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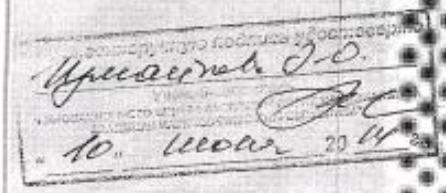

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Pharmacological premises of the creation new antitumor preparations of the class of Nitrosoalkylurea

J. A. Djamanbaev, Ch. Kamchybekova, J. A. Abdurashitova, G. E. Zaikov*

Institute of Chemistry and Chemical Technology, Kyrgyz National Academy of Sciences 720071, Kyrgyzstan. Bishkek, 267 Chui Prospect e-mail: Djamanbaev-J@mail.ru

*N. M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences 119334, Russia, Moscow, 4 Kosygin Str., e-mail: Chembio@sky.chph.ras.ru

Perspectives in the field of creation highly effective anticancerogenic preparations have been evaluated. For their creation it is offered a new regioselective method ofglycosylation alkylurea in conditions nucleophilic catalysis with the following nitrozing of glycosyl carbamides of the D- and L-rows.

This method opens principal new possibilities of modification of compounds by means of glycosylamides bond allowing to get the preparations, possessing small toxicity and selectivity of the action.

Key words: monosaccharides, glycosylureas, N-glycosyds.

Interest to nitrosoalkylurea. as potentially antitumor agents was shown at the beginning of 60th years, after opening high antileukemic activity N-methyl-N-nitrozoguanidin and N-methyl-N-nitrosourea [1-2]. These compounds have soon increased the essential arsenal of antitumor preparations of alkylation action [3-4]. However, a number of side effects of the compounds of this type, first of all high myelotoxic , restrained thus introduction to medical practice.

Modification of preparations by introduction to the molecular structure of different substituent though has increased the range of potentially active compounds, however has not brought to eliminating undesirable influence of preparations on organism. The success reached in pharmacology of the nitrosoalkylureas is described in particular in works [1,5]. First natural carbohydrates analogue N-nitrosomethylurea the antibiotic - "streptosotocin" got from cultural

E-mail: Djamanbaev-J@mail.ru
267 Chui Ave., 720071 Bishkek, Kyrgyzstan
4 Kosygin Str.. 119334 Moscow, Russia. E-mail: Chembio@sky.chph.ras.ru

liquid - a streptomycin was found in the same years [3, 6]. It was realized that "streptosotocin" possesses the broad spectrum of actions - an antidiabetic, diabetogenic, mutagenic and antitumor and presents itself carbohydrate derivative of nitrosomethylurea from secondary carbon atom of glucoses.

The multiple pharmacological studies having been earned out, showed that though "streptosotocin" has above mentioned side effects, its general toxicity much below the most citotoxic fragment, connected with atom C2 D-glucopiranosyd ring. These observations stimulated studies on syntheses and test on antitumor activity carbohydrate derivatives of N-methyl-N-nitrosourea. Repeatedly spoken out suggestions that carbohydrates molecule can enter as special transport carrier, relieving carrying the function active groups (in this instance - an citostatic of the groups) in the tumors fabric promoted the development of this work.

In this work we tried to motivate searching and elaboration of new methods of the syntheses more active antitumor preparations among derivatives of nitrosomethylurea.

The study of the reaction with the participation of glycosyl bonds is important not only for the theory of the carbohydrates structure and reactional ability of carbohydrates.

They present also the significant interest for solving a number of actual problems of bioorganic chemistry as the glycosyl bond is one of the most important structural elements of many biologically active compounds.

Studying of the reactions of glycosyl centre has allowed determining some typical . peculiarities of this type of nucleophilic catalysis.

In this connection, the attention was concentrated on synthetic aspects of the homogeneous catalysis and elaboration of methods of directing synthesis of carbohydrates physiologically active substances. They attack great importance to the creation of medical preparations, in particular antitumor preparations, possessing the low of toxic activity, the high of solubility in water and selectivity of actions.

These investigations are of great interest for solution of practical important problems for ennoble physiologically active substances and medical preparations with the known therapeutic action. Given direction provides working out of the recommendations on decrease of toxicity, change of water and lipid solubility preparations as well as obtaining derivatives with selective permeability through cell membranes [7].

In the process of pharmacological investigations there was ascertained that glycosylation leads to the sharp decrease of toxicity of medicinal preparations (LD50 falls, as a rule, on two orders).

In clinical oncology there is of great importance not only high antitumor activity of preparations of the group of nitrosourea but also their ability to run through hematoencephalitic barrier that opens the real possibilities for chemotherapy metastasis and primary tumors of the cerebrum. The majority of known preparation do not get through hematoencephalitic barrier and so do not warn spreading a metastasis in cerebrum, and they aren't practically efficient at defeat of the central nervous system.

As to selectivity of the action, it is known, that permeability of some cell membranes of animals regarding to monosaccharides is different, and the degree of permeability correlates with nucleophilic reactional ability of monosaccharides (tabl. 1) [8].

Thereof comes the principle possibility of the processes regulation of the passing carbohydrates preparation through cell barriers by changing the nature of carbohydrates carrier, as well as their biological activity. It drams attention the fact that a number of therapeutic characteristic greatly depends on place of joining of a physiological active fragment to the carbohydrates ring. Especially it reveals in the process of study preparations of antitumor action.

Table 1

Comparative absorption (B i) and comparative reactional ability (B_2) of monosaccharides on C_1

Monosaccharides	B_1	B_2
glucose	1,0	0
galactose	1,1	0,64
fructose	0,4	-
mannose	0,2	0,73
ksilose	0,15	0,81
arabinose	0,09	1,03
ribose	-	1,19
licsose	-	1.25

Rather perspective for practical application, in our opinion, is usage as "blending links" more acid stable amide bonds. What is the value of the amid bond forming? What are the prospects of their use in applied aspects of the chemistry carbohydrates? It is enough to point to broad circulation of urea fragment amongst natural material - the derivatives of pyrimidin of the row:

nucleosides, riboflavin, teobromin, caffeine and others, and development of the direction of heterocycles syntheses, including analogues of the nucleosides on the base of carbohydrates derivatives of urea.

The development of the work on specified directions greatly depends on elaboration technically acceptable and economic profitable methods of putting the carbamides fragment in to mono-, oligo- and polysaccharides.

As a result of searching conditions of the synthesis of N-nitroso derivatives of monosaccharides unprotected hydrocsyl groups, providing the simplicity, effectivity of the process, it is perfected the general methods of getting N-alkil-N-((3-D-glykopiranozyl)nitrosourea in which there were combined reactions: a) the interaction of monosaccharides with alkylurea in condition of nucleophilic catalysis with addition aryl amines and b) nitrozilation N-alkylglycosylureas [9, 10, 11].

Thus, rather easy and mobile method of syntheses of big group of casrbohydrates derivatives of nitrosoalkylureas was worked out. On this base are it seems to be perspective investigations of biological activity of modified medical preparations with the help of glycosylamides bond.

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