CHEMICAL SCIENCES

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Synthesis and antimicrobial activity of functionally substituted 1,3-dioxacycloalkanes

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Abstract. *One of the directions in the development of organic chemistry is the synthesis of biologically active compounds, including those with bactericidal activity, based on available petrochemical raw materials. In order to expand the library of bioactive compounds containing a 1,3-dioxacyclane fragment, the synthesis of derivatives of 5-acyl-5-isopropyl-1,3-dioxane – 1-(5-isopropyl-1,3-dioxane-5-yl)ethanol and (5-isopropyl-1,3-dioxane-5-yl)ethyl phenyl carbamate was carried out. The effect of synthesized compounds containing a 1,3-dioxacyclane fragment on the growth of strains of gram-negative and gram-positive bacteria, lower fungi Candida albicans was studied. It was found that 2-methyl-2-ethyl-4-chloromethyl-1,3-dioxolane, containing a chloromethyl group, has an antimicrobial effect against gram-positive and gram-negative test cultures and weak antifungal activity (minimum inhibitory concentration is 100 μg/mL) against lower fungi Candida albicans. 1-(5-Isopropyl-1,3-dioxan-5-yl)ethanol exhibits antifungal activity (minimum inhibitory concentration is 2 μg/mL) and sharply reduces antimicrobial activity against Klebsiella pneumonia, Staphylococcus aureus, Enterobacter aerogenes (minimum inhibitory concentration is 100 μg/mL), in contrast to the structurally similar 2-methyl-2-ethyl-4-hydroxymethyl-1,3-dioxolane, which did not show similar properties. 5-Acyl-5-isopropyl-1,3-dioxane, containing a carbonyl group in its structure, showed antimicrobial activity (minimum inhibitory concentration is 25 μg/mL) against gram-negative test cultures, with the exception of Pseudomonas aeruginosa. Heterocycles (2-methyl-2-ethyl-4-chloromethyl-, 2-isobutyl-2,4-dimethyl-, 2-methyl-2-isobutyl-4-chloromethyl- and 2-methyl-2-isobutyl-4-hydroxymethyl-1,3-dioxolane) at concentrations up to 100 μg/mL did not inhibit the vital activity of the studied bacteria and lower fungi. The results obtained show the prospect of continuing the search for new antimicrobial and antifungal drugs of the series of 1,3-dioxacycloalkanes, the structure of which is fundamentally different from the known antibacterial drugs.*

Keywords: *polyols, condensation, 1,3-dioxacycloalkanes, antimicrobial activity, antifungal activity*

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ХИМИЧЕСКИЕ НАУКИ

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Синтез и антимикробная активность функционально замещенных 1,3-диоксациклоалканов

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Аннотация. *Одним из направлений развития органической химии является синтез биологически активных соединений, в том числе обладающих бактерицидной активностью, на основе доступного нефтехимического сырья. С целью расширения библиотеки биоактивных соединений, содержащих 1,3-диоксациклановый фрагмент, осуществлен синтез производных 5-ацил-5-изопропил-1,3-диоксана – 1-(5-изопропил-1,3-диоксан-5-ил)этанола и (1-(5-изопропил-1,3-диоксан-5-ил)этилфенилкарбамата. Изучено влияние функционально 2,2,4-тризамещенных 1,3-диоксоланов и синтезированных соединений, содержащих 1,3-диоксановый фрагмент, на рост штаммов грамотрицательных и грамположительных бактерий, низших грибов Candida albicans. Исследования структуры и активности показали, что 2-метил-2-этил-4-хлорметил-1,3-диоксолан, содержащий хлорметильную группу, обладает противомикробным действием в отношении грамположительных и грамотрицательных тест-культур и слабой противогрибковой активностью (минимальная ингибирующая концентрация 100 мкг/мл) в отношении более низких грибов Candida Albicans. 1-(5-Изопропил-1,3-диоксан-5-ил)этанол проявляет противогрибковую активность (минимальная ингибирующая концентрация 2 мкг/мл) и резко снижает антимикробную активность против Klebsiella pneumonia, Staphylococcus aureus, Enterobacter aerogenes (минимальная ингибирующая концентрация 100 мкг/мл), в отличие от сходного по строению 2-метил-2-этил-4-гидроксиметил-1,3-диоксолана, не проявившего аналогичных свойств. 5-Ацил-5-изопропил-1,3-диоксан, содержащий в структуре карбонильную группу, проявил антимикробную активность (минимальная ингибирующая концентрация 25 мкг/мл) в отношении грамотрицательных тест-культур, за исключением Pseudomonas aeruginosa. Гетероциклы (2-метил-2-этил-4-хлорметил-, 2-изобутил-2,4-диметил-, 2-метил-2-изобутил-4-хлорметил- и 2-метил-2-изобутил-4-гидроксиметил-1,3-диоксоланы) в концентрациях до 100 мкг/мл не ингибировали жизнедеятельность изученных бактерий и низших грибов. Полученные результаты показывают перспективность продолжения поиска новых антимикробных и противогрибковых препаратов ряда 1,3-диоксациклоалканов, структура которых принципиально отличается от известных антибактериальных препаратов.*

Ключевые слова: *полиолы, конденсация, 1,3-диоксациклоалканы, противомикробная активность, противогрибковое действие*

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INTRODUCTION

It is known that during the processing of plant raw materials, various cyclic acetals are formed, which are used as components and additives to motor fuels [1–6]. The use of substituted 1,3-dioxolanes for the synthesis of pharmaceutical or polymer products is also described [7]. 2-(2-Beta-bromoethyl)-1,3-dioxolane is used to obtain substances exhibiting anti-cancer properties [8]. Hydroxyacetals – "sol-ketal" and a mixture of 4-hydroxymethyl-1,3-dioxane and 4-hydroxymethyl-1,3-dioxolane have proven to be effective additives to repellents [9], and diacetals of diglycerol or dipentaerythritol are proposed as components for polymeric materials [10]. Like molecules containing cycloacetal moiety are important intermediates that can be modified into more complex structures exhibiting a broad spectrum of biological activity [11]. Thus, derivatives of 2,2-dissubstituted-1,3-dioxolanes exhibit antiviral, antiplatelet, anticoagulant, fungicidal, herbicidal activity, and can also be used to produce pheromones [12–20]. In addition, it is known that the introduction of

the acetal fragment enhances the antibacterial activity of the compounds due to an increase in the lipophilicity of the molecule [21].

In the present work, the synthesis of 5,5-disubstituted 1,3-dioxanes was carried out and the antimicrobial activity of substituted 5- and 6-membered cyclic acetals was studied.

MATERIALS AND METHODS

All reagents and starting materials were obtained from commercial sources and used as received. All solvents were dried according to standard literature procedures. All reactions were performed under an atmosphere of argon unless indicated otherwise. ^{1}H NMR, and ^{13}C NMR spectra were recorded on a Bruker Avance-III 500 MHz spectrometer with chemical shift values in parts per million (ppm) relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional HSQC, HMBC, COSY and DEPT experiments. Mass spectra were obtained using Thermo Finnigan MAT 95 XP spectrometer. Melting points were measured on a micro melting point apparatus.

2,2,4-Trisubstituted 1,3-dioxolanes **1–6** were prepared according to the previously described procedure [22].

Synthesis of 5-acyl-5-isopropyl-1,3-dioxane **7**. A mixture of 6.3 mL (0.05 mol) of 4-methyl-2-pentanone, 0.225 g (0.075 mol) of paraformaldehyde, 80 mL of benzene, and 0.4 mL of concentrated sulfuric acid (d = 1.84 g/mL) and was stirred at 80 °C until the calculated amount of water was released. Then the mixture was cooled to room temperature, washed with water, dried over calcium chloride, filtered and evaporated. The product was isolated by vacuum distillation.

Yield 80%, colorless liquid, bp 129–131 °C (3 mmHg). ^{1}HNMR(500 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 0.90 d (3H, *J* = 7.0,CHC$\underline{H}_3$); 1.00 d (3H, *J* = 7.0,C$\underline{H}$CH$_3$); 1.63 m (1H, C$\underline{H}$CH$_3$); 2.27 s (3H, CH_3CO); 3.48 d (2H, *J* = 11.5, 4-CH_2); 4.34 d (2H, *J* = 11.4,6-CH_2); 4.62 d (1H, *J* = 6.0 2-CH_2^a); 4.98 d (1H, *J* = 6.0,2-CH_2^b). ^{13}C NMR (125 MHz, $CDCl_3$), *δ*, ppm: 16.0 (2CH_3CH); 26.9 (CH_3CO); 29.3 ($CHCH_3$); 51.2 (C-5); 71.8 (C-4, C-6); 94.1 (C-2); 209.9 (C=O). Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 158 (2) [M]+, 12 (50), 110 (20), 99 (30), 86 (70), 83 (80), 71 (20), 57 (40), 43 (100).

The procedure for the hydrogenation of ketones **7**. The Pd/C catalyst (CAS 7440-05-3, TU 2172-013-94509069-200, palladium content 5%) was ground in a mortar before use, sieved, and kept in a desiccator. For hydrogenation, a flow-through catalytic apparatus Catakon was used, consisting of a metal reactor with a heating jacket, a burette for feeding raw materials, an automatic pump, and a control unit. Operating parameters of the apparatus are volume of the reaction zone – 15 cm^3, temperature range – 50–600 °C, pressure up to 100 atm. An activated Pd/C catalyst was put into a flow reactor. At a given temperature (250 °C) at a rate of 0.27 mL/min, 15 mL of ketone **7** (0.01 mol), hydrogen were fed at a rate of 0.23 mL/min, and the pressure was about 8 kg/cm. The obtained catalyzate was filtered off and evaporated.

Yield 85%, colorless liquid, bp 131–132 °C (2 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$), *δ* ppm (*J*, Hz): 0.90 s (6H, CH_3CH); 1.00 d (3H, *J* = 7, CH_3); 1.73–1.81 m (1H, $CHCH_3$); 3.09 s (br OH); 3.72 dd (2H, *J* = 6.0, *J* = 11.0,4-CH_2); 4.00 d (1H, *J* = 11.6, CH); 4.12 dd (2H, *J* = 6.6, *J* = 11.5, 6-CH_2); 4.67 d (1H, *J* = 5.8, 2-CH_2^a); 4.88 d (1H, *J* = 5.8, 2-CH_2^b). ^{13}C NMR (125 MHz, $CDCl_3$), *δ*, ppm: 16.0 (2CH_3CH); 19.3 ($CHCH_3$); 26.9 (CH_3CO); 39.2 (C-5); 68.4 (CHOH); 72.4 (C-4); 72.7 (C-6); 94.1 (C-2). Mass spectrum (*EI*, 70 eV), m/z (I_{rel}, %): 160 (2) [M]+, 72 2 (60), 57 (50), 45 (30), 43 (70), 39 (20), 32 (100).

Synthesis of 1-(5-isopropyl-1,3-dioxane-5-yl)ethylcarbamate **9**. To a mixture of 8.7 g (0.05 mol) of alcohol 8 in 15 mL of hexane was added 3 g (0.025 mol) of phenyl isocyanate in 5 mL of hexane. Then reaction mass was heated with stirring to 30 °C. Upon completion of the reaction (TLC monitoring), the mixture was cooled to room temperature, the precipitated crystals were filtered off on a Buchner funnel, washed with water, separated from hexane, dried in air, and recrystallized from isopropanol.

Yield 92%. White powder, *mp* = 101–103 °C ^{1}H NMR (500 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 0.90 s (6H, CH_3CH); 1.11, 1.28 d (3H, *J* = 7, CH_3); 1.91–1.95 m (1H, $CHCH_3$); 3.67–4.01 m (5H, 4-CH_2, 6-CH_2, $CH(CH_3)O$); 4.88 d (1H, *J* = 6.6, 2-CH_2^a); 5.12 d (1H, *J* = 6.6, 2-CH_2^b); 7.00–7.50 m (5H); 9.49, 9.67 s (1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$), *δ*, ppm: 15.8 (CH_3CH); 21.4 (CH_3CH); 21.4 (CH_3CH); 29.4 ($CHCH_3$); 68.2 (C-4); 71.4 (C-6); 72.3 ($CH(CH_3)O$); 91.1 (C-2); 127.9 (Ph); 128.5 (Ph); 138.9 (Ph); 163.7 (CO_2).

Antimicrobial activity. Antibacterial and antifungal activities of 1,3-dioxolane and 1,3-dioxane derivatives were analyzed using the agar diffusion and the twofold broth (pH 7.2–7.4) dilution methods[1]. Microbial strains of the department of Microbiology and Virology, Bashkir State Medical University deposited at L.A. Tarasevich State Institute of Standardization and Control of Biomedical Preparations, the Ministry of Health of the Russian Federation were used as test organisms: *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Streptococcus pyogenes* and lower fungi *Candida albicans*. Ceftriaxone ("Biokhimik", Russia), pimafucin (natamycin, Astellas, Netherlands) were taken as reference standards. Test compounds (100 mg) and reference standards were dissolved in 1 mL of dimethyl sulfoxide (DMSO). These solutions were diluted in beef extract broth to achieve a final concentration of 10 mg/mL (stock solution). The nutrient broth inoculated with 2.0×10^{-6} colony forming units (c.f.u)/mL, was used. The cultures were incubated for 72 h at 37 °C and for 48 h at 25 °C, then the growth was monitored visually. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC).

RESULTS AND DISCUSSION

In the work we studied 2,2,4-trisubstituted 1,3-dioxolanes **1–6**, which were synthesized by us earlier (Fig. 1) [22], as well as novel 5,5-dialkyl substituted-1,3-dioxanes (Fig. 2)

[1] Руководство по проведению доклинических исследований лекарственных средств. Часть первая / ред.: А.Н. Миронов, Н.Д. Бунятян, А.Н. Васильев, О.Л. Верстакова, М.В. Журавлева, В.К. Рамн Лепахин. М.: Гриф и К, 2012. 944 с. EDN: SDEWMP.

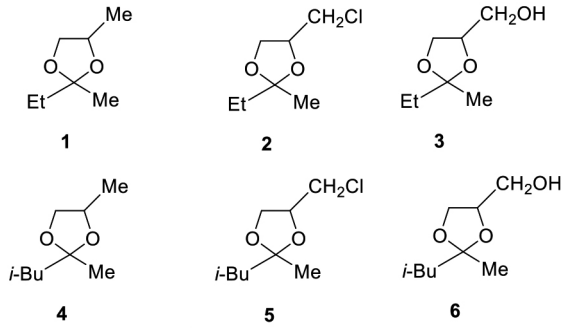

Fig. 1. 2,2,4-Trisubstituted 1,3-dioxolanes **1–6**

Рис. 1. Структуры 2,2,4-тризамещенных 1,2-диоксоланов **1–6**

Dioxane **7** was prepared by reaction of ^{i}BuCOMe with paraformaldehyde in presence of sulfuric acid (C_6H_6, 80 °C) (path *a*) [23]. Subsequent hydrogenation of dioxane **7** in the presence of metal-containing catalysts (Pt/Re, Pd/C, Ni/kieselguhr, and Ni/Mo) led to target product **8** with 60–90% yield (path *b*) [24]. Dioxane **8** reacted smoothly with phenyl isocyanate in hexane at 30 °C degrees to form the corresponding carbamate **9** (path *c*) in 90% yield (see Fig. 2).

Carbamate **9** is formed as a mixture of two isomers due to inversion of nitrogen atoms. The ^{1}H and ^{13}C NMR spectra show a doubled set of signals of hydrogen and carbon atoms, respectively (Fig. 3).

In the ^{1}H NMR spectrum (see Fig. 3) of carbamate **9** recorded in solution of DMSO-*d*6, there are signals characteristic for two double signals of 1,3-dioxane cycle which are registered in weak field in interval *δ* H 3.67 to 4.01 ppm. Protons at C(2) carbon atom is also manifested by two doublets in the weak field δ_H 4.88–5.12 ppm with spin-spin coupling constant 6.6 Hz. Additionally, we note that the protons of the phenyl group are manifested by complexes in the area δ_H 7.00–7.50 ppm, and protons of secondary NH group from two isomers as expanded synthetics at δ_H 9.49 and 9.67 ppm respectively.

All synthesized functionally substituted 1,3-dioxacyclanes **1–9** were tested for antimicrobial activity. The results of the screening demonstrated that 1,3-dioxacycloalkanes **2** and **8** exhibited pronounced antimicrobial activity against the most of the studied test cultures, the MIC values were 2–8 *μ*g/mL, while 1,3-dioxane **9** at a concentration of 100 *μ*g/mL did not suppress the growth of the studied microbial strains as shown in Table.

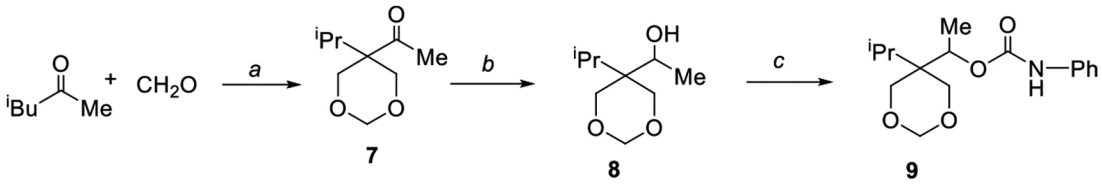

Fig. 2. Scheme for the preparation of (1-(5-isopropyl-1,3-dioxan-5-yl)ethyl phenyl carbamate **9**

Рис. 2. Схема получения (1-(5-изопропил-1,3-диоксан-5-ил)этилфенилкарбамата **9**

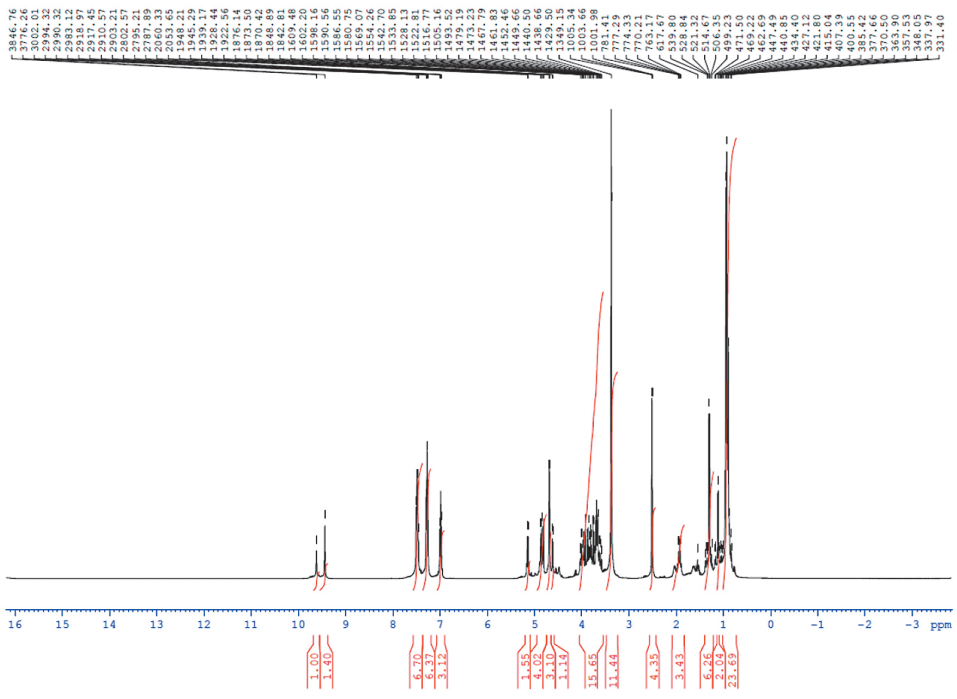

Fig. 3. ^{1}H NMR Spectrum of (1-(5-isopropyl-1,3-dioxan-5-yl)ethyl phenyl carbamate **9** in dimethyl sulfoxide-*d*6

Рис. 3. Спектр ЯМР ^{1}H (1-(5-изопропил-1,3-диоксан-5-ил)этилфенилкарбамата **9** в диметилсульфоксиде-*d*6

Antibacterial and antifungal activities of new 1,3-dioxolane and 1,3-dioxane derivatives

Антибактериальная и противогрибковая активность новых производных 1,3-диоксолана и 1,3-диоксана

Compound		Minimum inhibitory concentrations, μg/mL								
		Escherichia coli	*Proteus vulgaris*	*Klebsiella pneunoniae*	*Staphylococcus aureus*	*Enterobacter aerogenes*	*Pseudomonas aeruginosa*	*Enterobacter cloacae*	*Streptococcus pyogenes*	*Candida albicans*
1	**1**	>100	>100	>100	>100	>100	>100	>100	>100	>100
2	**2**	2	2	2	8	2	8	2	8	100
3	**3**	>100	>100	>100	>100	>100	>100	>100	>100	>100
4	**4**	>100	>100	>100	>100	>100	>100	>100	>100	>100
5	**5**	>100	>100	>100	>100	>100	>100	>100	>100	>100
6	**6**	>100	>100	>100	>100	>100	>100	>100	>100	>100
7	**7**	25	25	25	100	25	100	25	100	100
8	**8**	8	8	100	100	100	8	8	100	2
10	**9**	>100	>100	>100	>100	>100	>100	>100	>100	>100
11	Ceftriaxone	0,1	0,1	0,1	1	0,1	10	0,5	0,5	–
12	Pimafucin	–	–	–	–	–	–	–	–	1

The structure-activity studies showed that 1,3-dioxolane **4**, containing chloromethyl group in the ethyl fragment, had an antimicrobial effect against gram-positive and gram-negative test cultures and a weak antifungal activity (MIC 100 μg/mL) against lower fungi *C. albicans*. Unlike 1,3-dioxolane 5 containing a hydroxymethyl group in the 4 position, 1-(5-isopropyl-1,3-dioxan-5-yl)ethanol 10 exhibits antifungal activity MIC 2 μg/mL and a sharp decrease in antimicrobial activity against *K. pneumonia*, *St. aureus*, *E. aerogenes* MIC 100 μg/mL. Similarly 5-acyl-5-isopropyl-1,3-dioxane **7**, containing carbonyl group in the structure, showed antimicrobial activity (MIC 25 μg/mL) against gram-negative test cultures except of *Ps. aeruginosa*. An interesting result was that the introduction of the isocyanate fragment into the 1,3-dioxane molecule(compound **9**) reduces the antibacterial and antifungal activities.

1,3-Dioxolanes **1**, **3–6** at concentrations up to 100 μg/mL did not inhibit the vital activity of the studied bacteria and lower fungi (see Table).

The obtained results show that it is promising to continue the search for new antimicrobial and antifungal drugs in the series of 1,3-dioxacycloalkanes, the structure of which is fundamentally different from the known antibacterial drugs.

CONCLUSIONS

Nine functionally substituted 1,3-dioxacycloalkanes have been synthesized and tested as anti-microbial and antifungal agents. Among the synthesized substances, the leading compounds were found to be: 2-methyl-2-ethyl-4-chloromethyl-1,3-dioxolane had antimicrobial effect against Gram-positive and Gram-negative test cultures, 5-acyl-5-isopropyl-1,3-dioxane showed antimicrobial activity (MIC 25 μg/mL) against Gram-negative test cultures except of *Ps. Aeruginosa*, and 1-(5-isopropyl-1,3-dioxan-5-yl)ethanol exhibits antifungal activity MIC 2 μg/mL and a sharp decrease in antimicrobial activity against *K. pneumonia*, *St. aureus*, *E. aerogenes* MIC 100 μg/mL. In summary, the results obtained show that the search for new antimicrobial and antifungal drugs in the series of functionally substituted 1,3-dioxacycloalkanes is promising, since their structure is fundamentally different from the known antibacterial drugs.

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