South Russian Journal of Cancer 2021, v.2, №3, p. 42-47
https://doi.org/10.37748/2686-9039-2021-2-3-5
REVIEW



# THE IMPORTANCE OF DEVELOPING NEW MANNAN TESTS IN THE DIAGNOSIS OF INVASIVE CANDIDIASIS IN ONCOLOGY PATIENTS

**O.Yu.Kutsevalova[1]*, Yu.Yu.Kozel[1], N.E.Nifantiev[2], A.V.Antonets[2,3], V.B.Krylov[2]**

1. National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation
2. N.D.Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, 47 Leninsky Prospekt, Moscow 119334, Russian Federation
3. Rostov State Medical University, 29 Nakhichevansky lane, Rostov-on-don, 344022, Russian Federation

## ABSTRACT

The regimens of anticancer therapy have been intensified and methods of high-dose chemotherapy (HDCT) have been introduced for recent years which made it possible to achieve significant progress in the results of tumor treatments. Intensification of chemotherapy regimens in cancer patients leads to the emergence of risk factors of invasive candidiasis (IC) development: agranulocytosis, disruption of the integrity of the mucous membranes, prolonged use of CVC, repeated antibiotic therapy, long-term parenteral nutrition. Thus, intensification of anticancer therapy may be accompanied by an increase in infection-mediated mortality.

IC is the most common invasive mycosis in Russia. More than 11 thousand cases of IC occur in our country every year. The frequency IC in Russia is 8.29 per 100 thousand of the population, which corresponds to the results of the LIFE study in European countries where this indicator varies from 2.2 to 11 per 100 thousand of the population. There are no clinical signs or symptoms specific for IC. It develops in patients with concomitant diseases, which significantly complicates the diagnosis. In this regard, an urgent issue is to improve the diagnosis of candidal infectious complications in cancer patients in order to optimize treatment by studying serological markers that have the greatest value in the diagnosis of infectious complications in cancer patients.

**Keywords:**
invasive, candidiasis, candidemia, oncology, *Candida spp*, mannan.

For correspondence:
Olga Yu. Kutsevalova – Cand. Sci. (Biol.), head of the laboratory of clinical Microbiology, bacteriologist National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: Olga_kutsevalova@mail.ru
ORCID: https://orcid.org/0000-0001-7452-6994
SPIN: 6271-1942, AuthorID: 363005
ResearcherID: AAM-9837-2020

Information about funding: the study was carried out with the financial support of the Russian Science Foundation (grant No. 19-73-30017).
Conflict of interest: authors report no conflict of interest.
Gratitude: the author expresses his gratitude to the Doctor of Medical Sciences, Professor, chief researcher of the Laboratory of Tumor Immunophenotyping National Medical Research Centre for Oncology of the Ministry of Health of Russia, Zlatnik E. Yu., for reviewing the article.

For citation:
Kutsevalova O.Yu., Kozel Yu.Yu., Nifantiev N.E., Antonets A.V., Krylov V.B. The importance of developing new mannan tests in the diagnosis of invasive candidiasis in oncology patients. South Russian Journal of Cancer. 2021; 2(3): 42-47. https://doi.org/10.37748/2686-9039-2021-2-3-5

Received 25.06.2021, Review (1) 14.07.2021, Review (2) 15.07.2021, Published 09.09.2021

Южно-Российский онкологический журнал 2021, т.2, №3, с. 42-47
https://doi.org/10.37748/2686-9039-2021-2-3-5
ОБЗОР

# ЗНАЧЕНИЕ РАЗРАБОТКИ НОВЫХ МАННАНОВЫХ ТЕСТОВ В ДИАГНОСТИКЕ ИНВАЗИВНОГО КАНДИДОЗА У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

**О.Ю.Куцевалова[1]*, Ю.Ю.Козель[1], Н.Э.Нифантьев[2], А.В.Антонец[2,3], В.Б.Крылов[2]**

1. ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
2. ФГБУН Институт органической химии им. Н.Д.Зелинского РАН, 119334, Российская Федерация, г. Москва, Ленинский проспект, д. 47
3. ФГБОУ ВО «РостГМУ» Минздрава России, 344022, Российская Федерация, г. Ростов-на-Дону, пер. Нахичеванский, д. 29

## РЕЗЮМЕ

За последние годы были интенсифицированы режимы противоопухолевой терапии и внедрены методы высокодозной химиотерапии (ВДХТ), что позволило достичь значимого прогресса в результатах лечения опухолевых процессов. Интенсификация режимов химиотерапии у онкологических больных приводит к возникновению факторов рисков развития инвазивного кандидоза (ИК): агранулоцитозу, нарушению целостности слизистых оболочек, длительному применению центральных венозных катетеров (ЦВК), повторной антибактериальной терапии, длительному парентеральному питанию. Таким образом, усиление противоопухолевой терапии может сопровождаться повышением инфекционно-опосредованной летальности.
Инвазивный кандидоз – самый распространенный микоз в России. Ежегодно в нашей стране возникает более 11 тысяч случаев ИК. Согласно данным многоцентровых исследований, частота ИК в России составляет 8,29 на 100 тысяч населения. В странах Европы, данный показатель варьируется от 2,2 до 11 на 100 тысяч населения. Не существует клинических признаков или симптомов, специфичных для инвазивного кандидоза который, как правило, развивается у пациентов на фоне сопутствующих заболеваний, что существенно затрудняет диагностику. В связи с этим актуальной задачей является улучшить диагностику кандидозных инфекционных осложнений у больных онкологического профиля для оптимизации лечения за счет исследования серологических маркеров, имеющих наибольшую диагностическую значимость в возникновении инфекционных осложнений у онкологических больных.

**Ключевые слова:**
инвазивный, кандидоз, кандидемия, онкология, *Candida spp*., маннан.

Для корреспонденции:
Куцевалова Ольга Юрьевна – к.б.н., заведующая лабораторией клинической микробиологии, врач-бактериолог ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: Olga_kutsevalova@mail.ru
ORCID: https://orcid.org/0000-0001-7452-6994
SPIN: 6271-1942, AuthorID: 363005
ResearcherID: AAM-9837-2020

Информация о финансировании: работа выполнена при финансовой поддержке Российского научного фонда (грант №19-73-30017).
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.
Благодарности: автор выражает благодарность д.м.н., профессору, главному научному сотруднику лаборатории иммунофенотипирования опухолей ФГБУ «НМИЦ онкологии» Минздрава России, Златник Е.Ю. за рецензирование статьи.

Для цитирования:
Куцевалова О.Ю., Козель Ю.Ю., Нифантьев Н.Э., Антонец А.В., Крылов В.Б. Значение разработки новых маннановых тестов в диагностике инвазивного кандидоза у онкологических больных. Южно-Российский онкологический журнал. 2021; 2(3): 42-47.
https://doi.org/10.37748/2686-9039-2021-2-3-5

Получено 25.06.2021, Рецензия (1) 14.07.2021, Рецензия (2) 15.07.2021, Опубликовано 09.09.2021

## RELEVANCE

In recent years, the regimens of antitumor therapy have been intensified and methods of high-dose chemotherapy (HDCT) have been introduced, which has made it possible to achieve significant progress in the results of treatment of tumor processes [1]. The intensification of chemotherapy regimens in cancer patients leads to the emergence of risk factors for the development of invasive candidiasis: agranulocytosis, violation of the integrity of the mucous membranes, prolonged use of central venous catheters (CVC), repeated antibacterial therapy, long-term parenteral nutrition. Thus, intensification of anticancer therapy may be accompanied by an increase in infection-mediated mortality [1-2].

Invasive candidiasis is the most common mycosis in Russia. Every year, more than 11 thousand cases of IC occur in our country [3]. According to the data of multicenter studies, the frequency of IR in Russia is 8.29 per 100 thousand of the population. In European countries, this indicator varies from 2.2 to 11 per 100 thousand population [4]. The most common variants of invasive candidiasis are candidemia, acute disseminated candidiasis and candidal peritonitis, other forms are somewhat less common [5].

According to the expert group of the Russian Association of Perinatal Medicine Specialists (RAPMS), the frequency of IC in newborns in the structure of infectious and inflammatory diseases is from 15 to 30 %. The incidence of IC in newborns is inversely proportional to the gestation period and body weight at birth and ranges from 2.6 % to 3.1 % in newborns with very low body weight and from 10 % to 16 % in newborns with extremely low body weight [6].

*Candida spp*. they are pathogens in 9-22 % of cases of all nosocomial infections. The frequency of invasive candidiasis in patients in intensive care units (ICU) varies from 0.3 to 10 %, depending on the profile of the departments. The mortality rate for invasive candidiasis in patients in the ICU is 10-47 % [7-9].

In 2020, due to the spread of the new coronavirus infection SARS-CoV-2, reports of cases of COVID-19-associated invasive candidiasis (COVID – 19 associated candidiasis-CAC) began to appear and systematize. To date, the development of acute respiratory distress syndrome with a concomitant risk of developing superinfection and stay in the ICU are identified as the main risk factors for the development of CAC [10].

IC usually develops in patients with concomitant diseases, which significantly complicates the diagnosis. The main risk factors for the development of IC are:

- surgical abdominal interventions, in particular, accompanied by the failure of anastamoses and repeated laparotomies;
- perforation of the gastrointestinal tract;
- staying in the ICU;
- chemo-and radiotherapy in cancer patients;
- oncohematological diseases;
- multiple and long-term colonization of *Candida spp*. (colonization index >0.5 or adjusted colonization index >0.4);
- the presence of a central venous catheter;
- complete parenteral nutrition;
- the use of broad-spectrum antibacterial agents;
- artificial ventilation of the lungs;
- infected pancreatic necrosis;
- hemo – and peritoneal dialysis;
- organ and tissue transplantation;
- the state of prematurity of children with very low and extremely low body weight;
- stay in burn units;
- diabetes mellitus;
- HIV infection;
- immunodeficiency conditions, including those caused by immunosuppressive therapy [6, 7, 11].

There are no clinical signs or symptoms specific to invasive candidiasis. Invasive candidiasis should be suspected in patients with known risk factors with fever of unknown origin that cannot be treated with antibacterial agents [12].

Thus, a large contingent of patients at risk of IC, a change in the structure of pathogens of nosocomial infections, accompanied by an increasing role of fungal pathogens, an increase in resistance to antimycotic drugs, bring the problem of diagnosing invasive mycoses to a new level. Timely diagnosis of IR is the key to ensuring a favorable outcome. In fact, 1-2 days of delay in starting effective antifungal therapy doubles the risk of death from IC [13, 14].

Microbiological methods and blood culture testing remain the gold standard for the diagnosis of inva-

sive candidiasis, but the difficulties of cultivating *Candida spp*. in the study of hemoculture, as well as a long growth time, this method is not sufficiently reliable [12]. Thus, a positive result of hemoculture is observed only in 21-71 % of patients with invasive candidiasis confirmed at autopsy, depending on the frequency of sampling and the volume of blood taken [15].

The development of additional molecular and serological methods for timely and accurate diagnosis of IR is becoming increasingly relevant.

One of the first commercial ELISA test systems were developed that allow detecting the mannan antigen – the main component of the *Candida spp*. cell wall and antibodies to mannan, PLATELIA™ Candida Ag PLUS and PLATELIA™ Candida Ab PLUS (Bio-Rad Laboratories, Marnes-la-Coquette, France). Under the auspices of the Third European Conference on Infectious Diseases in Leukemia, the characteristics of these test systems were analyzed based on the results of published studies [16, 17]. The diagnosis of IC in this study was established in accordance with the 2008 recommendations of the European Organization for Research and Treatment of Cancer / Mycoses Study Group. Sensitivity and specificity were calculated for the separate determination of mannan antigen, mannan antibodies and for combined testing. Data from 14 studies were analyzed (all studies, with the exception of one, were retrospective). The total number was 453 patients and 767 control cases. In the studies, the sample was represented by patients of oncological and oncohematological departments, departments of surgery and intensive care. The sensitivity of the determination of the mannan antigen was 58 % (95 % confidence interval [CI], 53-62); the specificity was 93 % (95 % CI, 91-94). When determining mannan antibodies, the sensitivity was 59 % (95 % CI, 54-65); the specificity was 83 % (95 % CI, 79-97). In the combined determination of mannan and antibodies to it, the sensitivity was 83 % (95 % CI, 79-87), the specificity was 86 % (95 % CI, 82-90). A significant heterogeneity of sensitivity was noted in the determination of both mannan and mannan antibodies for different *Candida* species. The highest was found for *C. albicans*, followed by *C. glabrata* and *C. tropicalis* [18].

However, in a 2016 study, including among patients in the ICU with severe abdominal pathology, a combined determination of mannan antigen and antibodies to the mannan antigen *Candida spp*. it turned out to be ineffective (sensitivity 55 % and specificity 60 %). Antibodies are often present in immunocompromised patients with previous candidemia or colonization [19].

Thus, the prognostic value of detecting antibodies remains low with a single test and the absence of subsequent detection of their increasing concentration. This observation and the unexplained variability of tests in various studies are an important warning for doctors, since the unreliability of the results of laboratory diagnostics can lead to unjustified prescribing of antifungal drugs to patients whose candidiasis is unlikely [20, 21].

According to the updated 2016 Guidelines for the Clinical Practice of IC Management of the American Society of Infectious Diseases (Infectious Diseases Society of America), the role of existing tests for the determination of *Candida spp*. mannan and mannan antibodies remains unclear. These tests are not approved by the US FDA and are available mainly in Europe, where their use is allowed [22]. A number of domestic clinical recommendations suggest the possibility of using tests to determine mannan and antibodies to mannan [6, 7, 23].

## CONCLUSION

The development of additional molecular and serological methods for timely and accurate diagnosis is becoming increasingly relevant. In this situation, it is necessary to search for biomarkers that would be an objective and reliable opportunity for a clinician to quickly respond to the possible development of a severe infectious complication [24-25]. The study of the structure of carbohydrate antigens of fungal pathogens is a key link in the successful development of more valid diagnostic tests. The development of additional molecular and serological methods for timely and accurate diagnosis is becoming increasingly relevant. The use of tests for the determination of *Candida spp*. mannan and antibodies to mannan will help to improve diagnosis and clarify the etiological factor of life-threatening infectious complications.

Authors contribution:
Kutsevalova O.Yu. – research concept and design, text writing, material processing
Kozel Yu.Yu. – scientific editing.
Nifantiev N.E. – scientific editing.
Antonets A.V. – collection, analysis and interpretation of data.
Krylov V.B. – collection, analysis and interpretation of data.

## References

1. Dinikina YuV, Shadrivova OV, Belogurova MB, Ignatyeva SM, Bogomolova TS, Klimko NN. Breakthrough invasive candidiasis in pediatric patient with Ewing's sarcoma: dinical case report and literature review. Oncohematology. 2019;14(4):59–66. (In Russian).
https://doi.org/10.17650/1818-8346-2019-14-4-59-66

2. Mikhalkina EV, Skachkova LS, Kit OI, Fomenko YuA. Socio-economic predictors of cancer. Journal of Institutional Research. 2020;12(3):122–141. (In Russian).
https://doi.org/10.17835/2076-6297.2020.12.3.122-141

3. Klimko NN, Kozlova YaI, Khostelidi SN, Shadrivova OV, Borzova YuV, Vasileva NV. The prevalence of serious and chronic fungal diseases in russian federation on life program model. Problems of medical mycology. 2014;16(1):3–8. Available at: https://mycology.szgmu.ru/files/MAPO_1_2014.pdf. Accessed: 16.05.2021. (In Russian).

4. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. J Fungi (Basel). 2017 Oct 18;3(4):E57.
https://doi.org/10.3390/jof3040057

5. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012 Dec 19;4(165):165rv13.
https://doi.org/10.1126/scitranslmed.3004404

6. Invasive candidiasis in newborns. Clinical Guidelines of the Ministry of Health of the Russian Federation. Moscow, 2017, 34 p. Available at: https://dzhmao.ru/spez/klin_recom/neonatologiya/invazKandidoz.pdf. Accessed: 16.05.2021. (In Russian).

7. Diagnosis and treatment of mycoses in intensive care units: Russian recommendations. Ed. by N. N. Klimko. 2nd ed. additional and re-edited by M.: Farmtek, 2015, 96 p. Available at: http://nasci.ru/?id=2269&download=1. Accessed: 16.05.2021. (In Russian).

8. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004 Aug 1;39(3):309–17.
https://doi.org/10.1086/421946

9. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014 Mar 27;370(13):1198–1208.
https://doi.org/10.1056/NEJMoa1306801

10. Arastehfar A, Carvalho A, Nguyen MH, Hedayati MT, Netea MG, Perlin DS, et al. COVID-19-Associated Candidiasis (CAC): An Underestimated Complication in the Absence of Immunological Predispositions? J Fungi (Basel). 2020 Oct 8;6(4):E211. https://doi.org/10.3390/jof6040211

11. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445–1456.
https://doi.org/10.1056/NEJMra1315399

12. Kutsevalova O, Antonets A, Kit O, Panova N, Lysenko I, Dmitrieva V, Pak E, Kozyuk O, Marykov E, Klyasova G. New approaches to the verification of bacterial and candidal bloodstream infection. J. Fungi. 2019 Dec;5(4):208–210.
https://doi.org/10.3390/jof5040095

13. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother. 2005 Sep;49(9):3640–3645.
https://doi.org/10.1128/AAC.49.9.3640-3645.2005

14. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. 2006 Jul 1;43(1):25–31.
https://doi.org/10.1086/504810

15. Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013 May;56(9):1284–1292.
https://doi.org/10.1093/cid/cit006

16. Kolupaev VE, Sokolinskaya IYu. The role of determining the mannan antigen and antibodies to manan in the diagnosis of invasive candidiasis. Remedium Privolzhye.

2015;4(134):34–35. https://www.remedium.ru/upload/iblock/023/Remedium_4.15%20SMALL.pdf

17. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C, Third European Conference on Infections in Leukemia Group. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. Crit Care. 2010;14(6):R222. https://doi.org/10.1186/cc9365

18. 18. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008 Jun 15;46(12):1813–1821. https://doi.org/10.1086/588660

19. León C, Ruiz-Santana S, Saavedra P, Castro C, Loza A, Zakariya I, et al. Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions. Crit Care. 2016 May 16;20(1):149. https://doi.org/10.1186/s13054-016-1324-3

20. Verduyn Lunel FM, Donnelly JP, van der Lee H. L, Blijlevens NMA, Verweij PE. Circulating Candida-specific anti-mannan antibodies precede invasive candidiasis in patients undergoing myelo-ablative chemotherapy. Clin Microbiol Infect. 2009 Apr;15 (4):380–386. https://doi.org/10.1111/j.1469-0691.2008.02654.x

21. Duettmann W, Koidl C, Krause R, Lackner G, Woelfler A, Hoenigl M. Specificity of mannan antigen and anti-mannan antibody screening in patients with haematological malignancies at risk for fungal infection. Mycoses. 2016 Jun;59(6):374–378. https://doi.org/10.1111/myc.12482

22. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15; 62 (4): e1-50. https://doi.org/10.1093/cid/civ933

23. Charushina IP, Feldblum IV, Vorobyeva NN, Balandina SYu, Kuznetsova MV, Verbitskaya TA. Invasive candidiasis in HIV-infected patients. Federal clinical recommendations. Moscow, 2017, 46 p. http://nasci.ru/?id=2883

24. Noskova OA, Agapova ED, Baturina EA, Gvak GV. Microbiological Monitoring in the System of Epidemiological Surveillance of Purulent-Septic Infections in a Multidisciplinary Hospital. Acta Biomedica Scientifica. 2019;4(5):122–126. (In Russian). https://doi.org/10.29413/ABS.2019-4.5.19

25. Gusarov VG, Lashenkova NN, Petrova NV, Dementienko MV, Shilkin DN, Nesterova EE, et al. Protocols of empirical antimicrobial therapy in improving quality of emergency medical care to patients with infection in multidisciplinary surgical hospital. Medical Alphabet. 2016;4(33(296)):24–28.

Information about author:

Olga Yu. Kutsevalova* – Cand. Sci. (Biol.), head of the laboratory of clinical Microbiology, bacteriologist National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-don, Russian Federation. ORCID: https://orcid.org/0000-0001-7452-6994, SPIN: 6271-1942, AuthorID: 363005, ResearcherID: AAM-9837-2020

Yuliya Yu. Kozel – Dr. Sci. (Med.), professor, head of the Department of pediatric Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-don, Russian Federation. ORCID: https://orcid.org/0000-0002-6681-3253, SPIN: 6923-7360, AuthorID: 732882

Nikolay E. Nifantiev – member of Russian Academy of Sciences, D.Sc. in Chemistry., Head of the Laboratory of Glycoconjugate Chemistry N.D.Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, Russian Federation. ORCID: https://orcid.org/0000-0002-0727-4050, SPIN: 5160-0379, AuthorID: 49545, ResearcherID: O-6579-2015

Anna V. Antonets – Cand. Sci. (Med.), MD, geneticist Rostov State Medical University, Rostov-on-don, Russian Federation, researcher at the Laboratory of Glycoconjugate Chemistry N.D.Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, Russian Federation. ORCID: https://orcid.org/0000-0002-8074-1890, SPIN: 9450-9127, AuthorID: 917704

Vadim B. Krylov – PhD in Chemical sciences, senior researcher at the Laboratory of Glycoconjugate Chemistry N.D.Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, Russian Federation. SPIN: 9750-0292, AuthorID: 153059