ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
Өсімдіктердің биологиясы және биотехнологиясы институтының

Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
Института биологии и биотехнологии растений

N E W S

OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

БИОЛОГИЯ ЖӘНЕ МЕДИЦИНА СЕРИЯСЫ

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СЕРИЯ БИОЛОГИЧЕСКАЯ И МЕДИЦИНСКАЯ

♦

SERIES OF BIOLOGICAL AND MEDICAL

6 (330)

ҚАРАША – ЖЕЛТОҚСАН 2018 ж.
НОЯБРЬ – ДЕКАБРЬ 2018 г.
NOVEMBER – DECEMBER 2018

1963 ЖЫЛДЫҢ ҚАҢТАР АЙЫНАН ШЫҒА БАСТАҒАН
ИЗДАЕТСЯ С ЯНВАРЯ 1963 ГОДА
PUBLISHED SINCE JANUARY 1963

ЖЫЛЫНА 6 РЕТ ШЫҒАДЫ
ВЫХОДИТ 6 РАЗ В ГОД
PUBLISHED 6 TIMES A YEAR

АЛМАТЫ, ҚР ҰҒА
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«ҚР ҰҒА Хабарлары. Биология және медициналық сериясы».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» РҚБ (Алматы қ.)
Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде 01.06.2006 ж. берілген **№5546-Ж** мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.
Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
www:nauka-nanrk.kz / biological-medical.kz

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Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

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«Известия НАН РК. Серия биологическая и медицинская».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Собственник: РОО «Национальная академия наук Республики Казахстан» (г. Алматы)
Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№5546-Ж**, выданное 01.06.2006 г.

Периодичность: 6 раз в год
Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
www:nauka-nanrk.kz / biological-medical.kz

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Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

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News of the National Academy of Sciences of the Republic of Kazakhstan. Series of biology and medicine.
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)
The certificate of registration of a periodic printed publication in the Committee of information and archives of the Ministry of culture and information of the Republic of Kazakhstan N 5546-Ж, issued 01.06.2006

Periodicity: 6 times a year
Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
http://nauka-nanrk.kz / biological-medical.kz

© National Academy of Sciences of the Republic of Kazakhstan, 2018

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES OF BIOLOGICAL AND MEDICAL
ISSN 2224-5308
Volume 6, Number 330 (2018), 44 – 49 **https://doi.org/10.32014/2018.2518-1629.16**

IRSTI 34.27.39
UDC 579. 61

A. K. Sadanov[1], M. A. Akylova[3], A. S. Balgimbaeva[1], L. N. Ibragimova[1], T. S. Bekezhanova[1], A. O. Itemirova[2], Z. Zh. Turlybaeva[1], A. Zh. Sultanova[1], R. Sh. Galimbayeva[1], L. P. Trenozhnikova[1]

[1]LLP Scientific Production Center for Microbiology and Virology, Almaty, Kazakhstan,
[2]Oblast Dermatovenerologic Dispensary under the Ministry of Health of the Republic of Kazakhstan, Almaty, Kazakhstan,
[3]Central Clinical Hospital JSC, Almaty, Kazakhstan.
E-mail: imv_rk@list.ru

ACTIVITY OF ANTIBIOTIC ROSEOFUNGIN AGAINST CLINICAL PATHOGENS OF VAGINAL CANDIDIASIS

Abstract. The polyene antibiotic roseofungin (registration number RK-LS-5No23224) is a new drug substance developed by the Kazakh scientists, on the basis of which the antifungal dosage form "Roseofungin-AS, ointment 2%" (registration number RK-LS-5№023225) was prepared for external application. In order to prepare a new dosage form for the treatment of vaginal candidiasis, activity of the antibiotic roseofungin was examined by the agar diffusion technique against 15 clinical fungal strains of the genus Candida: Candida albicans (9 strains), Candida krusei (2 strains), Candida tropicalis (2 strains), Candida glabrata (1 strain), Candida parapsilosis (1 strain). The antibiotic roseofungin exhibited high antifungal activity against clinical pathogens of vaginal candidiasis, the minimum inhibitory concentration varied in the range of 1.66-2.5 μg/mL. The highest activity of the antibiotic roseofungin was observed against clinical Candida albicans strains, MIC values were within the 1.66-2.0 μg/L range. Activity against Candida non-albicans strains was lower: MIC for Candida tropicalis was of 2.0 μg/mL, for Candida krusei, Candida glabrat, and Candida parapsilosis of 2.5 μg/mL. The presence of high activity in the antibiotic roseofungin against clinical pathogens of candidiasis indicates the possibility of developing new drugs on its basis that can improve the condition of patients in Kazakhstan and beyond.

Key words: antibiotic roseofungin, antifungal activity, minimum inhibitory concentration, vaginal candidiasis.

Introduction. Candidal vulvovaginitis relates to infectious diseases that cause inflammation of the vulvar and vaginal mucosa with yeast-like fungi belonging to the genus Candida [1]. Treatment and prevention of candidal vulvovaginitis is currently an urgent problem in gynecology. This disease occupies a leading position among vaginal infections, since almost every woman had at least one episode of the disease during her life, and more than 70% of women experienced relapses [2-5]. The major cause of candidal vulvovaginitis is an infection with yeast-like fungi of the genus Candida against the background of decreased immune status [6-7].

Currently, there are more than 170 species of Candida, of which no more than twenty species are registered as infection causative agents in humans [8]. Although Candida albicans is the most common cause of vulvovaginal candidiasis, the frequency of this disease caused by other Candida species, such as C. tropicalis, C. glabrata, and C. krusei, is increasing, especially in HIV-infected women [9]. The diversity of Candida spp. that are encountered in infections is expanding, and other species are emerging that have rarely been seen before [10, 11].

Polyenes, azoles, echinocandins, nucleoside analogs and allylamines are used with different effectiveness to treat infections caused by fungi of the genus Candida, depending on the type and location of infection and susceptibility of Candida species [12-15]. Candidal vulvovaginitis is usually treated with

local antimycotic drugs, which improve the microscopy parameters of the vaginal and cervical canal discharge (reduced leukocytosis, decrease in the number of coccal and bacterial flora, and disappearance of fungi) in 93.3% of patients [16]. The treatment of candidal vulvovaginitis varies significantly, and the most common drugs include azole agents [17], of which fluconazole is the most frequently prescribed antifungal agent. The widespread use of these drugs as preventive and therapeutic agents contributes to the emergence of resistant Candida strains, thereby causing serious problems in the successful treatment of vulvovaginitis [18]. There is a higher level of resistance, especially to azoles, in most species of Candida non-albicans, many of which have a natural resistance to antifungal agents [19, 20]. C. glabrata has the highest resistance to azoles among clinical isolates of Candida and exhibits a natural reduced susceptibility to this group of chemical compounds [21, 22].

In connection with the foregoing, the search for new antifungal drug substances and the development of effective drugs on their basis for treatment of candidal vulvovaginitis accessible to the general population is an urgent necessity.

The purpose of this study was to examine the activity of the antifungal polyene antibiotic roseofungin against the clinical pathogens of vaginal candidiasis and assess the possibility of its use for the development of a new dosage form.

Materials and Methods. The object of the study was a polyene antibiotic roseofungin, registered in the Republic of Kazakhstan under the number RK-LS-5N023224 [23].

Antifungal activity of the antibiotic roseofungin was examined against 15 clinical fungal Candida strains: 9 strains of Candida albicans (Berkhout, 1923) (strains R-11, R-25, R-28, R-29, R-33, R-41, R 44, R-46, R-50), 2 strains of Candida krusei (Berkhout, 1923) (R-19, R-47), 2 strains of Candida tropicalis (Berkhout, 1923) (R-5 .R-39), 1 strain of Candida glabrata (SA Mey. & Yarrow, 1978) (R-17), 1 strain of Candida parapsilosis (Langeron & Talice 1932) (R-14). Fungal isolates belonging to the genus *Candida* were obtained from patients living in the Almaty region in the microbiological laboratory at the Regional Dermatovenerologic Dispensary under the Ministry of Health of the Republic of Kazakhstan and bacteriological laboratory at the Central Clinical Hospital. Identification of clinical fungal strains of the genus Candida was carried out using the BIO MERIEUX automated MINI API bacteriological analyzer. The bacteriological analyzer has an expert system for interpreting the results obtained on antibiotic resistance and species identification of microorganisms based on international standards (NCCLS).

Antifungal activity of the antibiotic roseofungin was studied by the agar diffusion method [24]. The nutrient agar medium F was used to determine the biological activity.

The composition of medium F (g /L): peptone - 9.4; yeast extract - 4.7; beef extract - 2.4; sodium chloride - 30.0; glucose monohydrate - 10.0; agar - 23.5; distilled water - up to 1000 ml, pH after sterilization - 7.0 ± 0.1.

Clinical fungal strains of the genus Candida were grown in Petri dishes on the surface of medium F for 24 hours at a temperature of 30 to 37 ^{0}C; typical colonies were selected, reinoculated onto agar slants of the same composition and grown under the conditions described above. The grown culture was washed from the slanted nutrient medium F with 10 ml of a sterile solution containing 9 g/L of sodium chloride. A working suspension was prepared from the resulting microbial suspension of such a density, which when diluted with a sterile solution containing 9 g/L of sodium chloride corresponded to the L.A. Tarasevich SISC turbidity standard (10 units).

The inoculation dose of the test microorganism was 1.0 ml of a working suspension per 100.0 ml of medium F. The inoculation was carried out at a temperature of 48-500 °C. 15.0 ml of the inoculated medium F was poured into each Petri dish, so that a uniform layer with a thickness of 2 mm to 5 mm was formed therein. Filling of the inoculated medium F into Petri dishes was carried out on a horizontally flat surface.

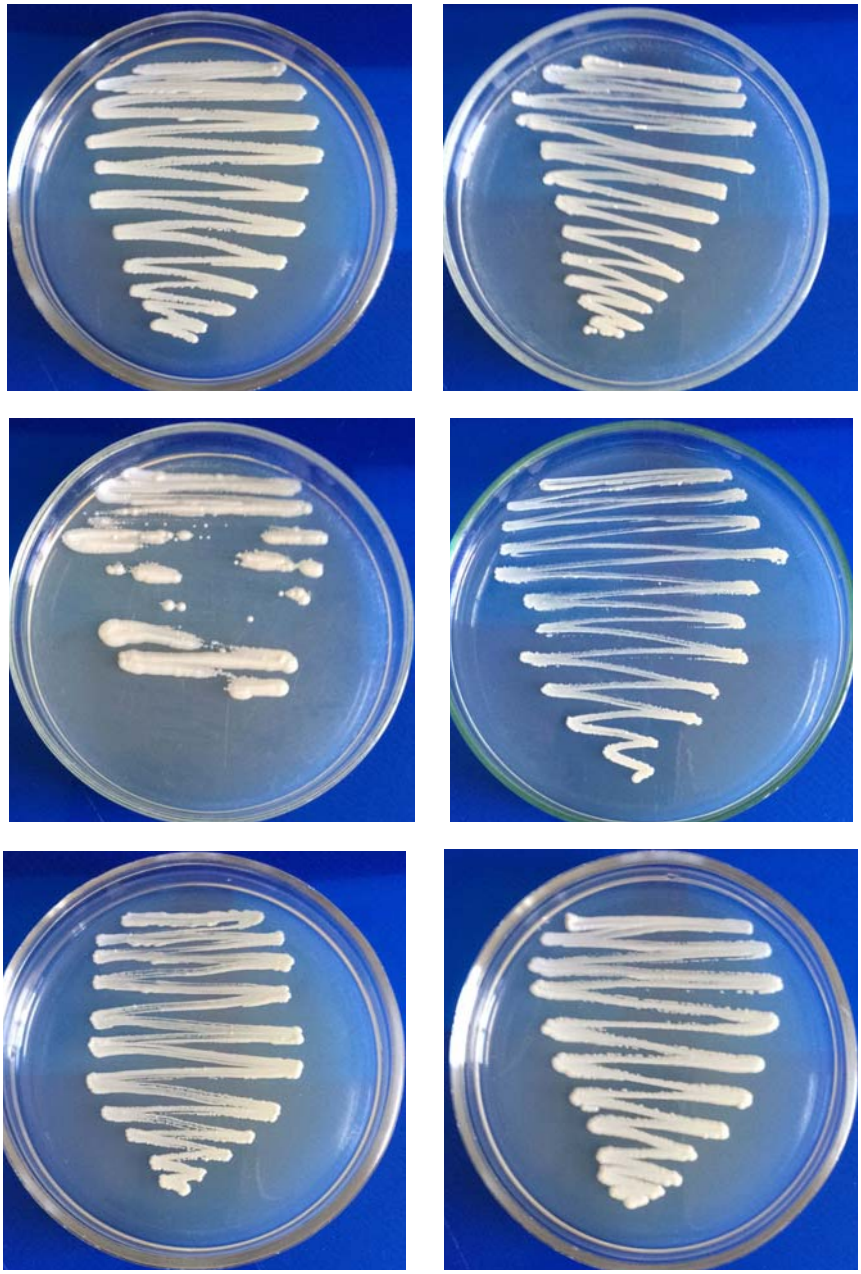
10.0 mg of roseofungin powder was placed in a 10.0 ml volumetric flask and dissolved in 5.0 ml of dimethylsulfoxide. The volume of the solution was adjusted to the mark with the same solvent and stirred. Further dilution of the stock solution was made with a phosphate buffer solution (pH 6.0) to the desired concentration.

To prepare a phosphate buffer, 50.0 ml of a 0.2 M potassium dihydrogen phosphate solution was transferred to a 200 ml volumetric flask, 5.7 ml of 0.2 M sodium hydroxide was further added and mixed. The resulting solution was then made up to the mark with distilled water.

Solutions with the calculated concentration were added to the wells of 7 mm in diameter prepared in the inoculated nutrient medium F. All wells were filled with equal volumes of solutions. The dishes were incubated at 37^0C for 18-24 hours. To reduce the influence of the time difference between addition of solutions and to refine a regression line, preliminary diffusion was used at a temperature of about 4 °C with 4-hour duration.

All studies were carried out in three to five replicates. The standard methods for finding mean values and their mean errors were used for mathematical processing of the results [25].

Results and discussion. As a result of the studies, activity of the antibiotic roseofungin was determined against 15 clinical fungal strains of the genus Candida: Candida albicans (9 strains), Candida krusei (2 strains), Candida tropicalis (2 strains), Candida glabrata (1 strain), and Candida parapsilosis (1 strain). Figure shows the growth of clinical pathogens of vaginal candidiasis on meat peptone agar.



The growth of clinical pathogens of vaginal candidiasis on meat peptone agar:
1 - *C. albicans* R-25; 2 - *C. albicans* R-33; 3 - *C. krusei* R-19; 4 - *C. glabrata* R-17;
5 - *C. tropicalis* R-39; 6 - *C.* parapsilosis R-14

Activity of antibiotic roseofungin against clinical pathogens of vaginal candidiasis

SN	Strain No.	Species of test microorganism	Minimum inhibitory concentration, μg/mL
1	R-11	Candida albicans	2,0
2	R-25	Candida albicans	2,0
3	R-28	Candida albicans	1,66
4	R-29	Candida albicans	1,66
5	R-33	Candida albicans	2,0
6	R-41	Candida albicans	1,66
7	R-44	Candida albicans	2,0
8	R-46	Candida albicans	1,66
9	R-50	Candida albicans	1,66
10	R-19	Candida krusei	2,5
11	R-47	Candida krusei	2,5
12	R-5	Candida tropicalis	2,0
13	R-39	Candida tropicalis	2,0
14	R-17	Candida glabrata	2,5
15	R-14	Candida parapsilosis	2,5

Results of determination of roseofungin activity are given in table.

The minimum inhibitory concentration (MIC, μg/mL) for the examined strains of the causative agents of vaginal candidiasis varied between 1.66-2.5 μg/mL. The highest activity of the antibiotic roseofungin has been observed against clinical Candida albicans strains, MIC values were within 1.66-2.0 μg/mL. Activity against Candida non-albicans strains was lower: MIC for Candida tropicalis was of 2.0 μg/mL, for Candida krusei, Candida glabrata, and Candida parapsilosis of 2.5 μg/mL. Our results correspond to the literature data according to which the causative agents of vulvovaginal candidiasis Candida non-albicans have less natural susceptibility to antifungal drug compounds [19, 20].

High antifungal activity of the antibiotic roseofungin has been thereby established against clinical pathogens of candidiasis (strains of Candida albicans, Candida krusei, Candida tropicalis, Candida glabrata, and Candida parapsilosis); the minimum inhibitory concentration was in the range of 1.66-2.5 μg/mL. The presence of high activity in the antibiotic roseofungin against clinical pathogens of candidiasis demonstrates the necessity for developing new drugs on its basis, including those for the treatment of candidal vulvovaginitis, which can improve the condition of patients in Kazakhstan and beyond.

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А. К. Саданов[1], М. А. Акылова[3], А. С. Балгимбаева[1], Л. Н. Ибрагимова[1], Т. С. Бекежанова[1], А. О. Итемирова[2], И. Р. Кулмагамбетов[1], З. Ж. Турлыбаева[1], А. Ж. Султанова[1], Р. Ш. Галимбаева[1], Л. П. Треножникова[1]

[1]«Микробиология және вирусология ҒӨО» ЖШС, Алматы, Қазақстан,
[2]ҚР ДМ "Алматы облыстық тері-венерологиялық диспансері", Алматы, Қазақстан,
[3]«Орталық клиникалық аурухана» АҚ, Алматы, Қазақстан

РОЗЕОФУНГИН АНТИБИОТИГІНІҢ ВАГИНАЛЬДІ КАНДИДОЗДЫҢ КЛИНИКАЛЫҚ ҚОЗДЫРҒЫШТАРЫНА ҚАТЫСТЫ БЕЛСЕНДІЛІГІ

Аннотация. Розеофунгин полиенді антибиотигі (тіркеу нөмірі ҚР-ДЗ-5№023224) Қазақстан ғалымдары әзірлеген жаңа дәрілік субстанция болып табылады, оның негізінде сыртқа қолдануға арналған «Розеофунгин-АС, 2% жақпамайы» (тіркеу нөмірі ҚР-ДЗ-5№023225) зеңге қарсы препаратының дәрілік үлгісі дайындалды. Вагинальді кандидозды емдеу ішін жаңа дәрілік үлгіні дайындау мақсатында Candida туысына жататын: Candida albicans (9 штамм), Candida krusei (2 штамм), Candida tropicalis (2 штамм), Candida glabrata (1 штамм), Candida parapsilosis (1 штамм) саңырауқұлақтарының 15 клиникалық штамдарына қатысты агарға диффузиялау әдісі арқылы розеофунгин антибиотигінің белсенділігіне зерттеу жүргізілді. Розеофунгин антибиотигі вагинальді кандидоздың клиникалық қоздырғыштарына қатысты жоғары антифунгальді белсенділікті көрсетті, минимальді тежейтін концентрациясы 1,66-2,5 мкг/мл дейін өзгерді. Розеофунгин антибио-

тигі Candida albicans түрінің клиникалық штамдарына қатысты ең жоғары белсенділікке ие болды, МТК – 1,66-2,0 мкг/мл. Candida non-albicans штамдарына қатысты белсенділігі төмен болды: МТК Candida tropicalis 2,0 мкг/мл, Candida krusei, Candida glabrata және Candida parapsilosis – 2,5 мкг/мл құрады. Розеофунгин антибиотигінің кандидоздың клиникалық қоздырғыштарына қатысты белсенділігінің болуы оның негізінде Қазақстан және одан тысқары жерлердегі науқастардың жағдайын жақсартатын жаңа дәрілік препараттарды әзірлеп шығарудың мүмкіндігін көрсетеді.

Түйін сөздер: розеофунгин антибиотигі, антифунгальді белсенділігі, минимальді тежейтін концентрация, вагинальді кандидоз қоздырғыштары.

А. К. Саданов[1], М. А. Акылова[3], А. С. Балгимбаева[1], Л. Н. Ибрагимова[1], Т. С. Бекежанова[1], А. О. Итемирова[2], И. Р. Кулмагамбетов[1], З. Ж. Турлыбаева[1], А. Ж. Султанова[1], Р. Ш. Галимбаева[1], Л. П. Треножникова[1]

[1]ТОО «НПЦ микробиологии и вирусологии», Алматы, Казахстан,
[2]Областной кожно-венерологический диспансер МЗ РК, Алматы, Казахстан,
[3]АО «Центральная клиническая больница», Алматы, Казахстан

АКТИВНОСТЬ АНТИБИОТИКА РОЗЕОФУНГИНА В ОТНОШЕНИИ КЛИНИЧЕСКИХ ВОЗБУДИТЕЛЕЙ ВАГИНАЛЬНОГО КАНДИДОЗА

Аннотация. Полиеновый антибиотик розеофунгин (регистрационный номер РК-ЛС-5№023224) является новой лекарственной субстанцией, разработанной учеными Казахстана, на основе которой создана лекарственная форма противогрибкового препарата «Розеофунгин-АС, мазь 2%» для наружного применения (регистрационный номер РК-ЛС-5№023225). С целью создания новой лекарственной формы для лечения вагинального кандидоза изучена активность антибиотика розеофунгина методом диффузии в агар в отношении 15 клинических штаммов грибов рода *Candida: Candida albicans* (9 штаммов), *Candida krusei* (2 штамма), *Candida tropicalis* (2 штамма), *Candida glabrata* (1 штамм), *Candida parapsilosis* (1 штамм). Антибиотик розеофунгин проявил высокую антифунгальную активность в отношении клинических возбудителей вагинального кандидоза, минимальная подавляющая концентрация изменялась в пределах 1,66-2,5 мкг/мл. Наиболее высокой активностью антибиотик розеофунгин обладал в отношении клинических штаммов вида *Candida albicans*, МПК – 1,66-2,0 мкг/мл. Активность в отношении штаммов Candida non-albicans была ниже: МПК для *Candida tropicalis* составила 2,0 мкг/мл, для *Candida krusei, Candida glabrata* и *Candida parapsilosis* – 2,5 мкг/мл. Наличие высокой активности у антибиотика розеофунгина в отношении клинических возбудителей кандидоза свидетельствует о возможности разработки на его основе новых лекарственных препаратов, способных улучшить состояние больных в Казахстане и за его пределами.

Ключевые слова: антибиотик розеофунгин, антифунгальная активность, минимальная подавляющая концентрация, возбудители вагинального кандидоза.

Сведения об авторах:

Саданов А. К. – д.б.н., профессор, генеральный директор ТОО «Научно-производственный центр микробиологии и вирусологии»;

Акылова М. А. – врач-бактериолог бактериологической лаборатории отделения лабораторной диагностики Центральной Клинической Больницы МЗ РК;

Балгимбаева А. С. – к.б.н., заведующий лабораторией антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Ибрагимова Л. Н. – к.фарм.н., с.н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Бекежанова Т. С. – PhD-доктор, н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Итемирова А. О. – врач-дерматовенеролог Областного кожно-венерологического диспансера МЗ РК;

Кулмагамбетов И. Р. – д.м.н., профессор, г.н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Турлыбаева З. Ж. – PhD-докторант, н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Султанова А. Ж. – магистр биологии, м.н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Галимбаева Р. Ш. – биолог, м.н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии»;

Треножникова Л. П. – к.б.н., г.н.с. лаборатории антибиотиков ТОО «Научно-производственный центр микробиологии и вирусологии».

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ISSN 2518-1629 (Online), ISSN 2224-5308 (Print)

http://www.biological-medical.kz/index.php/ru/

Редактор *М. С. Ахметова, Т. М. Апендиев, Д. С. Аленов*
Верстка на компьютере *Д. Н. Калкабековой*

Подписано в печать 06.12.2018.
Формат 60x881/8. Бумага офсетная. Печать – ризограф.
4,5 п.л. Тираж 300. Заказ 5.