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Piperidine-Containing Phosphonates As Immunocorrectors

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Abstract. The objective of Research is the target synthesis of azaheterocyclic systems as potential immunomodulators. Encouraging results had been obtained from the biotesting of structures combining the piperidine cycle and the phosphonate fragment in the molecule (where, R=alkoxyalkyl or arylalkyl, A=OH, Ph, fluorophenyl, heteterocyclic moiety, etc). Target piperidine-containing phosphonates (PP) are synthesized quite simply either by nucleophilic addition via the ketone group of piperidone or under the Kabachnik-Fields reaction conditions.

INTRODUCTION

The effect of heavy metal compounds on humans leads to a violation of the adaptive reactions of the organism, which is appeared by a decrease in its general biological resistance. The study of the immunotoxic effects of chemical factors in the environment and/or the working environment has received close attention throughout the world. Immunological shifts caused by toxic substances are based on various mechanisms: from gross damage to bone marrow stem cells to changes in cytokine production, quantitative and qualitative disruption of immune system cells [1].

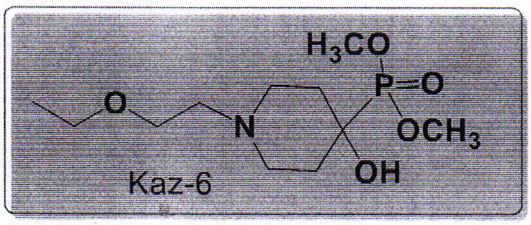
MATERIAL AND METHOD

Treatment begins in the second week after injection of vanadium or chromium salts to rats at a dose of 5 mg / kg. The preparation PP is inputted intramuscularly at a dose of 50 mg /kg 1 time per day for one week. Control animals receive an equal volume of 0.9% NaCl solution.

Visual observation for the general state dynamics of the experimental animals treated with PP shows a favorable course of treatment. In the studied animals, a marked revival of motor activity and improvement in appetite were noted.

RESULTS AND DISCUSSION

The objective of Research is the target synthesis of azaheterocyclic systems [2] as potential immunomodulators. The impetus for Research was the hydroxyphosphonate (Kaz-6) synthesized by us with the N-(2-ethoxyethyl) piperidine fragment [3], which stimulates the growth and resistance to drought of plants. As a stimulator of maize growth, Kaz-6 is tested at a concentration of 0.01–0,0001%. Corn is cultivated for silage (the area of the plots was 25 m2, the repetition of the experiment was 4 times). In the presowing treatment of corn seeds with a 0.001% solution of Kaz-6, the yield of green mass is increased by 21% compared with the control. Kaz-6 at similar concentrations is studied on early sowing tomatoes. The preparation application is carried out by continuous spraying of plants with a 0.0001% solution during the flowering period (an average of 10–12 flowers per plant). Kaz-6 increases the yield of tomatoes in the amount and weight of fruits by 19%. Next, it is tested the effect of Kaz-6 on the germination of corn seeds. Seeds treated before sowing with a concentration of 0.01 and 0.001% were sown on experimental plots of 5 m2. After the treatment of corn seeds with a 0.01% solution of Kaz-6, the germination rate increases by 65% compared with the control in the stiletto phase (8 days after sowing). It turned out that pre-sowing treatment of



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seeds leads to an increase in the drought resistance of plants. In addition, some derivatives of 2-(2-chloroethyl) piperidine in the experiment on animals have myerostimulating activity, that is, they are immunocorrectors [2].

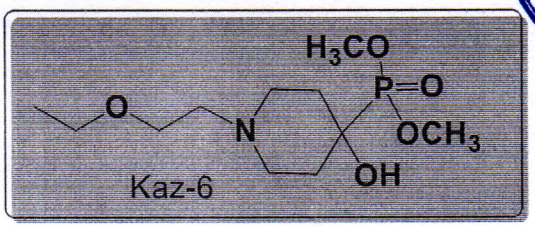

FIGURE 1. Kaz-6 structure

It is known that the toxic effect of xenobiotics is manifested in the blood by a decrease of the amount of red and white blood cells. Indicators of the state of the hematopoietic system of the body can be considered as markers of adverse environmental impact [4,5]. Encouraging results had been obtained from the biotesting of structures combining the piperidine cycle and the phosphonate fragment in the molecule (where, R=alkoxyalkyl or arylalkyl, A=OH, Ph, fluorophenyl, heteterocyclic moiety, etc). Target piperidine[6-8]-containing phosphonates (PP) are synthesized quite simply either by nucleophilic addition via the ketone group of piperidone or under the Kabachnik-Fields reaction conditions [9].

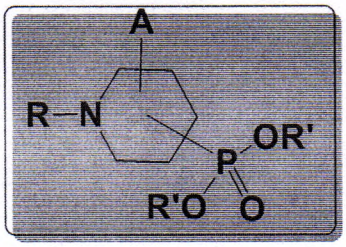

FIGURE 2. Structure of xenobiotics

On the one hand, it is difficult to overestimate the physiological role for the human body of chromium and vanadium, which are involved in vital processes. On the other hand, chromium and vanadium compounds are attributed to environmental pollutants [10-11].

The main source of chromium in the environment are mining and processing enterprises (for the production of chromium, Kazakhstan ranks second in the world after South Africa). Direct human contact with chromium is also possible in various industries that widely use chromium compounds, such as metallurgy, mechanical engineering, oil refining, paint and varnish and leather industries, as well as in agriculture. The main source of vanadium in the groundwater is iron and polymetallic ores containing a small admixture of vanadium, as well as wastewater from ferrous and nonferrous metallurgy enterprises, oil production and refining, etc.

It had turned out that in the treatment of PP in rats previously poisoned with vanadium or chromium salts, the total amount of peripheral blood leukocytes increased by 65%. In this case, the relative amount of lymphocytes almost returns to the original level, and the absolute - increases by 76.7% of the level of untreated rats. Granulocyte leukocytes and monocytes range within control values. The total content of erythrocytes and hemoglobin significantly increased by 19% and 6%, significantly approaching the control level. The values of the immunoreactivity index became equal to the control, exceeding the data of untreated animals by 2.6 times. It is established that the horizontal motor activity of rats significantly increases. At the same time, the degree of emotional anxiety and arousal under the influence of PP is noticeably reduced.

Checking the mink reflex of treated animals shows that the time spent in the light compartment is reduced by 32.6% compared with the data of untreated individuals. When checked a week later, under the influence of PP, animals do not enter the dark compartment 158% longer than animals without treatment. The corrective effect of PP is appeared as the lengthening of the time spent in the light compartment, which indicates the restoration of the processes of consolidation and reproduction of the temporal links of the passive avoidance reaction.

Under the influence of PP in the experience of 50 combinations of conditioned and unconditioned stimuli in rats there was a 2.2-0.74 avoidance, which is 144.4% more than in untreated rats. Also, the latent period of avoidance is reduced by 25.6%. A check of the fixation of the temporal links of the active avoidance reaction in rats, treated with PP shows that the number of correct avoidance reactions increases more than 4 times with a 30% reduction in the latent period, which is a symptom of a noticeable improvement in the ability to learn.

CONCLUSION

Treatment with PP of animals poisoned with salts of vanadium and chromium has a significant effect on the processes of formation, fixation and reproduction of the defensive reflexes of rats. Correction with the PP help of violations caused by metal salts significantly weakens the destructive effect of the latter, providing a membrane stabilizing effect. Thus, the destruction of neutrophil membranes from exposure to salts of vanadium and chromium is approximately 30% less pronounced than in untreated animals.

Thus, the combination of a substituted piperidine and a phosphonate group as structural units in a molecule leads to the appearance of the properties to correct the immune status of rats poisoned with vanadium and chromium salts.

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