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New about uracils

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Abstract
Comparative activity of uracil derivative: bis-(N,N-uracil-l-yl)-selenium oxomethane was studied on the model of avian plague virus. It was found that compound with remantadin effectively inhibits virus reproduction in cultures of chick embryo chorioallantoic membrane.

Keywords: Uracil derivatives, remantadin, 5-fluorouracil, biological activity, strain Weybridge

1. Introduction
One of the growing areas of synthetic organic chemistry is the chemistry of pyrimidine bases. Uracils are of great importance in this group of compounds, which is due to an extensive range of practically useful properties. We would like to highlight the study that detects a high biological (antiviral and antimicrobial) activity of uracils which defined their application in the composition of many medicinal and cosmetics products [1, 4].
Synthesis of metabolites also belongs to the question of searching active antiviral agents.
The article presents the data on study of antiviral properties of bis-(N,N′-uracil-1-yl) – selenium oxomethane (I), obtained from the reaction of uracil with sodium selenide in carbon tetrachloride in the presence of a catalyst – copper monochloride [5].
Study of activity (I) was carried out on avian plague virus (strain Weybridge, H7N7) with infectious titre of 9.5lg embryo infectious dose $EID_{50/0.2ml}$ and hemagglutinating activity of 1280 Hemagglutinating Unit HAU/ml using the chick embryo chorioallantoic membrane (CAM). The data of biological activity (I) were compared with the activity of known antiviral preparations like 5-fluorouracil (5-FUr), remantadin, sodium selenide (Na_2Se) and in combination with them. The presence of virus was determined in hemagglutination reaction with 0.5% of chicken erythrocytes added upon termination of incubation. Virus infectivity (in lg Infective Dose ID_{50}) was calculated by Reed–Muench method.
Sensitivity of virus to drugs was determined by titration on chorioallantoic membrane (CAM), infecting them with 10-fold dilutions of virus prepared in Eagle's medium. Chorioallantoic membrane (CAM) was incubated at 37 ^{0}C for 48 hours both with abovementioned preparations and without them.
The synthesis of cellular DNA (cells of chick-embryo fibroblasts) was judged according to addition of ^{3}H-uridine (specific activity 16.2 mg/ml) into acid-insoluble fraction. The results of studies were statistically processed and mean-square deviation was defined by the formula:

$$\sum = \pm \frac{\sqrt{\Sigma (M-V)^2}}{(N-1)}$$

Where (M - V) – deviation of variant (V) from arithmetic-mean (M), N – number of observations.
Error of mean-square deviation was defined by the formula:

$$m = \pm \frac{\Sigma}{\sqrt{m_0^2 - m_k^2}}$$

Validity of difference between the control and practice was defined according to «P» by Fisher test (P = 95) using t-test method by the formula:

$$t = \frac{M_0 - M_k}{\sqrt{m_0^2 - m_k^2}}$$

(Indexes o and k are practice and control, correspondingly).

2. Results and discussion

Studying the influence (I) on reproduction of virus over chorioallantoic membrane it was found that the preparation used at concentrations of 5, 12.5 and 25 mcg/ml inhibited infectiousness of virus in 1.5, 1.8 and 2.5 lg ID_{50}, correspondingly.

The most inhibition of infectiousness of virus was registered at a concentration of 25 mcg/ml. In this case inhibiting effect was due to cytotoxic effect (I) on cell reproduction. At this concentration (I) changed morphology of cells causing their 25% degeneration 24 hours after applying.

These data are correlated with the results of studies on the action of preparation on the synthesis of cellular RNA. At a concentration of 25 mcg/ml the preparation inhibited the synthesis of cellular RNA to 35%, but at lower concentrations (5 and 12.5 mcg/ml) it practically did not influence on the morphology of cells and the synthesis of cellular RNA.

Further studies were carried out using the preparation with a concentration of 5 mcg/ml.

Comparative data on the study of antivirus activity of preparation (I) with sodium selenite and 5-fluorouracil is provided in the below table.

As shown in table inhibition degree of infectiousness of influenza virus with (I), Na_2Se and 5-Fur, used at concentrations of 5 mcg/ml (Na_2Se and 5-Fur at the same concentration were also non-toxic for cells of chick-embryo fibroblasts) is different.

The most inhibition (2.0lg) of infectiousness of virus was observed with Na_2Se and 5-Fur. Preparation (I) inhibited infectiousness of virus to 1.5 lg. Weak inhibiting effect was observed with 5-FUr.

To enhance the antivirus action (I) on reproduction of influenza virus we studied it in combination with remantadin (the data is provided in table). For this purpose we used effective and non-effective concentrations of inhibitors. As table shows the combination (I) with non-effective concentration of remantadin causes additive effect (decrease to 2.5 lg).

Table 1: Influence of inhibitors on reproduction of influenza virus in combination and separately

Preparation and its concentration, mcg/ml	Titre of virus, lg ID_{50}/ml	Inhibition of virus titre, lg ID_{50}/ml
-	9.5±0.2	-
(I), 5	8.5±0.2	1.5
Sodium selenite, 5	7.5±0.3	2.0
Remantadin:		
0.05	8.4±0.1	1.1
l	6.5±0.12	3.0
5-FUr, 5	8.30±0.09	1.25
(I)+ remantadin:		
5+0.05	7.0±0.3	2.5
5+1	6.3±0.25	3.2
Sodium selenite +remantadin:		
5+0.05	6.7±0.25	2.8
5+1	5.6±0.2	3.9

The action of Na_2Se on reproduction of virus in combination with remantadin was studied similarly. Additive effect was observed only when Na_2Se was used with an effective concentration of remantadin.

A number of researchers [6] showed that selenium compounds block replication of some RNA viruses. Obtained data show that enhancement of antivirus activity of inhibitors occurs when selenium is added into the composition of not only nucleosides, but also pyrimidine bases.

Therefore, according to the results we can suggest that unlike its analog, 5-fluorouracil bis-(N, N′-uracil-1-yl) - selenium oxomethane with remantadin effectively inhibits reproduction of virus over chorioallantoic membrane. Probably, introduction of selenium into the molecules of basic nitrogen analogs promotes intense incorporation of the last into newly synthesized RNA that causes inhibition of virus replication.

3. References

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