Minireviews

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IZATIZON — ANTIVIRAL AND IMMUNOMODULATING SUBSTANCE: OVER HALF A CENTURY HISTORY

Tribute to Anatoly Potopalsky

Anatolii Potopalsky (1938 – 2025), a prominent scientist-innovator who worked long-time as the Head of the Laboratory of Modification of Biologically Active Compounds at the Institute of Molecular Biology and Genetics, the NAS of Ukraineand. He also was a founder and director of the Institute of Health Promotion and Rebirth of People of Ukraine.

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Infectious diseases, causing about 20% of all deaths worldwide, remain one of the main factors in both human morbidity and mortality. The development of novel antiviral substances remains an urgent problem, given the widespread expansion of viral infections that are threatening humanity.

Izatizon, a substance with antiviral and antitumor activity, was developed in 1973 by Anatoly Potopalskyi together with his student and follower Lyubovya Lozyuk. Along with other inventions, izatizon is the brainchild of Dr. Potopalskyi and his collaborators developed on the basis of the well-known substance metisazone, a condensation product of N-methylisatin with thiosemicarbazide. Metisazone, also known as marborane, belongs to the class of thiosemicarbazones and historically was used as a substance with antiviral activity, especially against poxviruses [1]. The molecular structure of methisazone, the main component of isatizon, is shown in the figure 1.

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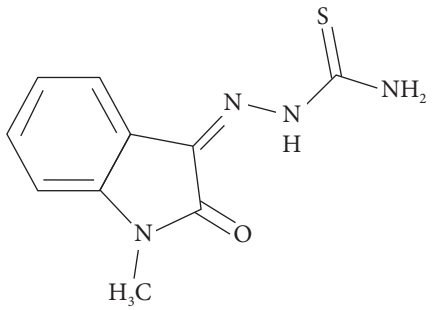

Fig. 1. Chemical structure of methisazone molecule

During the study on the mechanisms of action of methisazone, it was noted that its antiviral effects are accompanied by a rather high toxicity of this substance, but this problem was solved thanks to the innovative approach developed by Dr. Potopalsky and his colleagues.

The essence of the invention was to create a soluble dosage form of methisazone based on a solvent mixture containing dimethyl sulfoxide and polyethylene glycol — 400 (PEO-400) [2]. This innovative composition, called "isatizon", was protected by the patent of Ukraine No. 1786 [3]. The new dosage form of methisazone turned out to have a broader spectrum of action with a significant reduction in the toxicity of methisazone.

To understand the mechanisms of action of isatizon, the structural and conformational features of the active ingredient — methisazone — were first carefully analyzed using physical chemistry methods. The conformations of the methisazone molecule were obtained at the level of theory using the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) method [4]. It was found that the methisazone molecule is a conformationally labile structure which in a mixture of polyethylene glycol and dimethyl sulfoxide acquires the highest energy "working" state and exhibits the ability to enter into intermolecular H-bonds, which underlie the biological activity of isatizon [5—8].

Studies of isatizon in experimental systems *in vitro* and *in vivo* have demonstrated high antiviral activity against a wide range of viruses [7]. Based on the results of these studies, isatizon was officially registered in veterinary medicine for the treatment and prevention of various viral diseases, and several methodological recommendations for its use were approved and published [8, 9]. The high effectiveness of isatizon for the prevention and treatment of animal diseases in combination with as a basic treatment has been proven in numerous studies in Ukrainian farms [10]. Among the officially approved veterinary indications for the use of isatizon are acute catarrhal bronchopneumonia of calves, Marek's disease, infectious laryngotracheitis of poultry, enteritis of pigs and enteroviruses of waterfowl [11, 12]. Isatizon has been recommended and practically tested as a remedy against viral, bacterial and fungal diseases of bees and oak silkworms [13, 14]. The activity of isatizon against some phytoviruses was also studied [15].

High effectiveness of isatizon and its analogues was confirmed in many works investigating isatizon and its analogues in the Institute of Epidemiology of Infectious Diseases of the National Academy of Medical Sciences of Ukraine named after L.V. Gromashevsky. Thus, izatizon showed a high antiviral effect at herpesvirus meningoencephalitis infection in white outbred mice: when administered to sick animals at a dose of 8 mg/kg, the survival of mice reached 72%, while the death of animals in the control group was 100%. It was also shown that izatizon inhibited the thymidine kinase activity of the herpes virus, which led to the suppression of viruse at the early stages of the infectious process [16, 17].

Acting through the DNA repair system, isatizon in experiments significantly increased the rate of repair of the damaged areas, which was accompanied by less active reproduction of the virus with its subsequent elimination, that increased survival of the experimental animals. The data obtained suggest that the drug stimulates the activity of DNA RS in lymphocytes, increasing it to the level of intact animals [18].

Thus, according to the results, isatizon significantly enhances the rate of repair of damaged DNA, apparently affecting endogenous stimulators of reparative synthesis and thereby showing antiviral activity.

In addition to antiviral activity, izatison exhibits pronounced immunomodulatory properties,

namely, in an *in vitro* system, at a dose of 10 μg/ml, it increases the number of T-lymphocytes with helper phenotypic markers in cultures of splenocytes and peritoneal exudate cells from mice. In the culture of lymphocytes *in vitro,* izatizon almost doubles the number of cells expressing the phenotypic marker of their activation — CD 69, and activates the proliferation of T- and B-lymphocytes both *in vitro* and *in vivo.* The drug stimulates synthesis of interleukin-1 by macrophages and interleukin-2 by T-lymphocytes in an *in vitro* system. [14]. Izatizon has antiseptic and anti-inflammatory properties. It does not inhibit hematopoiesis. When used in the inductive phase of immunogenesis, izatizon reduces the manifestations of anaphylactic shock. It can regulate the parameters of specific and nonspecific resistance in cases of impaired immune status [12].

Despite its long story, izatizon opens the way for new applications. Recently, the antiviral activity of izatizon against the highly contagious coronavirus — transmissible porcine gastroenteritis virus has been proven in *in vitro* experiments by a multidisciplinary group of Ukrainian scientists, indicating its potential for further research as an agent against SARS-CoV-2 [19].

The promising potential of the drug has been recently demonstrated by scientists from the Department of Human Genetics (Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine). The inclusion of izatizon with recombinant endothelial monocyte-activating polypeptide II (EMAP II) into a temporary dermis-equivalent complex (bioconstructs «membrane-gel-cell») opens up prospects for improving the treatment of burn wounds [20].

Actally, in the experiments izatizon in combination with the recombinant EMAP II protein significantly enhanced the effect of dermal equivalents on wound healing., This complex is currently being studied as an effective agent for military personnel with burns and wounds (Zhytomyr Military Hospital) and cancer patients (Zhytomyr Regional Oncology Dispensary). Preliminary promising results of the clinical studies have been obtained.

Long-term research on isatizon has demonstrated a wide range of its preventive and therapeutic effects across various animal and human diseases, indicating the need for its further practical application and the development of new analogues.

In 1986, isatizon received two silver medals at the International Exhibitions in Budapest. Introducing izatizon as an innovative antiviral and antitumor drug produced in Ukraine, we pay tribute to Anatoly Potopalsky (03/25/1938—07/31/2025), Honored Inventor of Ukraine, author of unique inventions aimed at improving health and treating diseases, as well as protecting the environment.

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ІЗАТІЗОН — ПРОТИВІРУСНИЙ ТА ІМУНОМОДУЛЮЮЧИЙ ПРЕПАРАТ: П'ЯТИДЕСЯТИЛІТНЯ ІСТОРІЯ

Більш ніж п'ятдесят років тому А. Потопальський та Л. Лозюк винайшли нову композицію, яка була розроблена на основі метисазону і отримала назву ізатізон. Цей препарат має противірусні та імуномодулюючі властивості. В стислому огляді розповідається про основні віхи становлення винаходу та його застосування у ветеринарії і на добровольцях у медицині, а також окреслено перспективи його використання як противірусного засобу.

***Ключові слова*:** тіосемикарбазони, ізатізон, противірсниій ефект, імуномодулюючий ефект.