THE STATE AND PROSPECTS OF WORK IN THE SEARCH FOR CHEMOTHERAPEUTIC AGENTS AGAINST VIRUS INFECTIONS

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Viruses give rise to widespread and serious diseases, such as influenza, small pox, encephalitis, poliomyelitis, rabies, etc. Under the influence of viruses, the cells of living organisms can undergo genetic changes, which sometimes leads to the formation of tumor cells [1, 2]. Both these circumstances permit us to consider the problem of the search for means of controlling virus infections as one of the most important problems of public health.

Definite successes have been achieved in the prophylaxis of influenza, poliomyelitis, and certain other virus diseases, through the use of vaccines. A new approach to the prophylaxis of virus infections has been outlined in connection with the discovery of interferon.

The successes achieved in elucidating the structure of RNA and DNA and other peculiarities of virus structures, as well as in the use of chemotherapeutic preparations for the treatment of bacterial infections, open up prospects for a search for chemotherapeutic agents against virus diseases. It is not accidental that experimental investigations along this line have been intensively conducted in many countries in recent years, and have revealed substances with antiviral activity both among the possible antimetabolites of the purine and pyrimidine bases included in the viral DNA and RNA, and among chemical substances capable of interacting with the protein coat of the virus.

A number of survey articles have been devoted to questions associated with the chemotherapy of virus diseases [1, 3-6]. Therefore, in this work we present information published chiefly in recent years, on the effects of chemical compounds on viruses. In addition, the article presents some of the previously unpublished data on the search for antiviral drugs in the S. Ordzhonikidze All-Union Pharmaceutical-Chemical Scientific-Research Institute (VNIKhFI).

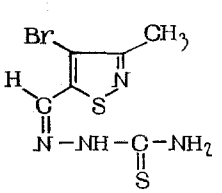
Substances with antiviral activity belong to varied classes of organic compounds. Antiviral activity has been detected in phenetyl alcohol [7]; propanediols-1,2 and 3-alkoxypropanediols-1,2 show appreciable activity against viruses that cause respiratory diseases [8, 9]. Considerable attention of researchers is being attracted by alcohols of the benzimidazole series [10], evidently because one of them – 2-(α-hydroxybenzyl)-benzimidazole – is generally considered as an antagonist of the purine bases, primarily adenine [11, 12]. It has been found that 2-(α-hydroxybenzyl)-benzimidazole is active against picornaviruses [11-13] and suppresses the cytopathogenic action of enteroviruses. Recently a large number of derivatives of 2-(α-hydroxybenzyl)-benzimidazole, containing various substituents both in the imidazole and in the benzene portions of the molecule, have been produced [14-16]. Some of them are active against polio- and adenoviruses [16]. The compounds showing antiviral activity include certain aldehydes, ketones, and their derivatives. It has recently been established [17] that glutaraldehyde also possesses antiviral activity. High antismallpox activity in vitro is exhibited by thiosemicarbazones of aldehydes of the isothiazole series [18]. One of them – the thiosemicarbazone of 3-methyl-4-bromo-5-formylisothiazole (I) – has been studied in the clinic as a prophylactic agent against smallpox, but it has proven relatively ineffective [19, 20]. Thiosemicarbazones of aldehydes of the benzene, naphthalene, thiazole, and imidazole series are also of interest as sub-

S. Ordzhonikidze All-Union Pharmaceutical-Chemical Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 5, pp. 6-15, May, 1970.

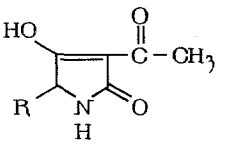
TABLE 1. Data on the Use of Methisazone during the Smallpox Epidemic in Madras

	Total number of persons in contact with patients	Became ill	Died
Subjected only to vaccination (control)	2,842	114	20
Administered methisazone together with vaccination	2,297	6	2

stances with antiviral activity [21-24]. For some of them, in addition, antismallpox and antiinfluenza (strain PR-8) activity has been detected in ovo and in vivo [21]. There is an indication in a patent that antiviral activity is possessed by aminoacetophenones [25]. Thiosemicarbazones of acetophenones substituted in the benzene ring by one or several methoxyl groups are active against vaccinia virus [26]. Antiviral activity has been detected in derivatives of 2-oxo-3-acetyl-4-hydroxydihydropyrrole (II) [27].

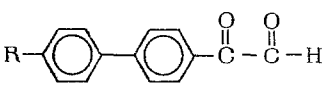


I

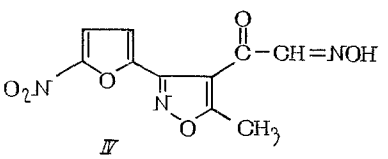


II

Antiviral activity is possessed by a number of glyoxal derivatives. Glyoxals of diphenyl (III) and their functional derivatives, including anils, are active against influenza virus in vivo [28, 29]. Antiviral activity has been detected for 3-(5'-nitrofuryl)-5-methyl-4-isoxazolylglyoxal and its functional derivatives; moreover, the oxime (IV) is the most highly active [29, 30].



III

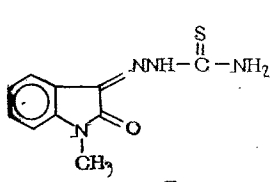


IV

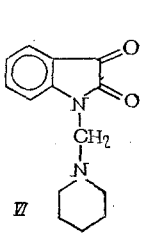
Carbonyl derivatives of heterocyclic compounds, primarily derivatives of isatin, have also been widely investigated. The thiosemicarbazone of N-methylisatin – methisazone (V) – is an extremely effective prophylactic preparation for smallpox [31, 32]. Of the series of thiosemicarbazones of substituted isatins studied, including isatin itself, only one compound – the thiosemicarbazone of N-ethylisatin – has an activity 40% greater than that of methisazone (V) [33], selected for production for economic considerations [34]. The results of the use of methisazone (V) as a prophylactic agent during the smallpox epidemic in Madras [31] are presented in Table 1.

In addition to its action on the reproduction of smallpox virus, methisazone inhibits the reproduction of adenoviruses [35]. Recently, high antiviral activity of N-dialkylaminomethylisatins [36] and their thiosemicarbazones [37] has been detected.

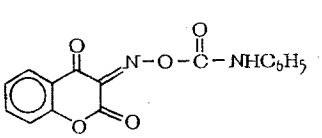
It has been established that the highest activity among the derivatives studied is possessed by 1-piperidinomethylisatin (VI).



V



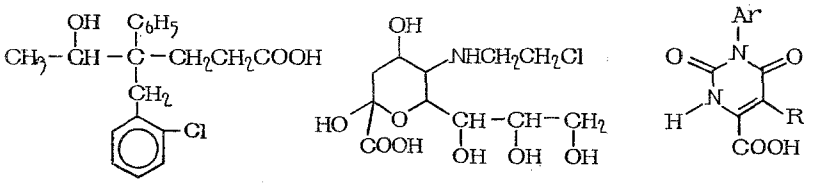
VI



VII

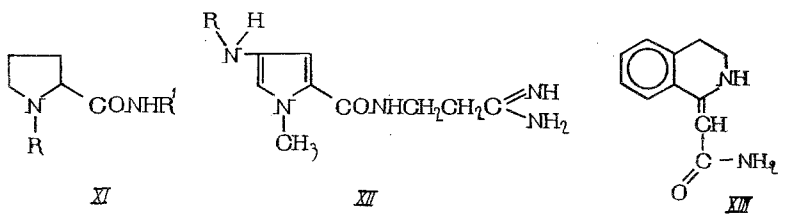
Among the other cyclic carbonyl derivatives, antiviral activity has been detected in trioxochromanes. The substituted oxime of 2,3,4-trioxochromane (VII) is highly active against herpes virus [38].

Substances with antiviral activity include rather structurally complex carboxylic acids. Recently activity has been detected in levorotatory 4-phenyl-4-(2'-chlorobenzyl)-5-hydroxyhexanoic acid (VIII) [39] and in sialylic acid (IX) [40].



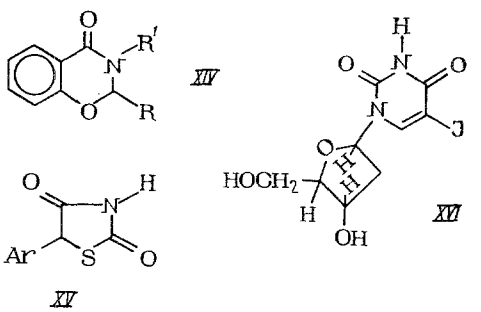
VIII IX X: R = H, Alk

The search for substances with antiviral activity has been conducted among derivatives of orotic acid (X). It has been shown that the introduction of fluorine into the aryl substituent substantially changes the activity of substituted orotic acids with respect to various viruses [41]. Antiinfluenza activity has been detected among amides of pyrrolidine-2-carboxylic acid (XI); the greatest inhibiting effect in vitro and in ovo is exhibited by amides substituted in the 1-position of pyrrolidine by a benzyl residue [42]. Among the substances with antiviral activity are amides of substituted pyrrolecarboxylic acid (XII) and the amide of a carboxylic acid of the isoquinoline series (XIII) [43, 44].



XI XII XIII

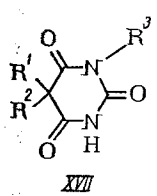
Antiviral activity is possessed by cyclic amides of 2,3-dihydro-4H-1,3-benzoxazine-4-ones (XIV) and thiazolidine-2,4-diones (XV) [24, 45].



XIV XVI XV

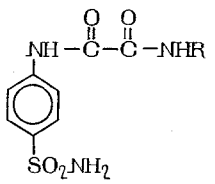
The derivatives of cyclic amides include 5-iodo-2'-deoxyuridine (XVI), which, as is assumed, represents an antimetabolite of the pyrimidine bases contained in the viral DNA. The mechanism of the action of iododeoxyuridine (XVI) is not entirely clear. It is known that it is incorporated into the viral DNA molecule, resulting in the formation of virus particles that differ substantially from the controls in external appearance [46]. Iododeoxyuridine is the first preparation successfully used for the treatment of virus diseases. It is active in cell culture in animals and in man and is not a prophylactic, but a therapeutic preparation. Iododeoxyuridine was first used in medical practice in 1967 in the United States [1]. It is widely used for the treatment of herpetic keratitis in ophthalmological practice. However, its prolonged application can lead to the appearance of strains resistant to the action of this preparation [47-49]. In addition, the use of iododeoxyuridine and other analogous compounds, including 5-fluorouracil [50-52] for the treatment of virus diseases, is limited in connection with their pronounced mutagenic properties and high toxicity [1, 51, 52]. Therefore, according to the latest data, iododeoxyuridine can be used only for the treatment of potentially lethal infections, caused by DNA viruses [1].

It has recently been established that cyclic amides [derivatives of pyridine with the general formula (XVII)] are active in vitro against Japanese encephalitis virus [53]. Antiviral activity is possessed by derivatives of guanidine and biguanidine [54-59], derivatives of urea and thiourea [21, 60-62], as well as substituted thiosemicarbazides [63, 64]. Some of them are active in ovo and in vivo against influenza virus (strain PR-8) and smallpox virus [21, 57, 63]. Antiviral activity has been detected among derivatives of sulfonic acids. A Japanese patent contains an indication of antiviral action of a substituted amide of sulfanilic acid (XVIII) [65]. Antiviral activity is also possessed by N-acyl-amides of 8-methoxyquinoline-5-sulfonic acid; caprinylamide (XIX) is the most active [66].

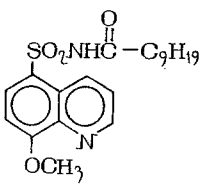


XVII

R', R², R³=Alk, Ar

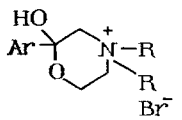


XVIII

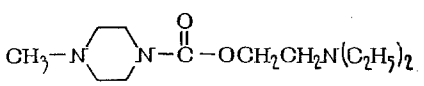


XIX

Recently compounds with antiviral activity have been found among derivatives of various amines, including ammonium picrate [67] and hydroxylamine [68]. Of considerable interest as potential antiviral preparations are quaternary salts of substituted morpholines (XX) [69] and derivatives of piperazine [70], of which the highest activity with respect to influenza virus (strain PR-8) is possessed by the diethylaminoethyl ester of 4-methylpiperazine-1-carboxylic acid (XXI).

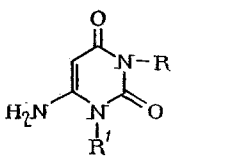


XX

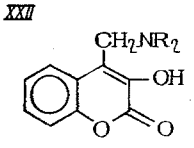


XXI

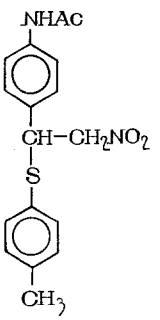
Antiviral activity in vitro has been noted among derivatives of 6-amino-pyrimidinone-2,4 (XXII) [71], in mannich bases of 3-hydroxycoumarin (XXIII) [72], and in acyl derivatives of phenylethylamine [74]. An acetyl derivative of an aromatic amine – 4-(2-nitro-1-(p-tolylthio))ethylacetanilide (XXIV) – is active against herpes virus [74]. Apparently of considerable interest is a derivative of 6-aminopurine (Apa-A), 9-β-D-arabinofuranosyladenine (XXV), active in cell cultures against viruses containing DNA, and exhibiting a therapeutic effect in experiments on animals in the case of herpes, smallpox, and certain other diseases caused by DNA viruses [75].



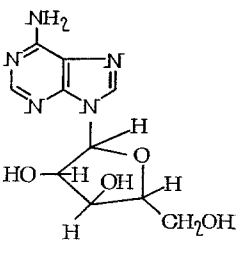
XXII



XXIII

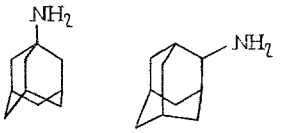


XXIV



XXV

Among the other amines, a special place is occupied by 1-amino-adamantane (XXVI). 1-Amino-adamantane (amantadine) has been confirmed in the United States as a prophylactic agent in diseases caused by influenza A2 virus [1]; the preparation does not act on other varieties of influenza virus [76-78]. The deficiencies of the preparation include not only the narrow spectrum of its action, but also its substantial toxicity. The therapeutic dose of amantadine, 200 mg per day, is close to the toxic dose (400 mg). Moreover, the administration of amantadine in certain cases leads to disorders of the central nervous system – it produces depression, a disturbance of the concentration of attention, tremors, insomnia, etc. [1, 79, 80].

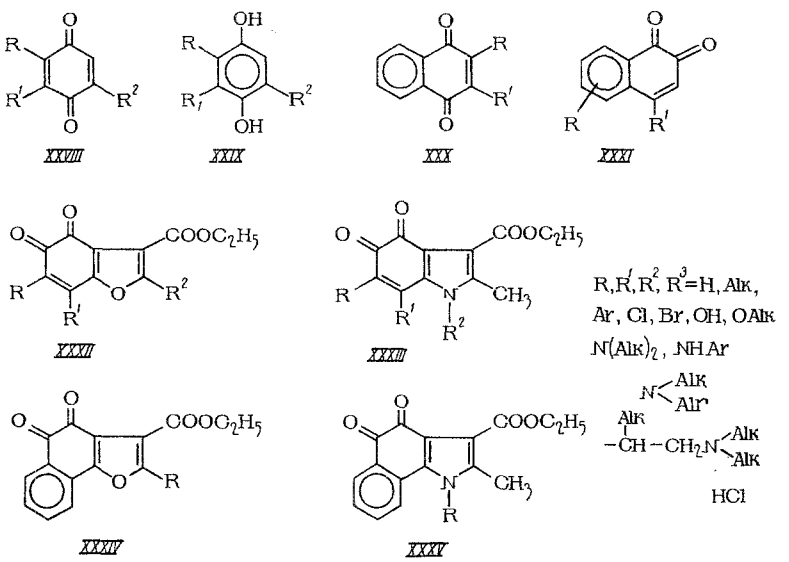


XXVI XXVII

Recently the synthesis of a number of analogs [81, 82] and a large number of derivatives of adamantane [83-95] has been performed for biological testing. One of them – 2-aminoadamantane (XXVII) – has been patented in the United States as an antiviral agent [95].

Substances with antiviral activity have been detected among the antibiotics. Antiviral activity is possessed by mitamycin S [96], formacin [97], alanosin [98], and distamycin [99].

The search for antiviral substances in VNIKhFI has been conducted as a result of joint work of the Laboratory of Chemotherapy and the Laboratory for Synthesis of Antiviral Agents. One of the directions of these investigations has been aimed at the selection of compounds active with respect to the protein coat of the virus. These include quinones. This circumstance, as well as the high antiviral activity of some of the simplest representatives of the class of quinones (p-benzoquinone, toluquinone, and α-naphthoquinone) with respect to myxoviruses – influenza virus, Newcastle disease virus, and fowl plague virus [100-102] – and the high viricidal activity of p-benzoquinone with respect to herpes virus [103], have prompted us to conduct a systematic investigation of the antiviral activity of varied quinones. Parallel with the quinones, in a number of cases the antiviral activity of the corresponding hydroquinones, which can be converted to quinones under oxidizing conditions, has been studied. The synthesis of quinones and hydroquinones has been conducted according to the method that we published earlier [104-111]. We studied the antiviral activity of more than 80 quinones and hydroquinones with the general formulas (XXVIII)-(XXXV).*



XXVIII XXIX XXX XXXI XXXII XXXIII XXXIV XXXV

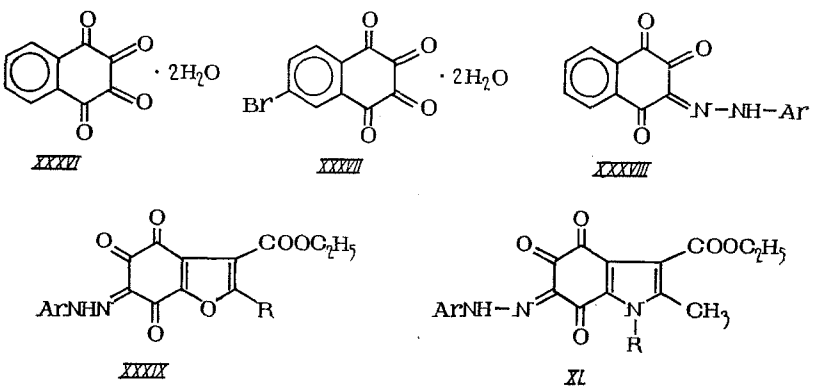
The overwhelming majority of the investigated compounds showed high viricidal activity with respect to the influenza A virus (strain PR-8). It was established that among alkyl-p-benzoquinones and alkylhydroquinones, as the chain of the alkyl substituent is lengthened, the antiviral activity decreases. In the series of aryl-p-benzoquinones, the activity depends both on the nature of the substituent in the aryl radical and on the nature of the substituents in the quinone ring. The highest activity was exhibited by 2,3-dichloro-5-phenyl-p-benzoquinone. It neutralizes the infectious properties of influenza virus at a dilution of 0.1 μg per ml. Other chloro- and bromo-substituted quinones and haloderivatives of hydroquinone also proved

* These and other investigations in search of antiviral agents, presented in this work, were conducted by coworkers of VNIKhFI, G. N. Pershin, A. N. Grinev, M. Ya. Kraft, N. S. Bogdanova, I. S. Nikolaeva, G. M. Borodina, V. I. Shvedov, G. Ya. Uretskaya, V. V. Katyshkina, N. V. Arkhangel'skaya, E. N. Sytina, S. F. Liberman, E. K. Panisheva, V. M. Lyubchanskaya, and G. V. Yaroslavtseva.

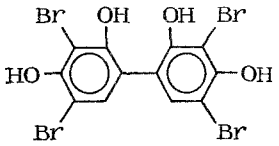
highly active. Four of them (chloro-p-benzoquinone, 2,3-dichloro-p-benzoquinone, 2,5-dibromo-p-benzoquinone, and 2,3-dichlorohydroquinone) possess viricidial activity at a concentration of 0.1 μg per ml. The activity of hydroquinone derivatives, as a rule, is approximately an order of magnitude less than that of the corresponding quinones. However, in contrast to most quinones, they are nontoxic. In a comparison of the results of an investigation of isomeric 2,3-, 2,5-, and 2,6-dichloro-p-benzoquinones, it was found that their antiviral activity depends on the position of the substituent. The highest indices were obtained for 2,3-dichloro-p-benzoquinone, and the lowest for 2,5-dichloro-p-benzoquinone. An analogous pattern is also observed in a comparison of the activities of the corresponding dichlorohydroquinones. A comparison of the viricidal action of chloro-p-benzoquinone (active concentration 0.1 μg per ml) and bromo-p-benzoquinone (10 μg per ml), as well as 2,5-dichloro-p-benzoquinone (10 μg per ml) and 2,5-dibromo-p-benzoquinone (0.1 μg per ml), indicates that the replacement of chlorine by bromine in compounds of the same structure can lead either to a decrease or to an increase in the activity. High viricidal activity is possessed by arylamino-p-benzoquinones. Among them, the most active are phenylamino-p-benzoquinone and arylamino-p-benzoquinones with electron donor groups in the aryl substituent. Among the α- and β-naphthoquinones studied, apparently the most interesting are β-naphthoquinones and especially β-naphthoquinones substituted in the benzene ring. Some of them, for example, 7-hydroxy-, 7-methoxy-, and 6-methoxy-β-naphthoquinones, are active in a dilution of 1-0.1 μg per ml. On the contrary, β-naphthoquinones with a dimethylaminomethyl substituent in the 4-position, which we produced recently [108], are inactive. Heterocyclic analogs of 4-dimethylaminomethyl-β-naphthoquinones – 2-methyl-3-carbethoxy-4,5-dioxo-7-dialkylaminomethylbenzofurans and 1-alkyl (aryl)-2-methyl-3-carbethoxy-4,5-dioxo-7-dimethylaminomethylindoles – also proved to be inactive or showed weak activity with respect to influenza virus [109]. Of the derivatives of 4,5-dioxoindole studied, pronounced viricidal activity was possessed by 1-alkyl-2-methyl-3-carbethoxy-4,5-dioxo-6,7-dichloroindoles.

Among the investigated naphthalene derivatives, high activity against influenza virus (strain PR-8) in vitro and in experiments on chick embryos was shown by tetrahydrotetraoxonaphthalene dihydrate (XXXVI), which has passed through clinical tests under the name of "oxoline" and has been approved by the Pharmacological Committee of the Ministry of Health of the USSR as a means for treatment of various virus diseases. It is used for diseases of the eyes – herpetic keratitis and adenovirus keratoconjunctivitis – and in virus diseases of the skin – herpes simplex and herpes zoster, for the removal of warts, etc.

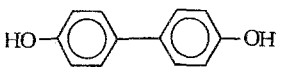
Oxoline XXXVI has been widely and successfully used during an epidemic of influenza A2 (Hong Kong strain) and has been confirmed by the Pharmacological Committee as a means of individual prophylaxis for influenza. It is interesting to note that compounds close in structure to oxoline, for example, tetrahydrotetraoxo-6-bromonaphthalene dihydrate (XXXVII), monoarylhydrazones of tetrahydrotetraoxonaphthalene (XXXVIII), and heterocyclic analogs of the latter (XXXIX, XL), which we produced [108, 109], show no activity at all with respect to influenza virus.



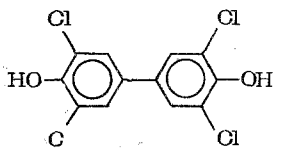
Another antiviral preparation, tebrophen, discovered in VNIKhFI, is 3,5,3',5'-tetrabromo-2,4,2',4'-tetrahydroxydiphenyl (XLI). It possesses high activity with respect to influenza virus (strain PR-8) in vitro and on chick embryos. Tebrophen (XLI) has successfully passed its clinical tests and has been confirmed by the Pharmacological Committee as a preparation for the treatment of virus diseases of the eyes – herpetic keratitis and adenovirus keratoconjuctivitis. Compounds close in structure to tebrophen – 4,4'-dihydroxydiphenyl (XLII), 3,5,3',5'-tetrachloro-4,4'-dihydroxydiphenyl (XLIII), and 3,5,3',5'-tetrabromo-4,4'-dihydroxydiphenyl (XLIV) – either showed weak activity or were entirely inactive with respect to influenza virus.



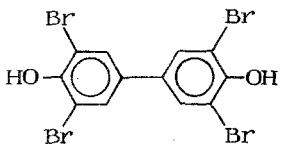
XLI



XLII



XLIII



XLIV

As a result of investigations conducted in VNIKhFI and presented in this survey, original preparations oxoline (XXXVI) and tebrophen (XLI) have been approved for prophylactic use.

In conclusion, it should be mentioned that the problem of the chemotherapy of virus infections, judging by the achievements obtained recently in our country and abroad, is not only important and urgent, but also (with a sufficient concentration of effort) quite solvable.

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