Candida albicans* [5].

Özkanli and co-authors, demonstrated that new derivatives of 2-acetylnaphthalene with the dioxolane structure have an anticonvulsant effect [11]. In addition, it has been shown that 1,3-dioxolane heterocyclic compounds are not only effective anticancer agents but are able to overcome the phenomenon of multidrug resistance, which is one of the main problems in successful cancer therapy [12]. We have previously reported compounds containing 1,3-dioxolane and *gem*-dichlorocyclopropane fragments with potential antitumor activity [3], and these heterocyclic compounds have also been shown to have herbicidal [1], antioxidant [3], antiviral [13, 14], anticoagulant, antiaggregatory [7], and anesthetic [15] activities. This breadth of activities and the fact that many groups are only partially studied means that the synthesis of novel 1,3-dioxolane and *gem*-dichlorocyclopropane fragment-containing compounds is a promising route to finding biologically active substances.

This study aimed to develop new methods for preparing novel bi- and polycyclic compounds, where 1,3-dioxolane and *gem*-dichlorocyclopropane fragments are bound by the stable but mobile CH_2–O–CH_2 group in acidic and alkaline media, as well as assessing their cytotoxic properties *in vitro*.

MATERIALS AND METHODS

The analysis of the reaction masses and the recording of the mass spectra of the compounds were carried out on a Chromatec-Kristall 5000M (*CHROMATEC*, Russia) hardware–software complex using the National Institute of Standards and Technology 2012 database (NIST, USA). The analysis conditions were as follows: 30 m long capillary quartz column, 20 min duration, 260°C ion source, 300°C transition line, 30–300 Da scanning range, 37–43 mTorr pressure, helium carrier gas, and a heating rate of 20°C/min. The mass spectra of the compounds were obtained using electron impact ionization. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AM-500 spectrometer (*Bruker Corporation*, USA) with operating frequencies of 500 and 125 MHz, respectively, and a $CDCl_3$ solvent. The chemical shifts were reported on a δ (ppm) scale relative to an internal tetramethylsilane standard. Spin-spin coupling constants (*J*) were recorded in Hz.

Synthesis of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane 1. A mixture of 0.49 mol of glycerol, 49 mol of acetone, and 0.22 g of *p*-toluenesulfonic acid was vigorously stirred at room temperature for 18 h followed by the addition of 3 g (anhydrous) K_2CO_3 and stirring for 1 h. The mixture was then filtered, concentrated, and the residue distilled at reduced pressure.

Physicochemical constants corresponded with previously reported data [16–22].

Synthesis of compounds 4–6, 11, and 15. Catamin-AB catalyst (0.22 g) and 100 g of 50% NaOH solution were added with vigorous stirring at 50°C (or 30°C for allyl chloride) to a solution of 0.06 mol 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane in 60 mL of benzene. After 2 h, 0.30 mol of the corresponding halogenated derivatives were added dropwise. Upon completion of the reaction, the mixture was washed with water, extracted with ethoxyethane (3 × 30 mL), and dried over anhydrous $MgSO_4$. Following the removal of the solvent, the residue was distilled under reduced pressure (a detailed procedure is described in [23]).

According to this method, the following were obtained:

4-[(Allyloxy)methyl]-2,2-dimethyl-1,3-dioxolane 4. The NMR spectrum of the compound is given in [24]. Yield (**4**) 90%, boiling temperature bp = 52–54°C (10 mm Hg). Mass spectrum, *m*/*z* (I_{rel}, %): 172 (≤2) [M]+, 157/70, 101/100, 73/25, 55/30.

4-({[(2Z)-4-chlorobut-2-en-1-yl]oxy}-methyl)-2,2-dimethyl-1,3-dioxolane 5. Yield (**5**) 80%, bp = 81–83°C (5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.33 t (3H, CH_3, *J* = 7.0), 1.40 t (3H, CH_3, *J* = 7.3), 3.44 t (1H, C^6H_a, *J* = 9.9, 5.2), 3.51 d (1H, C^6H_b, *J* = 10.0, 3.0), 3.70 t (1H, C^5H_a, *J* = 8.2, 6.4), 4.03 d (1H, C^5H_b, *J* = 8.2, 6.5), 4.09 d (2H, C^7H_2, *J* = 11.8, 7.5), 4.14 d (2H, $C^{10}H_2$, *J* = 11.1, 5.8), 4.22–4.27 m (1H, C^4H), 5.69–5.81 m (2H, C^8H, C^9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.31 (CH_3), 26.68 (CH_3), 38.98 (C^{10}), 63.88 (C^5), 66.62 (C^6), 71.33 (C^7), 74.65 (C^4), 109.44 (C^2), 128.37 (C^8), 130.53 (C^9). Mass spectrum, *m*/*z* (I_{rel}, %): 220/222 (≤1) $[M]^+$, 205/207 (40/15), 115/117 (10/5), 101/100, 89/91 (55/30), 73 (25), 43 (90).

4,4-[(2Z)-but-2-en-1,4-diyl(oxymethylene)]-bis-(2,2-dimethyl-1,3-dioxolane) 6. Yield (**6**) 60%, bp = 101–103°C (3 mm Hg). ^{1}H NMR spectrum

($CDCl_3$), δ, ppm (*J*, Hz): 1.35 s (6H, 2 CH_3), 1.42 s (6H, 2 CH_3), 3.44 t (2H, $C^{6+6"}H_a$, *J* = 9.1, 6.9), 3.51 d (2H, $C^{6+6"}H_b$, *J* = 10.7, 7.0), 3.72 t (2H, $C^{5+5"}$Ha, *J* = 8.0, 6.2), 4.00 d (2H, $C^{5+5"}$Hb, *J* = 8.2, 6.1), 4.08 dt (4H, $C^{7+10}H_a$, *J* = 11.8, 7.5), 4.15 dd (4H, $C^{7+10}H_b$, *J* = 11.1, 5.8), 4.24–4.29 m (1H, $C^{4+4"}$H), 5.69–5.81 m (2H, C^8H, C^9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.28 (CH_3), 26.44 (CH_3), 64.23 ($C^{5+5"}$), 66.62 ($C^{6+6"}$), 71.35 (C^{7+10}), 73.69 ($C^{4+4"}$), 109.44 ($C^{2+2"}$), 127.32 (C^8), 130.55 (C^9). Mass spectrum, *m*/*z* (I_{rel}, %): 316 (≤1) $[M]^+$, 300 (70), 215 (50), 101 (100), 73 (20), 43 (70).

4-({[(2Z)-4-(alloxy)-but-2-en-1-yl]oxy}methyl)-2,2-dimethyl-1,3-dioxolane 11. Yield (**11**) 40%, bp = 99–101°C (4 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.41 t (3H, CH_3, *J* = 7.7), 1.45 t (3H, CH_3, *J* = 7.5), 3.45 t (1H, C^6H_a, *J* = 8.9, 5.9), 3.54 д (1H, C^6H_b, *J* = 10.0), 3.74 t (1H, C^5H_a, *J* = 8.0, 6.0), 4.11 d (1H, C^5H_b, *J* = 8.2), 3.72 t (1H, $C^{11}H_a$, *J* = 10.3, 5.8), 4.06 d (3H, $C^{11}H_b$, *J* = 5.9), 4.09 d (2H, C^7H_2, *J* = 7.7), 4.17 t (2H, $C^{10}H_2$, *J* = 10.4, 5.9), 4.25–4.29 m (1H, C^4H), 5.18 d (1H, $C^{13}H_a$, *J* = 1.3, 10.4), 5.26 d (1H, $C^{13}H_b$, *J* = 15.0), 5.83–5.93 m (1H, C^{12}H), 5.70–5.81 m (2H, C^8H, C^9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.31 (CH_3), 26.68 (CH_3), 63.84 (C^{10}), 65.30 (C^5), 67.02 (C^6), 67.77 (C^7), 69.32 (C^{11}), 71.55 (C^4), 107.50 (C^2), 122.92 (C^{13}), 127.93 (C^9), 131.02 (C^8). 132.53 (C^{12}). Mass spectrum, *m*/*z* (I_{rel}, %): 242 (≤3) $[M]^+$, 300 (70), 275 (60), 215 (35), 145 (60), 101 (100), 73 (34), 43 (50).

4-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolane 15. ЯМР спектр соединения описан в работе [25]. Yield (**15**) 90%, bp = 138°C (5 mm Hg). Mass spectrum *m*/*z* (I_{rel}, %): 222 (≤1) $[M]^+$, 207 (27), 164 (34), 101 (41), 91 (100), 43 (23).

4-[(2-chloromethyl-benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolane 16. Yield (**16**) 90%, bp = 138°C (5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.33 t (3H, CH_3, *J* = 7.5), 1.41 t (3H, CH_3, 6.8), 3.49 t (1H, C^6H_a, *J* = 11.5), 3.54 d (1H, C^6H_b, *J* = 11.2), 3.67 t (1H, C^5H_a, *J* = 9.6), 3.78 d (1H, C^5H_b, *J* = 10.0), 4.45–4.82 m (1H, C_4H), 4.89 (s, 1H, C^8H_a), 4.91 (s, 1H, C^8H_a), 7.07–7.16 m (4H, 4 CH). ^{13}C NMR spectrum, δ_C, ppm: 25.47 (CH_3), 26.54 (CH_3), 47.13 (C^8H_2), 66.43 (C^5H_2), 67.83 (C^6H_2), 68.37 (C^7H_2), 68.28 (C^4H), 105.29 (C^2), 127.07–139.61 (Ph). Масс-спектр *m*/*z* (I_{rel}, %): 270/272 (≤1) $[M]^+$, 255/257 (25/5), 101 (40), 73 (56), 91 (70), 77 (100), 41 (30).

Synthesis of compounds 7–9 and 12. Compounds **7**–**9** and **12** were obtained similarly to the procedure [25–27] using chloroform, 50% alkali solution, and catamine AB phase transfer catalyst.

4-{[(2,2-dichlorocyclopropyl)methoxy]-methyl}-2,2-dimethyl-1,3-dioxolane 7. Yield (**7**) 70%, bp = 74–76°C (8 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95–0.1.04 m (1H, C^8H), 1.37 t (3H, CH_3, *J* = 7.0), 1.43 t (3H, CH_3, 6.8), 1.62 t (1H, C^9H_a, *J* = 5.3), 1.68 d (1H, C^9H_b, *J* = 5.4), 3.45 t (1H, C^7H_a, *J* = 11.0, 7.0), 3.57 d (1H, C^7H_b, *J* = 11.2), 3.61 t (1H, C^6H_a, *J* = 9.0, 7.0), 3.69 d (1H, C^6H_b, *J* = 8.9), 3.84 d (1H, C^5H_a, *J* = 6.0), 4.02 t (1H, C^5H_b, *J* = 6.7), 4.33–4.38 m (1H, C^4H). ^{13}C NMR spectrum, δ_C, ppm: 24.52 (CH_2), 25.46 (CH_3), 27.34 (CH_3), 28.49 (CH), 61.03 (C), 67.83 (CH_2), 68.58 (CH_2), 69.42 (CH_2), 69.78 (CH), 108.96 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 225/227/229 (≤3) $[M]^+$, 219/221 (40/15), 145 (45), 115/117 (30/8), 101 (100), 89/91 (60/35), 43 (80).

4-({[2,2-dichloro-3-(chloromethyl)-cyclopropyl]methoxy}methyl)-2,2-dimethyl-1,3-dioxolane 8. Yield (**8**) 50%, bp = 88–90°C (8 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 t (3H, CH_3, *J* = 7.0), 1.41 t (3H, CH_3, *J* = 6.8), 1.54–1.58 m (1H, C^8H), 1.78–1.85 m (1H, C^9H), 3.46 t (1H, C^7H_a, *J* = 9.0), 3.51 d (1H, C^7H_b, *J* = 9.3), 3.63 t (1H, $C^{10}H_a$, *J* = 9.2), 3.71 d (1H, $C^{10}H_b$, *J* = 8.8), 3.88 d (1H, C^6H_a, *J* = 6.5), 3.93 t (1H, C^6H_b, *J* = 6.6), 4.04 d (1H, C^5H_a, *J* = 6.8), 4.07 t (1H, C^5H_b, *J* = 6.5), 4.28–4.35 m (1H, C^4H). ^{13}C NMR spectrum, δ_C, ppm: 24.48 (CH_3), 25.49 (CH_3), 34.87 (C^9H), 36.39 (C^8H), 43.42 ($C^{10}H_2$), 63.06 (C), 67.86 (C^6H_2), 68.73 (C^7H_2), 69.42 (C^5H_2), 71.74 (C^4H), 108.69 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 304/306/308 (≤2) $[M]^+$, 269/271/273 (35/15/4), 219/221 (60/45), 145/65, 101/100, 89/91 (30/15), 41 (70).

4.4-[(3,3dichlorocyclopropane-1,2-diyl) bis(methyleneoxymethylene)]bis(2,2-dimethyl-1,3-dioxolane) 9. Yield (**9**) 60%, bp = 102–104°C (5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.29 t (3H, CH_3, *J* = 6.9), 1.34 t (3H, CH_3, *J* = 6.7), 2.24 dt (2H, 2 C^{8+9}H, *J* = 5.9, 8.9), 3.39 t (2H, 2 $C^{7+10}H_a$, *J* = 10.9), 3.42 d (2H, 2 $C^{7+10}H_b$, *J* = 10.2), 3.56 t (2H, 2 $C^{6+6"}H_a$, *J* = 9.6), 3.63 d (2H, 2 $C^{6+6"}H_b$, *J* = 8.2), 3.82 d (2H, 2 $C^{5+5"}H_a$, *J* = 6.4), 4.00 t (2H, 2 $C^{5+5"}H_b$, *J* = 6.6), 4.45–4.60 m (2H, 2 $C^{4+4"}$H). ^{13}C NMR spectrum, δ_C, ppm: 25.45 (CH_3), 26.30 (CH_3), 34.76 (2 C^{8+9}H), 64.55 (C), 67.93 (2 $C^{5+5"}H_2$), 68.81 (2 $C^{7+10}H_2$), 72.66 (2 $C^{6+6"}H_2$), 72.75 (2 $C^{4+4"}$H), 106.44 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 400/402/404 (≤10) $[M]^+$, 384/386/388 (30/14/6), 298/300/302 (40/22/12), 145/40, 115/117 (32/11), 101/100, 89/91 (80/30), 43 (80), 41 (50).

4-{[(2,2-dichloro-3-{[(2,2-dichlorocyclopropyl)-methoxy]methyl}-cyclopropyl)methoxy]methyl}-2,2-dimethyl-1,3-dioxolane 12. Yield (**12**) 50%, bp = 134–136°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.90–1.01 m (1H, C^{12}H), 1.26 t (3H, CH_3, *J* = 6.4), 1.31 t (3H, CH_3, *J* = 6.3), 1.57 t (1H, $C^{13}H_a$, *J* = 6.9), 1.62 d (1H, $C^{13}H_b$, *J* = 5.9), 2.05 qu (1H, C^8H, *J* = 9.7), 2.23 qu (1H, C^9H, *J* = 9.9), 3.56–3.61 m (4H, 2 $C^{7+10}H_2$), 3.66 t (1H, $C^{11}H_a$, *J* = 10.0), 3.73 d

(1H, $C^{11}H_b$, J = 9.9), 3.85 d (1H, C_6H_a, J = 7.9), 4.00 t (1H, C^6H_b, J = 6.9), 4.22 d (1H, C^5H_a, J = 6.9), 4.25 t (1H, C^5H_b, J = 7.8), 4.42–4.63 m (1H, C^4H). ^{13}C NMR spectrum, δ_C, ppm: 24.44 ($C^{13}H_2$), 25.45 (CH_3), 26.30 (CH_3), 28.56 ($C^{12}H$), 35.39 (2 $C^{8+9}H$), 61.20 (C), 63.91 (C), 67.58 (C^5H_2), 67.92 ($C^{10}H_2$), 69.34 ($C^{11}H_2$), 70.62 (C^6H_2), 71.28 (C^7H_2), 72.55 (C^4H), 110.29 (C). Mass spectrum, m/z (I_{rel}, %): 408/410/412/414 (≤5) $[M]^+$, 393/395/397/399 (35/40/16/9/3), 372/374/376/378 (17/25/8/3), 298/300/302 (60/35/18), 154/156/158 (55/36/14), 115/117 (32/11), 101/100, 89/91 (70/25), 41 (70).

Assessment of the cytotoxicity of the substances *in vitro*

The cytotoxicity of the substances was studied using SH-SY5Y (human neuroblastoma), A549 (human lung adenocarcinoma), and MCF-7 (adenocarcinoma of the human mammary gland ducts) tumor cell lines and the HEK293 (immortalized human embryonic kidney cells) normal cell line, which were obtained from the Russian collection of cell cultures (Institute of Cytology, Russian Academy of Sciences, St. Petersburg). HEK293 cells (25×10^3 cells per well), SH-SY5Y (50×10^3 cells per well), MCF-7 (12×10^3 cells per well), and A549 (10×10^3 cells per well) were seeded in 96-well plates in 100 μL of DMEM medium containing 10% FBS (*Gibco*, USA), 2 mM L-glutamine (*PanEco*, Russia), and 50 μg/mL gentamicin (*Biolot*, Russia). After 24 h, the candidate substances were added to the cells at concentrations of 1, 10, and 100 μM in 0.1% DMSO, followed by incubation for 48 h at 37°C in 5% CO_2. The cytotoxic properties of the substances were then assessed using PrestoBlue® vital dye according to the manufacturer's protocol (*Invitrogen*, USA), and fluorescence was detected using a 2300 EnSpire® Multimode Plate Reader (*Perkin Elmer*, USA). The IC_{50} value (substance concentration at which 50% inhibition of cell viability is observed) was calculated using the GraphPad Prizm 4.0 program (*GraphPad Software Inc.*, USA).

The selectivity index (SI) of each substance was determined to reveal the possible selectivity of its cytotoxic effects against tumor cells, i.e., its potential antitumor properties. The HEK293 cell line served as control cells of normal origin, and the SI of the substance was calculated as the ratio of the IC_{50} value in HEK293 cells to the IC_{50} in tumor cells.

Statistical analysis of the obtained data was carried out using the standard Statistica 6.1 software package (*StatSoft Inc.*, USA). The results were presented as the arithmetic mean of 3 independent experiments (M), including the standard error of the mean (±m). Analysis of variance using the Dunnett's test was used to determine the significance of differences in the IC_{50} values of the substances between cells of normal and tumor origin.

RESULTS AND DISCUSSION

The *O*-alkylation of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane **1** with allyl chloride **2** and *cis*-1,4-dichlorobutene-2 **3** resulted in the corresponding ethers **4**–**6** being obtained in yields of 60–90%. The subsequent dichlorocarbenation of compounds **4**–**6** according to a previously reported procedure [25–27] synthesized products **7**–**9** in yields of 50–70%, which contained heterocyclic and carbocyclic fragments (Scheme 1).

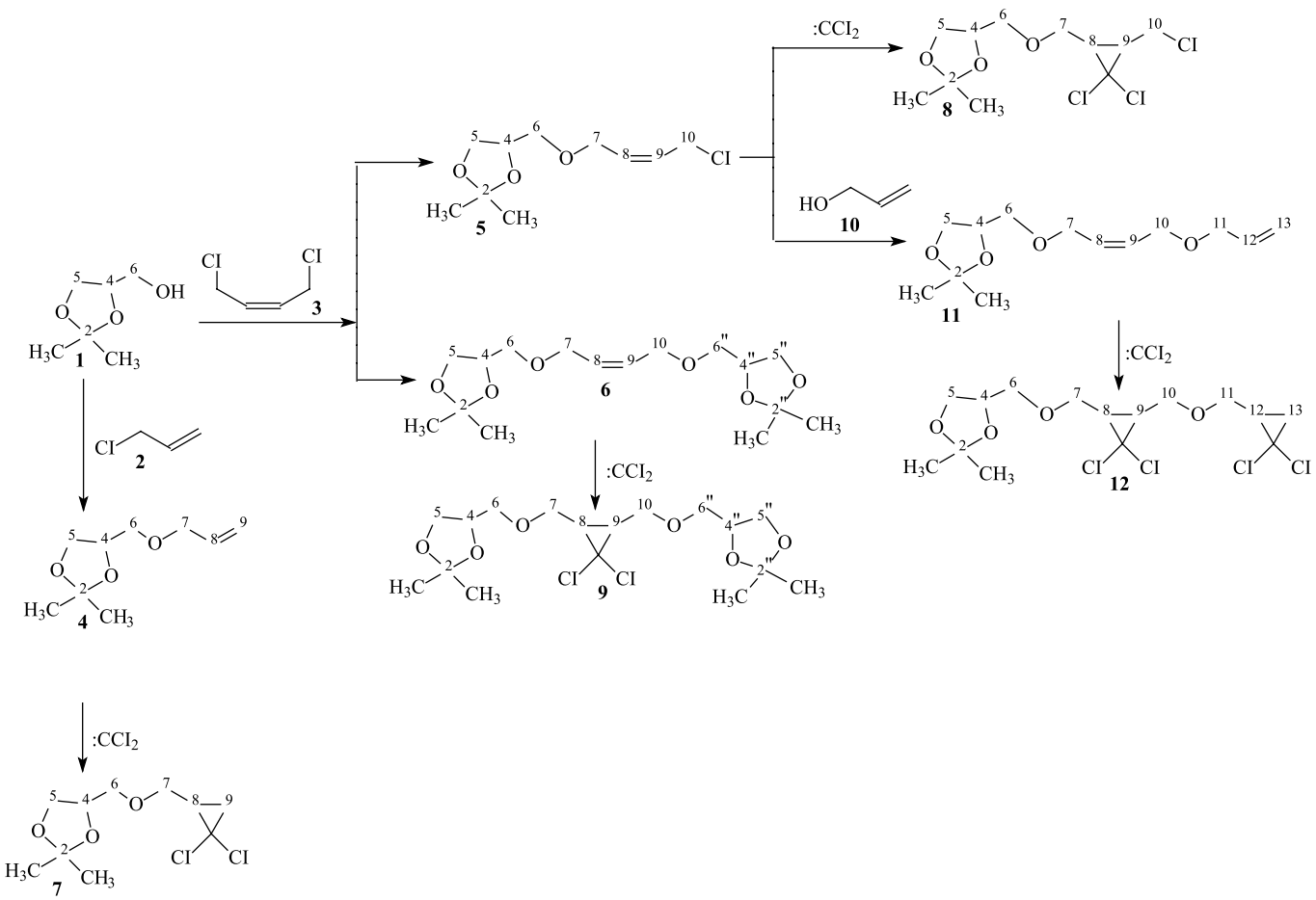
Chloromethyl derivative **5** was used for the *O*-alkylation of allyl alcohol **10**, which produced compound **11** with two double bonds in a yield of 40%. Its exhaustive dichlorocarbenation led to diester **12** (50% yield), which contained one 1,3-dioxolane and two *gem*-dichlorocyclopropane fragments (Scheme 1).

Competitive kinetics was used to determine the relative reactivity of chlorides **2** and **3** in the reaction with 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane **1**. Judging by the rate of product accumulation of **4** and **5**, allyl chloride **2** was 2 times more active than *cis*-1,4-dichlorobutene-2 **3**. By considering the number of reaction centers, the CH_2Cl group in olefin **2** is 4 times more active than the analogous group in compound **3**, which is likely due to the chlorine atoms in position 1 and 4 making it difficult for the bulky alcoholate to approach the CH_2–Cl group. This assumption was confirmed by the competitive *O*-alkylation of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane **1** with benzyl chloride **13** and 1,2-dichloromethylbenzene **14** (Scheme 2) resulting in the accumulation of esters **15** and **16**, which means that monochloride **13** is also 1.5 times more active than dichloride **14**.

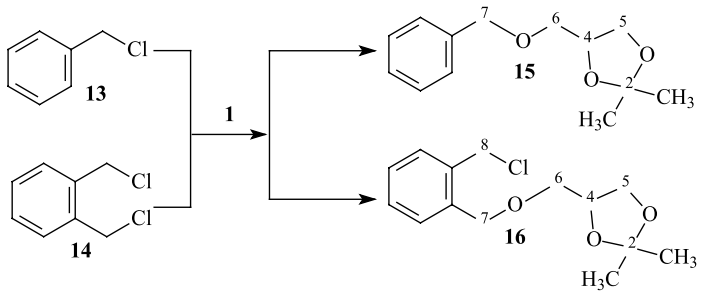
The structures of **4**–**9**, **11**, **12**, **15**, and **16** were elucidated by ^1H and ^{13}C NMR spectroscopy and chromatomass spectrometry.

The initial biological screening of new substances, regardless of their intended use, is the assessment of their basic cytotoxicity *in vitro*, which is defined as the negative effect of chemical compounds on the vital functions of the cell, e.g., damage to cell membranes, disruption of the metabolic activity of cells, changes in the processes of cell division, and protein synthesis. Continuous cell lines of various origins are used in this analysis.[1] The *in vitro* cytotoxicity assessment of polycyclic compounds **7**–**9** and **12** was performed using normal (HEK293) and tumor (SH-SY5Y, MCF-7, A549) cell lines to reveal both possible cytotoxicity and also the selectivity of their action, e.g., organ specificity or antitumor activity. The PrestoBlue® test used for

[1] Vakhitova Yu.V., Tselousova O.S. *Kletochnye mekhanizmy toksichnosti ksenobiotikov* (*Cellular mechanisms of xenobiotic toxicity*). Textbook. 2nd ed., revised and add. Ufa: BSPU, 2015. 104 p.



Scheme 1. Synthesis of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane ethers **1**.



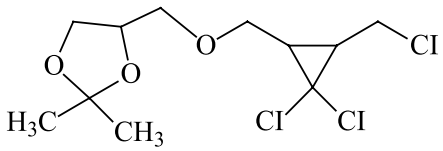
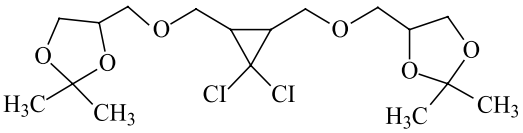
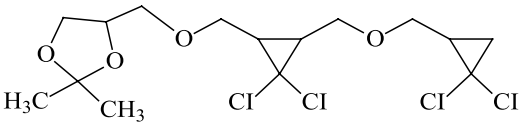
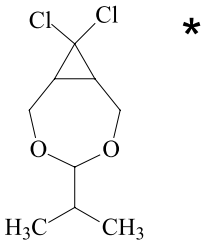
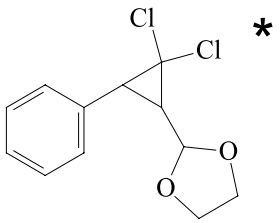
Scheme 2. Alkylation of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane 1 by chlorides **13** and **14**.

these screens allows for the detection of changes in the metabolic activity of cells against the background of the substances under study, which acts as a proxy for cell viability.

From the obtained data (see Table) only compound **12** (IC_{50} < 100 μM) exhibited moderate cytotoxic activity against the HEK293, SH-SY5Y, MCF-7, and A549 cell lines. Substances **8** and **9** did not affect the viability of cell lines in the concentration range of 1–100 μM. The activity of the tricyclic compound **12** against the HEK293, SH-SY5Y, and A549 cell lines is in agreement with the previously studied corresponding bicyclic compound 8,8-dichloro-4-isopropyl-3,5-dioxabicyclo-octane [28] but is inferior to the cinnamaldehyde derivative 2-(2,2-dichloro-3-phenylcyclopropyl)-1,3-dioxolane. No pronounced selectivity in the cytotoxic effects of compound **12** was observed for a particular tumor cell line (the maximum SI value was 1.18 for A549 cells).

Considering the structure of the synthesized substances and their cytotoxicity we assumed that the toxicity of compound **12** was due to an increase in the amount of gem-dichlorocyclopropane fragments compared with compound **8**. This is confirmed by

Influence of compounds on cell viability (48 h, $M \pm m$)

Formula and compound number	IC_{50}, μM			
	Hek293	SH-SY5Y	MCF-7	A549
 **8**	>100	>100	>100	>100
 **9**	>100	>100	>100	>100
 **12**	57.4 ± 4.3	86.2 ± 2.1 SI = 0.67**	72.7 ± 1.7 SI = 0.79**	48.8 ± 2.3 SI = 1.18**
 *	73.0 ± 5.7	93.2 ± 9.6 SI = 0.78**	21.0 ± 1.8 SI = 3.45**	56.0 ± 4.2 SI = 1.30**
 *	48.0 ± 3.1	58.67 ± 3.6 SI = 0.82**	27.6 ± 0.7 SI = 1.74**	33.7 ± 2.8 SI = 1.42**

Note: The results are presented as the arithmetic mean of three independent experiments (M), indicating the standard error of the mean ($\pm m$).

* Results from work [10].

** Selectivity Index (SI) is the ratio of the IC_{50} of the test compound for control HEK293 cells to IC_{50} for tumor cells.

comparing **12** with substances reported in [28]; the presence of the *gem*-dichlorocyclopropane group with the 1,3-dioxalane radical through oxygen in **12** reduces its negative impact on cell viability.

Thus, the analysis of compound **12** showed that an increase in the amount of *gem*-dichlorocyclopropane fragments caused cytotoxicity resulting from a change in the metabolic activity of the studied cells. The exact mechanism causing this effect is currently unknown and is the subject of our current research. Our results elaborate our understanding of the relationship of the structure of heterocyclic compounds containing *gem*-dichlorocyclopropane groups and/or 1,3-dioxalane radicals and their subsequent cytotoxic activity. Compounds **8**, **9**, and **12** may be promising candidates for the study of other types of biological activity.

CONCLUSIONS

Ethers containing *gem*-dichlorocyclopropane and 1,3-dioxolane fragments were synthesized in the presence of a catamine AB catalyst. The structures of the obtained substances were confirmed using mass spectrometry and NMR spectroscopy. Only one of several obtained compounds, 4-{[(2,2-dichloro-3-{[(2,2-dichlorocyclopropyl)methoxy]methyl} cyclopropyl)-methoxy]methyl}-2,2-dimethyl-1,3-dioxolane, had a negative impact on the metabolic activity of cells, regardless of their normal or tumor origin. Our analysis of the obtained data allowed us to establish that the toxic properties manifest due to an increase in the amount of *gem*-dichlorocyclopropane fragments in the candidate molecule and, subsequently, the cell.

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Authors' contribution

Sh.Sh. Dzhumaev – conducting research, reviewing publications on the topic of articles;

Y.G. Borisova – collecting and processing the material, writing the text of the article;

G.Z. Raskil'dina – collecting and processing the material, statistical processing;

U.Sh. Kuzmina – conducting biological research;

R.R. Daminev – consultation on planning, methodology and research implementation;

S.S. Zlotskii – development of the concept of the study, critical revision with the introduction of valuable intellectual content.

The authors declare no conflicts of interest.

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