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ВЕСТНИК

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NAS RK is pleased to announce that Bulletin of NAS RK scientific journal has been accepted for indexing in the Emerging Sources Citation Index, a new edition of Web of Science. Content in this index is under consideration by Clarivate Analytics to be accepted in the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index. The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of Bulletin of NAS RK in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential multidiscipline content to our community.

Қазақстан Республикасы Ұлттық ғылым академиясы "ҚР ҰҒА Хабаршысы" ғылыми журналының Web of Science-тің жаңаланған нұсқасы Emerging Sources Citation Index-те индекстелуге қабылданғанын хабарлайды. Бұл индекстелу барысында Clarivate Analytics компаниясы журналды одан әрі the Science Citation Index Expanded, the Social Sciences Citation Index және the Arts & Humanities Citation Index-ке қабылдау мәселесін қарастыруда. Web of Science зерттеушілер, авторлар, баспашылар мен мекемелерге контент тереңдігі мен сапасын ұсынады. ҚР ҰҒА Хабаршысының Emerging Sources Citation Index-ке енуі біздің қоғамдастық үшін ең өзекті және беделді мультидисциплинарлы контентке адалдығымызды білдіреді.

НАН РК сообщает, что научный журнал «Вестник НАН РК» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Вестника НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному мультидисциплинарному контенту для нашего сообщества.

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INDICATORS OF CELL METABOLISM *IN VITRO* IN RESEARCHES OF ANTI-INFLAMMATORY AND CYTOTOXIC EFFECTS OF FULLEROPYRROLIDINES C60 AND THEIR INITIAL SUBSTRATES

Abstract. The article considers data on the *in vitro* study of new fulleropyrrolidine compounds for anti-inflammatory and cytotoxic activity in cultures of human monocyte cell lines *MonoMac-6* and *THP-1Blue* and also as inhibitors of human neutrophil elastase. This enzyme is a regulator of inflammation. In different situations, it can act both as a pro-inflammatory and as an anti-inflammatory agent. An imbalance in the regulation of elastase activity plays an important role in the pathogenesis of cystic fibrosis, acute respiratory distress syndrome, bronchiectasis, chronic obstructive pulmonary disease, type 2 diabetes mellitus, atherosclerosis and hypertension. In the future, such studies should lead to the creation of optimal *in vitro* models that most adequately reflect the situation *in vivo* and establish the relationship between the structure and activity of the studied drugs. It is noted that the presence of lipophilic properties in fullerene C60 derivatives is especially important in the development of pharmaceuticals for the control of pathogens of various infectious diseases. Fullerene C60 derivatives have the ability to easily penetrate lipid membranes, overcome the blood-brain barrier, and modulate ion transport. Compounds were tested for anti-inflammatory and cytotoxic activity (*in vitro*) on cultures of human monocytic cell lines *MonoMac-6* and *THP-1Blue*. Modified fullerene compounds of various structures were tested for their inhibitory ability against neutrophil elastase enzyme (*in vitro*). Elastase activity was evaluated by the ability of fulleropyrrolidine compounds to hydrolyze the synthetic substrate *N-methylsuccinyl-Ala-Ala-Pro-Val-7-amino-4-me-thylcoumarin* (*Calbiochem*). The results of studies of fullerene compounds in relation to their anti-inflammatory and cytotoxic activity are obtained. The analysis of the fluorescence kinetics of the compounds was carried out. The cytotoxic activity of the samples was investigated in the *Brine Shrimp* test using *Artemia salina*. All compounds have cytotoxicity, which suggests a lack of selectivity of chemotherapeutic action. In general, the presence of a cytotoxic effect confirms the reality of antimicrobial action. The results of the study of the antibacterial and antifungal activity of the synthesized new fulleropyrrolidines and their starting substrates are described (*S. aureus* 505, *Bacillus subtilis*, *Str.agalactiae*, *E. Coli M-17*, *Ps.aeruginosa*, *Candida albicans*, *Penicillium citrinum*, *Aspergillus niger*, *Aspergillus flavus*, *Trichophyton mentagraphytos*, *Epidermophyton floccosum*). As a result of the study of the potential antifungal activity of the compounds, it was found that only two drugs inhibit the growth of test cultures *in vitro*. All other studied samples have practically no activity against the yeast fungi *Candida albicans*. In general, the presence of a cytotoxic effect in the studied fullerene compounds confirms the reality of the antimicrobial action.

Key words: fulleropyrrolidines, fullerene C60, neutrophil elastase inhibitors, anti-inflammatory activity, cytotoxicity.

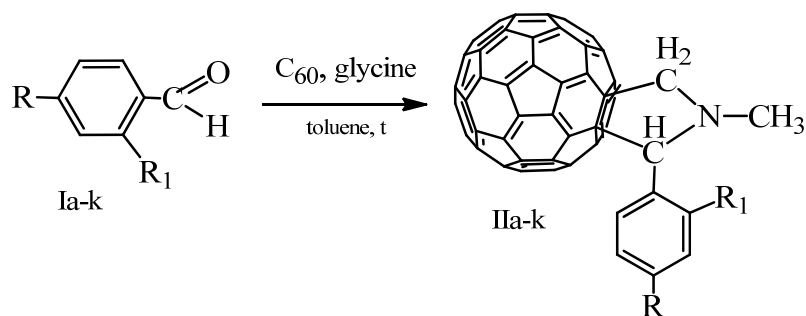
Introduction. Nowadays, using of fullerene C60 in the field of biology and medicine is of particular interest. Fullerenes themselves are extremely hydrophobic and not very suitable for introduction into a living organism. However, the methods developed in recent years for the chemical modification of fullerenes using water-soluble and lipophilic adducts have revealed the widest range of their biological effects [1]. It was found that many organic derivatives of fullerene C60 have the ability to penetrate

through lipid membranes, overcome the blood-brain barrier and modulate ion transport [2]. First of all, it is the absorption of free radicals and protection against oxidative stress. Secondly, fullerenes can serve as carriers, for example, for HIV proteases [3]. Finally, fullerenes can produce singlet oxygen and cause DNA damage to transformed (tumor) cells [4]. The presence of lipophilic properties in fullerene C60 derivatives is especially important in the development of pharmaceuticals for the control of pathogens of various infectious diseases. The possibility of using C60 as a cytoprotective agent is one of the most developed areas due to fundamental research by Dugan and other authors [5-7], who established the ability of fullerene to trap superoxide radicals. Fullerene derivatives using in medical practice is necessary to understand the causes and mechanisms of the direct and long-term consequences of their *in vivo* and *in vitro* effects, based on the introduction of proliferation and apoptosis of cell necrosis into the regulation. A great influence on the subsequent properties of fullerene nanoparticles has a method for their preparation and functionalization, as well as morphology - their size, shape, surface topography, affinity for cellular structures, i.e. parameters depending on which the biological effects of nanoparticles can vary from cytoprotective to cytotoxic. The proposed article considers the possibility of such an approach for the quantitative assessment of anti-inflammatory and cytotoxic activity in cultures of human mono-monocytic cell lines MonoMac-6 and THP-1 Blue, as well as human neutrophil elastase inhibitors using some fulleropyrrolidines C60 and its structural fragments as an example.

In the future, such studies should lead to the creation of optimal models *in vitro* that most adequately reflect the *in vivo* situation and establish the characteristics of the relationship between the structure and activity of the studied drugs. Assessment of the anti-inflammatory and cytotoxic effects of potentially bioactive substances is a necessary step in the study at the preclinical stage in the framework of the GLP system [8]. This enzyme is a regulator of inflammation, and in different situations it can act both as a pro-inflammatory and as an anti-inflammatory agent. Imbalance of elastase activity regulation plays an important role in the pathogenesis of cystic fibrosis, acute respiratory distress syndrome, bronchiectasis, chronic obstructive pulmonary disease, type 2 diabetes, atherosclerosis, arterial hypertension. The results of a study of a number of compounds on antibacterial and antifungal activity with various test cultures are presented

Materials and methods. Synthesis methods and data on the synthesis, structure and physicochemical properties of fulleropyrrolidines (IIa-e) and their tartrate salts are described in [9-12], are presented in figures 1, 2 and table 1. The antibacterial and antifungal activity of the newly synthesized fulleropyrrolidines (IIa-d) was held at the Department of Microbiology of the Karaganda Medical University. Compounds (IIa-e) were tested for anti-inflammatory and cytotoxic activity (*in vitro*) in cultures of human monocytic cell lines *MonoMac-6* and *THP-1 Blue*. The anti-inflammatory effect was evaluated by the ability of the compounds to suppress lipopolysaccharide (LPS) -induced production of anti-inflammatory cytokines interleukin-6 (IL-6) and as a tumor necrosis factor (TNF) in *MonoMac-6* cells, as well as NF-κB-dependent production of alkaline phosphatase (ALP) in transfected THP-1 Blue cells. Cells were treated with the compound for 30 min, then 0.5 Lg / ml LPS was added to the cell culture. Cytokine or alkaline phosphatase levels were evaluated after 24-hour incubation.

Cytokines were measured in cell supernatants using an enzyme immunoassay (Elisa). AP production was measured using a specific Quanti-Blue™ substrate. The level of cytotoxicity was evaluated using the chemiluminescent CellTiter-Glo kit. The effective concentration causing a 50% suppression of the response (IC₅₀) was found using regression analysis using dose-dependent curves (at least 5 concentrations).



I, IIa: R = F, R₁ = H; I, IIb: R = Cl, R₁ = H; I, IIc: R = Br, R₁ = OH; I, IId: R = (C₂H₅)₂N-, R₁ = H;
I, IIe: R = (C₂H₅)₂N-, R₁ = OH;

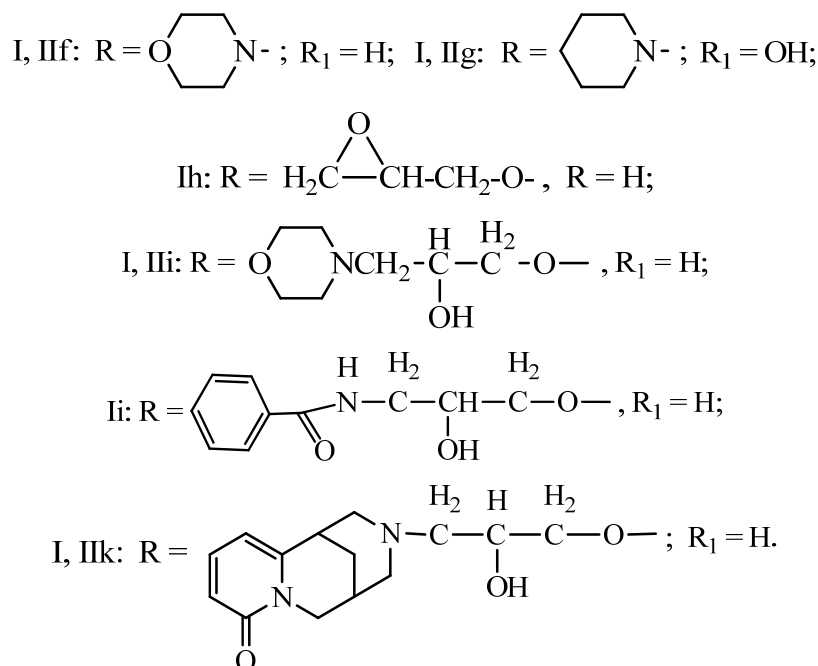
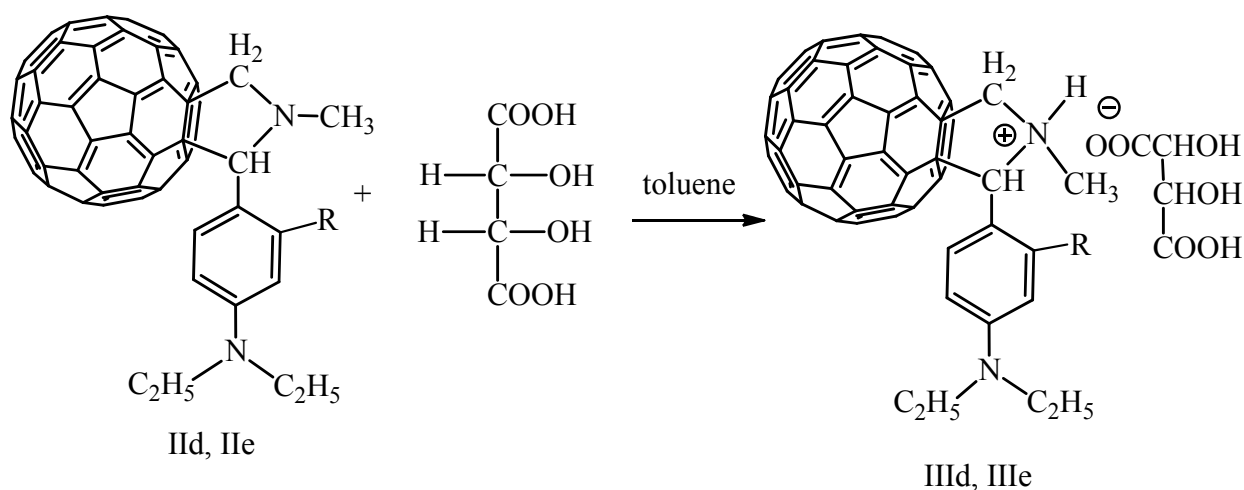


Figure 1 – The reaction of the formation of fulleropyrrolidines (IIa-e)



R = H (IId, III d); R = OH (IIe, IIIe).

Figure 2 – The synthesis of tartrate salts of fulleropyrrolidines

Results and discussion. Compounds (I, II d-k) were tested to evaluate their inhibitory effect on the activity of the neutrophil elastase enzyme (EC 3.4.21.37). Elastase activity was assessed by the ability of the compounds to hydrolyze the synthetic substrate N-methylsuccinyl-Ala-Ala-Pro-Val-7-amino-4-methylcoumarin (Calbiochem). The formation of a fluorescent product was measured with excitation of 355 nm and emission of 460 nm with a Fluoroskan-Ascent FL instrument. An effective concentration causing a 50% inhibition of enzyme activity (IC₅₀) was found by regression analysis. The inhibitory activity of compounds with relation to human neutrophil elastase is shown in table 1.

Table 1 – Inhibitory activity of the compounds (Id-k) in relation with human neutrophil elastase

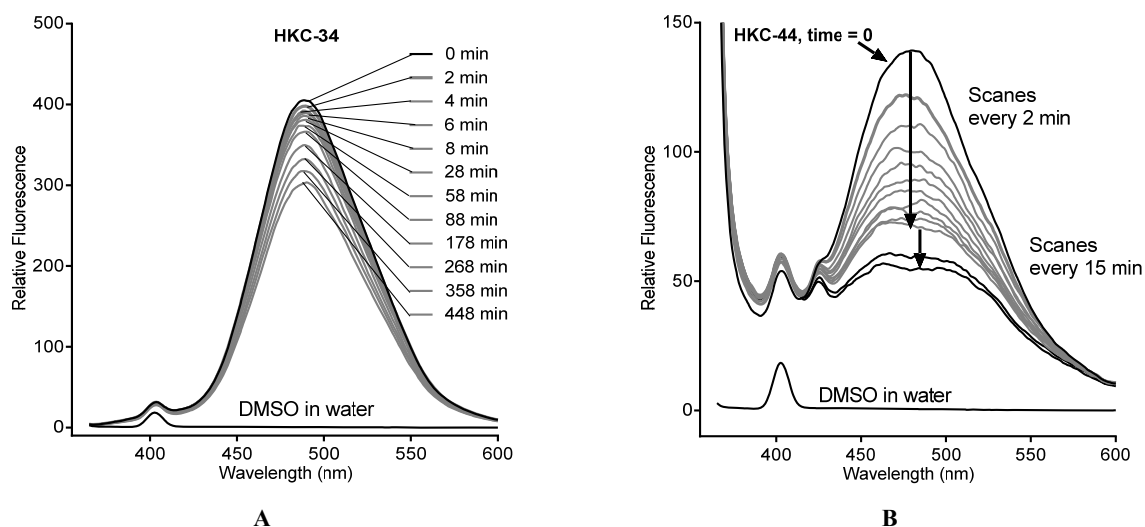
Compounds	IC ₅₀ , μM
Id	NA ^a
Ie	NA ^a
If	NA ^b
Ih	NA ^c
Ii	NA ^b
Ij	33,3±0,13
Ik	NA ^a
IIa	0,09±0,10
IIb	0,10±0,01
IIc	0,18±0,15
IId	0,02±0,02
IIe	0,09±0,23
IIf	0,12±0,10
IIh	0,07±0,04
IIi	0,15±0,12
IIk	0,03±0,02
IIIe	0,12±0,05

^a Compound is rapidly hydrolyzed, which is accompanied by either a decrease or an increase in intrinsic fluorescence at 460 nm; ^b no inhibition of enzyme activity at a concentration of <100 μM; adhesion has a high level of intrinsic fluorescence.

As follows from the data in table 1, only compound (Ij) showed the highest activity with an IC₅₀ of about 33.3 μM, while fullerene derivatives showed weak activity.

The rapid hydrolysis of most compounds does not allow the correct registration of the kinetics of the hydrolysis of the fluorescent substrate with N-methylsuccinyl-Ala-Ala-Pro-Val-7-amino-4-methylcoumarin by the elastase enzyme at the same fluorescence parameters ($\lambda_{\text{ex}} = 355 \text{ nm}$, $\lambda_{\text{em}} = 460 \text{ nm}$) Although compound (Ih) is sufficiently stable for the 5 min necessary for registration of the enzymatic reaction, it has a high basic autofluorescence, which also negatively affects the correct registration of the reaction kinetics. The kinetics of the compound (Ih) and (Ik) fluorescence spectra, which are noted above as compounds with a high level of intrinsic fluorescence, were recorded on a Perkin Elmer LS50B instrument at $\lambda_{\text{ex}} = 355 \text{ nm}$. Compound (Ih) has a specific fluorescence peak ($\lambda_{\text{ex}} = 355 \text{ nm}$; $\lambda_{\text{em}} = 489 \text{ nm}$). In an aqueous medium, compound (Ih) is slowly hydrolyzed, which is accompanied by a decrease in fluorescence (figure 3A). Compound (Ik) has a specific fluorescence peak ($\lambda_{\text{ex}} = 355 \text{ nm}$; $\lambda_{\text{em}} = 475 \text{ nm}$). In an aqueous medium, compound (Ik) is almost completely hydrolyzed in 60 minutes, which is accompanied by a decreasing in fluorescence in the region of 460-475 nm (figure 3B).

Compounds (Ih-k) of various structures were tested in relation to their anti-inflammatory and cytotoxic activity and inhibitory ability against neutrophil elastase enzyme (in vitro). The results of compounds (Ih-k) studies in relation to their anti-inflammatory and cytotoxic activity are presented in table 2.



A. Spectra (Ih) were taken at the indicated time after adding it to water. B. Spectra (Ik) were taken for the first 20 minutes every 2 minutes; the last 2 spectra were recorded with an interval of 15 min
Figure 3 – Kinetics of the fluorescence spectra of compounds (Ih) and (Ik) (25 μ M solution in water with 0.25% dimethyl sulfoxide) at $\lambda_{\text{exc}} = 355$ nm (gap width 5 nm).

Table 2 – Effect of the compounds (Ih-k) on LPS-induced production of cytokines (TNF and IL-6) and alkaline phosphatase (AP) in a cell culture and an estimation of their cytotoxicity

Compounds	MonoMac-6 cells			THP-1 Blue cells	
	TNF	IL-6	Toxicity	Alkaline phosphatase	Toxicity
	IC ₅₀ , μ M				
Ih	NA	NA	NT	NA	NT
Ii	NA	NA	NT	NA	NT
Ij	NA	0,11	NT	NA	NT
Ik	NA	NA	NT	NA	NT
Ile	NA	NA	NT	NA	NT
IIf	NA	NA	NT	NA	NT
Ilg	NA	NA	NT	NA	NT
IIk	NA	0,03	NT	NA	NT

NA and NT - no inhibition of production or cytotoxicity at concentrations <100 μ M.

From the data presented in table 2 it follows that the studied compounds do not have cytotoxicity, but Ij and Iik in low concentrations are able to suppress the production of IL-6, but not TNF. This property seems to be very interesting, since the production of IL-6 and TNF in cells is regulated by various mechanisms [15-17].

The results are present in a table 3 of a study a number of compounds for antibacterial and antifungal activity. Test method for antimicrobial and antifungal activity - disco-diffuse in agar with test cultures: *S. aureus* 505, *Bacillus subtilis*, *Str. agalactiae*, *E. Coli*M-17, *Ps. aeruginosa*, *Candida albicans*, *Penicillium citrinum*, *Aspergillus niger*, *Aspergillus flavus*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*.

Benzylpenicillin sodium salt was chosen as the standard for antimicrobial activity, and nystatin was chosen for antifungal activity. The concentrations of the tested drugs were 1 μ g for antibacterial activity, 10 μ g for antifungal activity. The concentration of the reference preparations was 1 mg. The antimicrobial activity of the samples was evaluated by the diameter of the zones of growth inhibition of the test strains (mm). The diameters of the zones are less than 10 mm and the continuous growth in the cup was evaluated as the absence of antimicrobial activity, 10-15 mm - weak activity, 15-20 mm - moderately pronounced activity, over 20 mm - pronounced. Each sample was tested in three parallel experiments. Statistical processing was performed using parametric statistics methods with calculation of arithmetic mean and standard error.

Table 3 – Antimicrobial activity of the samples

Compounds	Staphylococcus aureus (mm)	Bacillus subtilis (mm)	Escherichia coli (mm)	Candida albicans (mm)
IId	11,3±1,1	10,1±1,2	10,1±1,3	9,1±1,2
IIE	14,2±1,2	16,4±1,1	14,3±1,2	12,4±1,1
Ij	16,1±1,3	15,2±1,3	15,1±1,0	13,2±1,3
IIIId	9,7±0,3	10,0±1,1	9,0±0,4	8,6±1,0
IIIe	12,3±1,1	14,3±1,3	15,1±1,3	10,2±1,1
Ih	15,2±1,3	15,2±1,1	17,2±1,4	11,3±1,3
IIi	11,5±0,4	10,2±0,5	9,2±1,1	10,0±0,1
IIj	15,2±1,2	14,3±0,1	16,0±0,9	14,3±1,1
IIk	10,1±0,5	9,1±1,4	8,0±0,7	7,8±1,4
Benzylpenicillin sodium salt	14,4±1,2	16,1±1,2	13,3±1,2	–
Nystatin				18,2±1,0

The cytotoxic activity of the samples was investigated in the Brine Schrimp test using artemiasalina 2-day-old shrimp larvae. The average lethal dose of the samples and the upper and lower toxic limits were calculated using the Finney program.

In the study of antimicrobial activity, dilution was carried out at the rate of 1 mg of substance per 1 ml of solvent, 4 types of bacteria were used: Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Candida albicans. These cultures were sown using the lawn method, respectively, on the following nutrient media: Lauryl Sulphate Agar, Endo medium, nutrient agar, and Saburo medium. Then Petri dishes were incubated for one day at 37 ° C. The results of the identified growth retardation in the media are shown in table 3.

In a result of the study of the potential antifungal activity of the compounds it was found that only IIE and IIIe inhibit the growth of test cultures in vitro. An exception is the culture of yeast Candida albicans, which does not respond to the studied compounds (table 4). All other studied samples have practically no activity against fungi.

Table 4 – Antifungal activity of the samples (Ie) и (IIIe)

Compounds	Diameter of growth inhibition zones, mm				
	Penicillium citrinum	Aspergillus niger	Aspergillus flavus	Trichophyton mentagrophytos	Epidermophyton fiocosum
IIE	13,3±1,1	12,4±1,1	14,2±2,1	–	11,4±1,3
IIIe	15,2±1,3	12,3±2,2	13,3±1,4	10,3±3,1	14,1±1,2
Nystatin	16,2±3,1	12,3±1,1	15,1±3,2	14,2±2,2	12,3±1,2

The cytotoxic activity of the samples was investigated in the Brine Schrimp test using Artemiasalina 2-day-old shrimp larvae. The medium for the removal of sea crustaceans was a 3.3% solution of sea salt. Larvae were grown by immersing eggs of sea crustaceans in artificial sea water and incubated for 48 h at a temperature of 37°C. Then, 10 pieces of Artemiasalina sea crustaceans were caught in each vial, and the studied pharmacological substances were added separately in dissolved form. Sea crustaceans in bottles with the addition of N-methyl-1-[(4-diethylamino-2-hydroxyphenyl)]-fullerene-C60-[1,9c] pyrrolidine (IIE) and N-methyl-1-[(4-diethylamino-2-hydroxyphenyl)]-fullerene-C60-[1,9c] -pyrrolidinium tartrate (IIIe), immediately died. Vials with substances Ih, Ij, IIf, IIi, IIk were stayed at room temperature in the light for 24 hours. After 24 hours, an average of 1-2 dead larvae were found.

As a result of studies, it was found that the presented substances, which showed weak antimicrobial and antifungal activity, have cytotoxicity, which are suggested have a lack of selectivity of the chemotherapeutic effect. In general, the presence of a cytotoxic effect confirms the reality of antimicrobial action.

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ФУЛЛЕРОПИРРОЛИДИНДЕР МЕН ОЛАРДЫҢ БАСТАПҚЫ СУБСТРАТТАРЫНЫҢ ҚАБЫНУҒА ҚАРСЫ ЖӘНЕ ЦИТОУЫТТЫ ӘСЕРІН ЗЕРТТЕУДЕГІ *IN VITRO* КЛЕТКАЛЫҚ МЕТАБОЛИЗМ КӨРСЕТКІШТЕРІ

Аннотация. Мақалада MonoMac-6 және THP-1Blue адам моноцитарлы клетка сызықтарының өсіндісінде *in vitro* қабынуға қарсы және цитоуытты белсенділігіндегі жаңа фуллеропирролидин қосылыстарын, сондай-ақ адам нейтрофилдерінің эластаза ингибиторлары ретінде зерттеу туралы мәліметтер қарастырылған. Бұл қарастырылған фермент қабынудың реттеушісі болып саналады. Әртүрлі жағдайларда олар қабынуға әсер етуші немесе қабынуға қарсы агент ретінде де белсенділік көрсетеді. Эластазаның осындай жағдайға байланысты әсер ететін белсенділігі муковисцидоз патогенезінде әсері жылдам респираторлық дистресс-синдром, қант диабетінің екіншілік түрінде және артериалық гипертензия кезінде маңызды қызмет атқарады. Болашақта мұндай зерттеулер *in vivo* жағдайын неғұрлым барабар көрсететін *in vitro* оңтайлы үлгілерін құруға және зерттелетін препараттардың құрылымы мен белсенділігі арасындағы арақатынас ерекшелігін анықтауы тиіс. Фуллерен C60 туындыларының липофильді қасиеттерінің болуы түрлі инфекциялық ауру қоздырғышына қарсы фармацевтика өндірісінде дәрі-дәрмек жасауда өте маңызды қасиет болып саналатыны айқындалды. Фуллерен C60 туындылары липофильді адам клеткасының мембранасынан, сонымен бірге гематоэнцефалитикалық кедергіден оңай шыға алады және иондарды тасымалдау қасиеттері бар. Синтезделіп алынған жаңа фуллерендік заттар адамның моноцитарлы сызықты *MonoMac-6* және *THP-1Blue* клеткаларында қабынуға және цитотоксикологиялық белсенділікке қарсы (*in vitro*) жағдайында зерттелді. Құрылысы түрлі фуллерендік түрлендірілген қосылыс нейтрофильдерінің ферментті эластазасына қарсы тежеуші, цитоуытты және қабынуға қарсы (*in vitro* жағдайында) әсерін тексеру нәтижелері қарастырылды. Эластаза белсенділігі фуллеропирролидинді қосылыстардың синтетикалық *N-methylsuccinyl-Ala-Ala-Pro-Val-7-amino-4-me-thylcoumarin (Calbiochem)* субстратті гидролиздеу қабілеттілігіне байланысты бағаланды. Фуллерендік туындылардың қабынуға және цитоуытқа белсенділік қасиеттері бойынша зерттеу мәліметтері алынды. Құрылысы әртүрлі фуллерендік қосылыстардың флуоресценциялық кинетикасына талдау жасалды. Синтезделіп алынған жаңа фуллеропирролидиндер мен олардың бастапқы субстраттарының бактерияларға және грибтарға қарсы әсерін зерттеу нәтижелері сипатталады. Кейбір заттардың бактерия мен грибке қарсы белсенділігін зерттеу нәтижелері келтірілген (*S. aureus 505, Bacillus subtilis, Str.agalactiae, E. Coli M-17, Ps.aeruginosa, Candida albicans, Penicillium citrinum, Aspergillus niger, Aspergillus flavus, Trichophyton mentagraphyos, Epidermophyton floccosum*). Фуллерендік туындылардың цитоуытты белсенділігі *Brine Schrimp* тексеру жүйесі арқылы теңіз креветкаларының *Artemia salina* кішкене құрттарын қолдану негізінде зерттелді. Грибтерге қарсы фуллеренді туындылар белсенділігін зерттеу нәтижесінде тек қана екі жаңа заттың *in vitro* жағдайында тестілік өсінділердің жетілу үдерісін тоқтатыны анықталды. Қалған барлық зерттелетін заттар *Candida albicans* грибіне қарсы белсенділік танытпады. Жалпы айтқанда зерттелген заттарда цитоуыттың болуы олардың микробтарға қарсы белсенділік көрсетуге мүмкіндігінің бар екенін көрсетеді.

Түйін сөздер: фуллеропирролидиндер, фуллерен C60, нейтрофильдер эластазасының тежеуші, қабынуға қарсы белсенділік, цитоуыт.

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ПОКАЗАТЕЛИ КЛЕТОЧНОГО МЕТАБОЛИЗМА *IN VITRO* В ИССЛЕДОВАНИИ ПРОТИВОВОСПАЛИТЕЛЬНЫХ И ЦИТОТОКСИЧЕСКИХ ЭФФЕКТОВ ФУЛЛЕРОПИРРОЛИДИНОВ И ИХ ИСХОДНЫХ СУБСТРАТОВ

Аннотация. В статье рассмотрены данные по изучению новых фуллеропирролидиновых соединений на противовоспалительную и цитотоксическую активности *in vitro* на культурах человеческих моноцитарных линий клеток *MonoMac-6* и *THP-1Blue*, а также в качестве ингибиторов эластазы нейтрофилов человека. Этот

фермент является регулятором воспаления. В разных ситуациях он может выступать и как провоспалительный, и как противовоспалительный агент. Дисбаланс в регулировании активности эластазы играет важную роль в патогенезе муковисцидоза, острого респираторного дистресс-синдрома, бронхоэктатической болезни, хронической обструктивной болезни легких, сахарного диабета второго типа, атеросклероза и артериальной гипертензии. В перспективе подобные исследования должны привести к созданию оптимальных моделей *in vitro*, наиболее адекватно отражающих ситуацию *in vivo* и установлению особенностей соотношения между структурой и активностью исследуемых препаратов. Отмечено, что наличие у производных фуллерена C₆₀ липофильных свойств особенно важно при разработке фармацевтических препаратов для борьбы с возбудителями различных инфекционных заболеваний. Производные фуллерена C₆₀ обладают способностью легко проникать через липидные мембраны, преодолевать гематоэнцефалитический барьер и модулировать транспорт ионов. Соединения были исследованы на противовоспалительную и цитотоксическую активности (*in vitro*) на культурах человеческих моноцитарных линий клеток *MonoMac-6* и *THP-1Blue*. Цитотоксическая активность образцов исследовалась в тесте *Brine Shrimp* с использованием личинок морских креветок *Artemia salina*. Проводились тестирования модифицированных фуллереновых соединений различной структуры в отношении ингибирующей способности против фермента эластазы из нейтрофилов (*in vitro*). Активность эластазы была оценена по способности фуллеропирролидиновых соединений гидролизовать синтетический субстрат *N-methylsuccinyl-Ala-Ala-Pro-Val-7-amino-4-me-thylcoumarin* (*Calbiochem*). Получены результаты исследований фуллереновых соединений в отношении их противовоспалительной и цитотоксической активности. Цитотоксическая активность фуллереновых образцов исследовалась в тесте *Brine Shrimp* с использованием личинок морских креветок *Artemia salina*. Все соединения обладают цитотоксичностью, что позволяет говорить об отсутствии избирательности химиотерапевтического действия. Проведен анализ кинетики флуоресценции фуллереновых соединений различной структуры. Представлены результаты изучения ряда соединений на антибактериальную и противогрибковую активности с различными тест-культурами (*S. aureus* 505, *Bacillus subtilis*, *Stragalactiae*, *E. Coli* M-17, *Ps.aeruginosa*, *Candida albicans*, *Penicillium citrinum*, *Aspergillus niger*, *Aspergillus flavus*, *Trichophyton mentagraphytos*, *Epidermophyton floccosum*). В результате исследования потенциала противогрибковой активности соединений установлено, что только два препарата тормозят рост тестовых культур *in vitro*. Все остальные исследованные образцы практически не обладают активностью против дрожжевых грибов *Candida albicans*. В целом наличие цитотоксического эффекта у изученных фуллереновых соединений подтверждает реальность антимикробного действия.

Ключевые слова: фуллеропирролидины, фуллерен C₆₀, ингибиторы эластазы нейтрофилов, противовоспалительная активность, цитотоксичность.

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