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DOSE-DEPENDENT IFN-STIMULATING AND IMMUNOMODULATING PROPERTIES OF 6H-INDOLO[2,3-B] QUINOXALINE DERIVATIVES

Two 6H-indoloquinoxaline derivatives were studied in different doses and schemes of application for their IFN-inducing potential and ability to effect functional activity of phagocytic cells. Tested compounds were shown to possess comparable or higher activity than reference drug Amixin in analogous doses. One indoloquinoxaline significantly elevated metabolic activity of macrophages and increased their potential for phagocytosis. Application of multiple treatments and higher doses allowed us to reveal differences between studied derivatives that were not obvious in previous in vivo experiment. Capacity of 6H-indoloquinoxalines to induce vast IFN amounts on in vivo level was demonstrated for the first time.

Key words: indoloquinoxaline derivatives, antiviral substances, interferon inducers

Insufficient effectiveness of modern medicine against many socially important viral infections is the reason for continious efforts to develop new antiviral drugs. Synthetic low-molecular heteroaromatic compounds are a group of chemicals that are paid particular interest to, since they are able to pass through cytoplasmic and nuclear membranes, which is crucial for combating intracellular pathogens. Many low-molecular antivirals are also capable to stimulate interferon (IFN) production. Tilorone hydrochloride is a classical example of such low-molecular agents, which both induces a range of antiviral interleukins and exerts direct antiviral action, not mediated through cytokines [14]. Although several other similar drugs, such as Amizon, Arbidol, Cycloferon, Larifan, etc. [15], are already present in pharmaceutical market, there is still a need to widen their range. In recent years we have demonstrated that two newly synthesized 6-aminoethyl-6H-indolo[2,3-b]quinoxaline derivatives possess antiviral potential against RNA and DNA viruses in vitro [7], and are able to stimulate IFN production in mice. However, initial experiments in vivo [1] involved a rather low dose – 5 mg/kg, and only single administration. At the current stage of investigation it is necessary to prove that the mentioned 6H-indoloquinoxalines possess higher activity or more advantageous set of biological properties than existing drugs. To increase earlier obtained results multiple administration scheme and elevated doses were applied. Besides IFN production, functional activity of phagocytic cells was measured to prove immunomodulating potential of tested compounds.

Materials and Methods

Compounds. In the current research 6-[3-(4-morpholine)ethyl]-6H-indolo[2,3-b] quinoxaline and 6-[3-(4-methyl-1-piperidinyl)ethyl]-6H-indolo[2,3-b]quinoxaline were tested and are henceforward referred to as **I1** and **I2**, respectively. Their structure is given in Fig. 1. Tilorone hydrochloride (2,7-bis[2-(diethylamino)ethoxy]fluoren-9-one), the official antiviral drug in Ukraine (Amixin IC, InterChem) was used as reference substance.

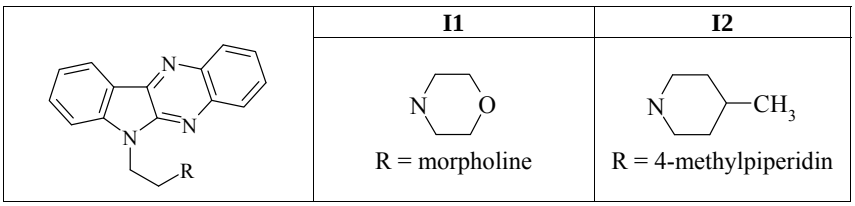

Fig. 1. Structure of tested 6H-indolo[2,3-b]quinoxaline derivatives

The compounds were initially dissolved in distilled water with subsequent addition of 0.01 M phosphate buffered saline (Sigma-Aldrich).

Mice. Experiments were carried out on 4-week old Balb/c mice, weighing 18-21 g. Animals were kept at 24-28 °C with *ad libidum* provision of adequate diet. Solutions were injected intraperitoneally, twice in 5 mg/kg dose with 48 h break between injections, and once in higher 12.5 and 25 mg/ kg doses. These doses are more than 10 times below maximal tolerable dose, estimated *in vivo* [20]. Control mice received analogous volume of physiological solution.

Determination of IFN levels. Blood, peritoneal exudates and spleens were taken 24, 72 and 120 hours after the injection. These were transformed into serum and cell cultures according to [5]. After 24 h incubation of *ex vivo* cells supernatants were sampled. Interferon levels in all biological fluids were assayed by their ability to protect test cell culture L929 from vesicular stomatitis virus (strain Indiana, Ukrainian Collection of Microorganisms at Zabolotny IMV NAS of Ukraine) [6].

Maximal IFN-producing potential of cells was assessed by addition of ridostin (Diapharm, Russia) and phytohaemagglutinin (PHA, Sigma-Aldrich), potent inducers of α- and γ-IFN, respectively [4]. Inducers were added to culture medium immediately after plating of *ex vivo* cells until final 5 μg/ ml concentration. Supernatants were sampled in 24 h, and IFN levels were measured as described above. Preliminary activation of cells with test agents *in vivo* can result in hyporeactivity, depletion of biosynthetic resources, or cytokine-mediated suppression. By another scenario, treatment with one IFN inducer can enhance the response to induction with the second one and broaden the maximal IFN-producing potential.

Functional activity of immunocompetent cells. Effect of indoloquinoxalines upon functional activity of peritoneal cells was assessed by reduction of tetrazolium salt in standard and latex-stimulated schemes. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, or MTT, was introduced into culture medium in 1 mg/ml concentration, and incubated with cells during 3 hours. In standard culture conditions diphenyltetrazolium bromide intake from media and its intracellular reduction to insoluble colored *diphormazan* depends directly on transmembrane transport rate and intensity of oxidative metabolism. This serves as a background for a simple spectrophotometric detection of phagocytes functional status. Addition of latex particles (1.7 μm, FGUP NIISK, Russia) to MTT-containing culture media forces peritoneal macrophages to phagocytize them. The process of phagocytosis dramatically intensifies the metabolism, which means more diphenyltetrazolium is reduced and higher optical density is obtained. Such a procedure allows to determine a so called functional reserve of the cells and to uncover details about their condition that might not be obvious in the standard scheme [9].

Statistics and graphing. Each test group comprised 5 animals. IFN levels in sera were measured separately for each mouse. Splenic and peritoneal cells were gathered in pull, but several samples of their condensed mediums were taken from different wells. IFN content in each sample was measured in triple replication. Obtained data were assessed using non-parametric statistical methods. Median was calculated for a range of analogous values of one sample. Mann-Whitney test was applied to compare samples with each other. The samples were considered statistically distinctive at significance coefficient $P \leq 0.05$ [2].

Results of MTT test, due to larger sampling and distribution, are provided as 10-90 percentile range [8]. The mentioned calculations and graphing were performed by means of Microsoft Exel 2003.

Results and Discussions

1. Double administration scheme

In the previous work [5] a single 5 mg/kg dose of tested compounds proved to be sufficient to elevate circulating IFN levels. We decided to study the potential of this dose in case of double administration. Considering small size and fast metabolism of mice, 48-hour interval between injections was chosen. The reference drug was used in analogous concentration and scheme of administration. Results are provided in Fig 2. Time count was started after the second injection.

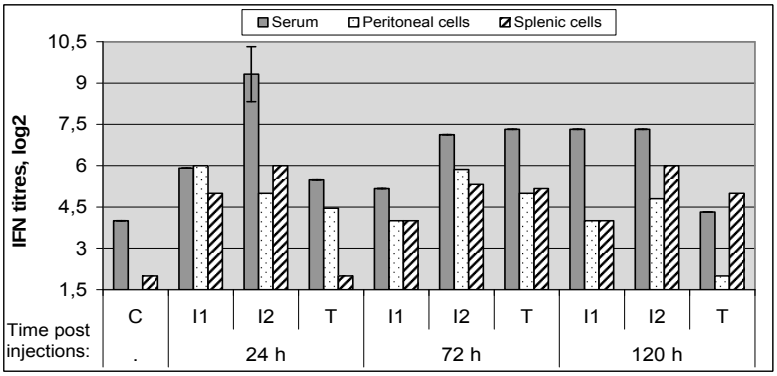

Fig. 2. IFN titres, induced by double administration of 5 mg/kg dose.
Abbreviations: "C" - Control group of animals
"T" –reference compound tilorone hydrochloride

The classically applied dose of tilorone according to [3] in case of intraperitoneal injections is 50 mg/kg. Double injection of a lower dose failed to provide effective activation of IFN production.

I2 yielded high serum IFN levels straight after the second stimulation and provided good cell activation throughout monitoring period. It should be noted that 24 h after the second injection levels of circulating IFN were non-uniform among animals of the group, log2 of titres ranged from 8.32 to 10.32. Dramatic boost of certain cytokine in the organism leads to numerous secondary interactions and side effects. Progression of this reaction and final result depend upon many variable factors, which explains diversified response of standardized linear animal group to hyperactivation, caused by I2. Despite diversified character of response, the described substance awaked significantly ($P<0,01$) greater IFN production than I1 or reference preparation in analogous dose/scheme of administration.

The dynamics of response to I1 was characterized by an unfavorable decrease in serum IFN content on the 3rd day after the second injection. Similar phenomenon at the same time interval was described in our previous work [5] and was explained by anti-inflammatory vector of cytokines in serum. In the current case instead of cytokine quantification we decided to evaluate the ability of cells to react adequately to additional stimulants: ridostin and PHA, inducers of alpha- and gamma-IFN, respectively. Results are provided on Fig.3.

The described trial was conducted only with peritoneal cells. This culture consists mainly of macrophages and is 95% homogenous, comprising a smaller fraction of lymphocytes than spleen cell culture. Therefore secondary intercellular interactions and co-stimulation are reduced, which grants greater chances to detect potential cytokine-mediated suppression or hyporeactivity.

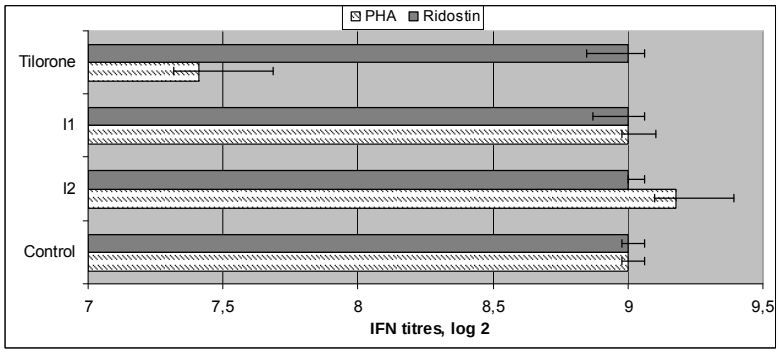

Fig. 3. Response of peritoneal cells, derived 72 h after the preliminary *in vivo* stimulation, to additional IFN inducers

Error bars indicate maximal/minimal values

Macrophages from the control group of animals responded with full scope of their intact biosynthetic potential and sensitivity to inducers, producing vast amounts of IFN. To the opposite, peritoneal cells from animals that had been stimulated with tilorone failed to react adequately to PHA, demonstrating greater discordance and lowered IFN yield. Macrophages treated with both indoloquinoxaline derivatives were characterized by normal response to additional inducers. Therefore, if the suspected suppression of cells indeed took place, it had a limited range.

Functional status of peritoneal macrophages, derived 72 h after the second introduction of substances to murine organism, was also assessed by means of the standard and latex-stimulated MTT test. Results are given in Fig. 4.

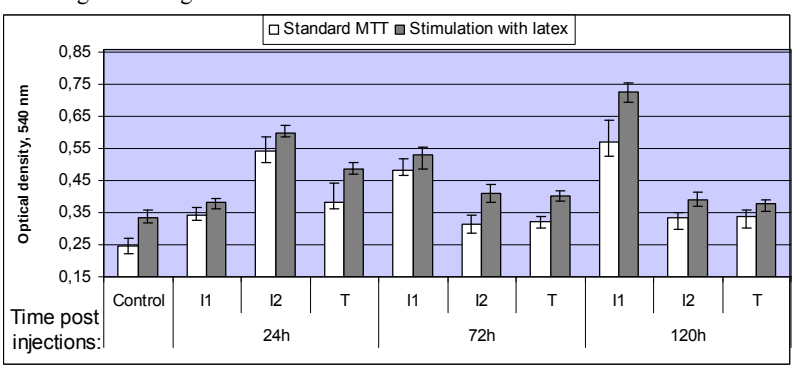

Fig. 4. MTT indices of peritoneal cells, treated with double 5 mg/kg dose of tested compounds.
Note: "T" stands for reference drug tilorone hydrochloride
Error bars indicate 10-90 percentile range

The ability of tested compounds to potentiate cell functional activity had been estimated in the previous work [5] and was confirmed again. However in case of single 5 mg/kg treatment stimulated MTT indices were elevated to much greater extent (up to 0.413) than standard ones. Double administration of the same dose increased standard MTT more effectively than in stimulated test, shortening the gap between these two parameters. The gap is called "functional reserve" of the cells [11]. It depicts the ability of macrophages to respond to the process of phagocytosis with a so called "oxidative burst", which is required to kill and destroy phagocytized pathogens. Low indices of functional reserve in clinics depict impaired phagocytosis or inability of immunocompetent cells for a rapid intensification of oxidative metabolism. In our case this quotient is low due to high standard indices and is not caused by inability of cells to cope with increased metabolic/phagocytic load. Moreover, two MTT parameters differed in speed of the reaction. In the standard scheme the control cells required 3.5-4 hours to reach maximal final optical density; latex introduction shortened this time to 140±25 minutes. Preliminary treatment of macrophages *in vivo* with both indoloquinoxalines enabled them to complete the reaction in 90 minutes or less in latex-stimulated scheme, while dynamics of the standard MTT-test remained mainly the same. The greatest rate was provided by I2 on the 5th day after injections: stimulated MTT-test was finished in 30 minutes, standard one – less

than in 60 minutes. Therefore, lack of a gap between standard and stimulated MTT should not be considered as a negative trait, since there still is a difference between these two parameters, not depicted on Fig. 4.

As in the previous experiment, I1 initiated the greatest activation of metabolism. I2 caused high tetrazolium reduction only on the first day after treatment, which correlated with remarkably high serum IFN titres, potentiated by the compound. Such cytokine overproduction and hyperactivation of phagocyte activity might have resulted in compensatory decrease of serum IFN and MTT indices in the next 48 hours. Growth of functional activity in response to I1 was gradual, reaching its maximum on the 5th day after injections. This dynamic differed from that of IFN secretion. Most importantly, for I1 the period of low IFN production by macrophages on the 3rd day did not correlate with growing MTT indices. For the second time the suspected suppression of cells was not confirmed by complementary test. We believe that a decrease of IFN production, observed 72 h after the substance administration was a compensatory reaction of the organism, aimed at preventing autoregulatory hyperactivation of cells. This assumption is confirmed by the fact that the most efficient cell activator – compound I1, was the only substance for which a decrease in serum IFN was detected in the middle of immune response.

Compound I2 activated IFN production by cells more effectively than I1 and reference drug and evoked significantly greater circulating IFN levels. To our belief, there was no need to further investigate this compound in higher doses.

Most remarkable feature of I1 is its low toxicity, which allows us to use this compound in a wide concentration range. That is why it was decided to inject the compound in higher doses with the purpose to obtain greater IFN-inducing effect.

Application of compounds in higher doses

As mentioned above, the recommended intraperitoneal dose of tilorone is 50 mg/kg [14]. In all previous *in vitro* experiments effective concentrations of I1 were lower than that of the reference drug, that is why 25 mg/kg and 12.5 mg/kg doses were chosen for subsequent trials. Results for IFN production are provided in Fig. 5.

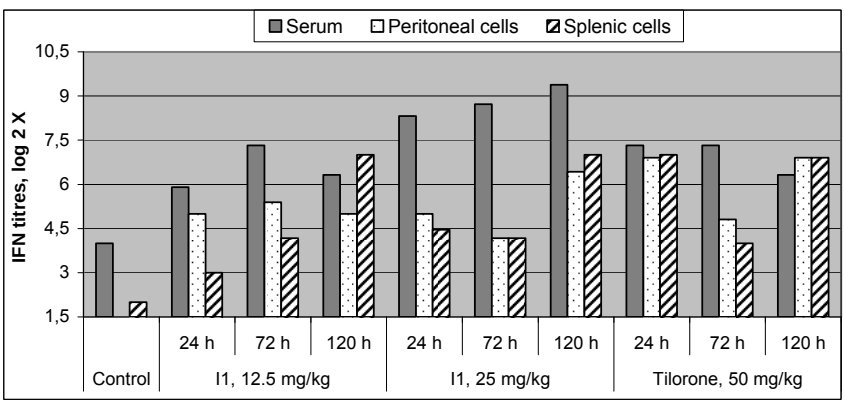

Fig. 5. IFN titres, induced by single administration of compounds in higher doses

Application of higher doses increased IFN indices of both I1 and tilorone. For I1, direct dependency of circulating IFN levels upon dose value is most obvious. In case of I1, cellular parameters were on the whole greater at 25 mg/kg. However this dose was characterized by a small decrease in IFN levels, produced by cells on the 3rd day after administration. Similar decrease in the same period (72 h after injections) was observed for tilorone. The reference drug proved to be the most potent activator of IFN production by cells, that is why a sudden decline, preceded and succeeded by very high cellular IFN indices, was especially evident.

As in case of lower doses, correlation between IFN production by cells and their functional activity (Fig. 6) was poor. Yet the 25 mg/kg dose of I1 was again obviously more advantageous than 12.5 mg/kg. Comparing MTT data of three different doses: 5, 12.5 and 25 mg/kg – it can be concluded that the ability of I1 to potentiate functional activity of cells is a dose-dependant and distinctive property of this indoloquinoxaline. Contrariwise, the increase of tilorone dose did not lead to higher MTT indices.

It should be noted, that high doses of I1 were not able to overcome MTT results, provided by double administration of 5 mg/kg dose. The latter, as can be seen in Fig. 4, already activated cells to a great extent. However, higher doses of I1 were characterized by different quotients of stimulated and standard MTT: the gap between these two parameters was wider. It is hard for us to judge, which quotient is more preferable for antiviral resistance. On the one hand, stimulation of functional activity and phagocytosis implies more effective clearance of blood and organs from viral particles and subsequent antigen presentation to B- and T-cells. On the other hand, many viruses use absorbing potential of macrophages as an easy way to get inside the cell and initiate replication [13, 19].

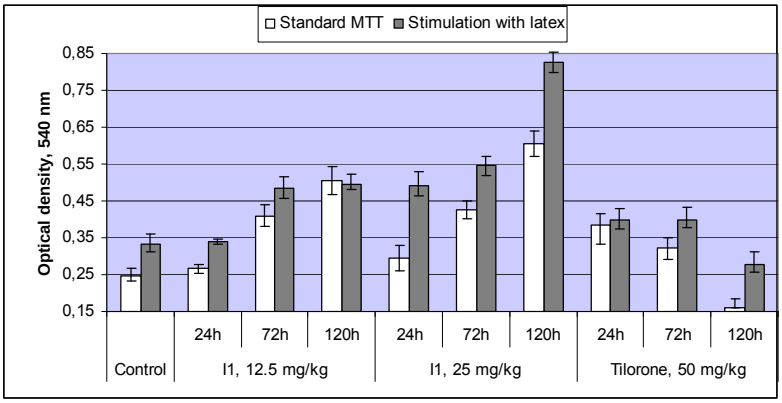

Fig. 6. MTT indices of peritoneal cells, treated with single high dose of tested compounds.
Note: "T" stands for reference drug tilorone hydrochloride
Error bars indicate 10-90 percentile range

Elevated indices of standard MTT in case of double stimulation of animals with low indoloquinoxaline dose suggest greater chances for macrophages to destroy phagocytized virions. However, if macrophages fail to cope with absorbed pathogen, they still can contribute to the conduct of antiviral response by secreting cytokines that would activate natural and T-killers [11]. This requires extra synthetic resources and can be sabotaged by depletion of metabolic reserve. Although it was proved (Fig. 3) that elevated metabolic activity, caused by double 5 mg/kg stimulation with I1, does not prevent macrophages from reacting adequately to additional IFN inducers, in normal conditions these cells yielded lower IFN titres than other tested agents (Fig 2). In comparison to double 5 mg/kg treatment, 25 mg/kg dose was characterized by lower standard- and higher stimulated MTT data. It can be presumed that macrophages of this group would have to switch into "oxidative burst" mode in order to destroy phagocytized viruses, providing chances for the pathogen to escape processing. But 25 mg/kg dose also led to significantly higher IFN production by cells. Final outcome of virus-macrophage interaction depends on many intra- and extra-cellular events, such as preliminary state of the cells, phenotypic traits/number of expressed receptors, cytokine and hormones [10], cellular environment [17], antigenic load, age [18] and genetic factors [16], that is why only additional evaluation of antiviral activity *in vivo* can determine which dose and scheme of treatment with I1 is more effective.

We also pointed out that greater cellular IFN levels for both indoloquinoxaline doses were observed at later stages of response – on the 5th day after injections, and were accompanied by maximal MTT indices during the same period. Therefore additional monitoring time is required to establish full scope and duration of indoloquinoxaline action.

In the current study two tested indoloquinoxalines were shown to induce considerable amounts of IFN production in murine organism. Repeated introduction of I2 in a low dose or single administration of I1 in a higher dose is required for effective inducing effect. High dose of I1 yielded greater serum IFN levels than the reference drug. Yet the ability of tilorone to initiate IFN secretion by peritoneal and splenic cells was not surpassed.

Although in previous *in vitro* studies involving different cell types the compound I1 was characterized by modest IFN-inducing properties, on the level of integral organism this indoloquinoxaline demonstrated much greater potential. Another characteristic trait of I1 – the ability to increase func-

tional reserve of the cells and their normally-expressed activity, could also be observed only *in vivo* and not *in vitro*. Apparently, intrinsic cellular resources were not enough for these effects to develop. This implies that mechanisms of indoloquinoxaline action require complex intracellular interactions and/or involve a mediator. At the same time, they are rather specific, since both IFN and MTT indices were dose dependant.

Demonstrated properties justify our expectations as for application of tested derivatives (compounds) in antiviral therapy. For example, long-lasting high IFN content in blood, induced by 25 mg/ kg dose, can contribute to therapy of hepatitis C and other chronic viral infections [12]. Taking into account relatively cheap and easy chemical synthesis of indoloquinoxalines and low toxicity of presented derivatives, their prospects for introduction into medical practice are rather strong.

It should be noted, that the current research was carried out on intact animals, without infectious or antigenic load. The observed effect of indoloquinoxalines upon cellular activity and integral IFN production allows us to presume that tested compounds could also promote antigen presentation, modulate counts of lymphocytic subsets and eventually grant antiviral resistance. These speculative assumptions will be a subject for our subsequent experiments.

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ДОЗОЗАВИСИМОСТЬ ИНТЕРФЕРОН-СТИМУЛИРУЮЩИХ И ИММУНОМОДУЛИРУЮЩИХ СВОЙСТВ ПРОИЗВОДНЫХ 6Н-ИНДОЛО[2,3-В] ХИНОКСАЛИНА

Р е з ю м е

Было изучено влияние разных доз и схем введения двух производных 6Н-индолохиноксалина на продукцию интерферона и функциональную активность фагоцитирующих клеток в организме мышей. Исследованные вещества продемонстрировали аналогичную либо более выраженную активность, нежели препарат сравнения амиксин. Одно из производных индолохиноксалина значительно увеличивало метаболическую и фагоцитарную активность макрофагов. Повышение вводимой дозы, либо повторные инъекции низких доз, позволили выявить различия в особенностях иммуномодулирующего действия опытных соединений, которые не были обнаружены в предыдущих экспериментах *in vivo*. Впервые показана способность приведенных 6Н-индолохиноксалинов индуцировать значительные уровни ИФН в организме в течение длительного времени.

Ключевые слова: производные индолохиноксалина, антивирусные соединения, индукторы интерферона

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ДОЗОЗАЛЕЖНІСТЬ ІНТЕРФЕРОН-СТИМУЛЮЮЧИХ ТА ІММУНОМОДУЛЮЮЧИХ ВЛАСТИВОСТЕЙ ПОХІДНИХ 6Н-ІНДОЛО[2,3-В] ХІНОКСАЛІНУ

Р е з ю м е

Було вивчено вплив різних доз та схем введення двох похідних 6Н-індолохіноксаліну на продукцію інтерферону та функціональну активність фагоцитуючих клітин в організмі миші. Дослідні сполуки продемонстрували аналогічну або більш виражену активність, ніж препарат порівняння аміксин. Одне

з похідних індолохіноксаліну значно збільшувало метаболічну та фагоцитарну активність макрофагів. Підвищення дози або повторне введення низьких доз дозволило виявити відмінності в особливостях імуномодулюючої дії дослідних сполук, які не спостерігались у попередніх експериментах *in vivo*. Вперше продемонстрована здатність наведених 6Н-індолохіноксалінів індукувати значні рівні ІФН в організмі впродовж тривалого часу.

Ключові слова: похідні індолохіноксаліну, антивірусні сполуки, індуктори інтерферону

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