SEARCH OF ANTITUMOUR MEDICAL DRUGS BY THE WAY OF CREATION OF NEW ANTIMETABOLITES OF PYRIMIDINES

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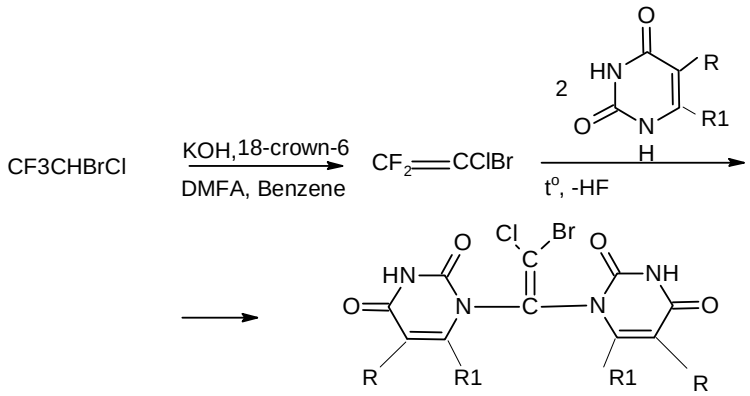
One of the perspective ways of the search of new antitumour medical drugs are the creation of new antimetabolites of pyrimidines and purines change which will influence on structure and functions of nucleonic acids. The current of these investigations confirmed by a lot of scientific works [1-3]. Heterocyclic systems such as unsubstituted and 5(6)-substituted uraciles are main components of antitumour drugs [4-6]. It is known tumors are using molecules of uraciles more active than normal cells. Therefore 5-fluorouracile (5-FU) and its derivatives will substrates and/or inhibitors of ferments and will swallow up by tumors cells. The bis-adducts I-V of 5(6)-substituted uraciles with ftorotan (1,1,1-threefluoro-2-bromo-2-chloroethane) are obtained under phase-transfer conditions in alkaline medium. The reactions are catalyzed by the 18-crown-6-complex. The general synthetic procedures used for their preparation are illustrated in Scheme 1.



I - V

R = H, R1 = CH_3 (I); R = CH_3, R1= H (II); R= F, R1 = H (III);
R= Br, R1 = H (IV); R= NO_2, R1 = H (V)

Scheme1. The general synthetic procedures used for preparation of compounds I–V

In this paper we report the synthesis, characterization, toxicity and antitumour activity of the heterocyclic bis-adducts I-V, bacterial lectins (*Bacillus subtilis 668 IMV and Bacillus polymyxa 102 KGU)* and their molecular complexes with bacterial lectins (*Bacillus subtilis 668 IMV and Bacillus polymyxa 102 KGU).* A strongly antitumour effect has been discovered for heterocyclic bis-adduct III, for lectins (*Bacillus subtilis 668 IMV and Bacillus polymyxa 102 KGU)* and for their molecular complexes with bis-adduct III for the first time. These were tested on the tumours: Lymphosarcoma Plissa (LS Plissa); Sarcoma 45. Lectins are a group of proteins interacts with polysaccharides and glycoproteines by binding to specific carbohydrate residues. The ability for lectins secretion of saprophit stammes of sporeform bacteria of the genus *Bacillus* has been elegantly shown by [7]. These lectins are non-toxic and specific for sialic acid. They are inductors of γ-interferones and antitumour

agents. More active producents of bacterial lectins (*Bacillus subtilis 668 IMV and Bacillus polymyxa 102 KGU)* from Ukrainian Collection of Microorganisms of Institute of Microbiology and Virology (IMV) of NAS of Ukraine were used for preparation of molecular complexes on the base of new bis-adducts and bacterial lectins. Bacterial lectins of two cultures (*Bacillus subtilis 668 IMV and Bacillus polymyxa 102 KGU)* were obtained from culture liquid of saprophit (harmless for man and animals) culture of *Bacillus* bacteria. Molecular complexes of bis-adducts and bacterial lectins were obtained by mixing of two components at physiological solution, 1:1. All isolated males of imbredical mice were provided with standard food ration in all groups with the same control. The quantity of animals in each group was ten. Minimum mass of mice body was 20±3-4 g. The age of the mice was 2-3 months. Percentage primary recovery and destruction was "0". Method of killing was decapitation, redosage of ethyl ether. The method of removal of the experimental tumours was sufginal.

There were six introductions of the physiological solutions of bis-adducts, bacterial lectins and their molecular complexes every day. The way of introduction was hypodermic. Preparation-standard was 5-fluorouracile. The dosage of the preparations corresponded to 1/4-1/6 of the LD_{50}. The express-method of definition of LD_{50} for bis-adducts, bacterial lectins and their molecular complexes was used [8, 9]. The main control data were: LD_{50}; middle mass of the tumour of the control animals (g); middle mass of the tumour of the experimental animals (g); % of growth relaxation of the tumour. Bis-adducts, which synthesized on the base of 5-methyluracile (II), 5-fluorouracile (III), 5-bromouracile (IV) and ftorotan as more relatives to 5-fluorouracile were choice for biological investigations. Data of investigations of toxicity of bis-adducts II, III, IV confirmed their little toxicity: LD_{50} of bis-adducts II and IV are 515 mg/kg and 415 mg/kg, corresponding. Bis-adduct III has little toxicity too: LD_{50} = 125 mg/kg; it is 4,12 and 3,32 times as much than toxicity of bis-adducts II and IV. LD_{50} of preparation-standard – 5-fluorouracile is 375 mg/kg. Bacterial lectins are more toxically than bis-adducts II, IV: *Bacillus subtilis 668 IMV* has moderate toxicity (LD_{50} = 89 mg/kg), *Bacillus polymyxa 102 KGU* has little toxicity (LD_{50} = 248 mg/kg). Molecular adducts of bis-adducts II, III, IV with *Bacillus subtilis 668 IMV* or *Bacillus polymyxa 102 KGU* has little toxicity too: LD_{50} from 635 to 137 mg/kg (table 1).

Table1. Data of toxicity for bis-adducts II-IV, lectins, molecular complexes

№	Bis-adduct	LD_{50}, mg/kg	Bacterial lectin	LD_{50}, mg/kg	Molecular complex	LD_{50}, mg/kg
1.	II	515	Lectin 102	248	II + Lectin 102	335
2.	III	125	Lectin 668	89	III + Lectin 668	137
3.	IV	415	Lectin 102	248	IV + Lectin 102	635
4.	5-FU	375				

Bis-adduct III – derivative of 5-fluorouracile and ftorotan as structural analogous of antitumour drug 5-fluorouracile, bacterial lectins (*Bacillus subtilis 668*

IMV, Bacillus polymyxa 102 KGU) and their molecular complexes were choice for investigations of antitumour activity on tumour growth (LS Plissa, Sarcoma 45). A strongly antitumour effect of bis-adduct III was registered on LS Plissa tumour: % of growth relaxation of the tumour was 75,3.

A strongly antitumour effects of bacterial lectins were registered too: for *Bacillus polymyxa 102 KGU* on LS Plissa tumour: % of growth relaxation of the tumour was 50,0%; for *Bacillus subtilis 668 IM* on Sarcoma 45: 52,5%. Stability in antitumour activity, high % of primary recovery of animals were registered for both molecular complexes (Bis-adduct III + *Bacillus subtilis 668 IMV*; Bis-adduct III + *Bacillus polymyxa 102 KGU*) on LS Plissa and Sarcoma 45: % of growth relaxation of the tumour was from 62,8% to 81,1%. It is 1,14 times for LS Plissa and 4,46 times for Sarcoma 45 as much than antitumour activity of 5-fluorouracile.

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