Reviews

Antiviral properties of cage compounds. New prospects

Yu. N. Klimochkin, V. A. Shiryaev, and M. V. Leonova*

Samara State Technical University,
244 ul. Molodogvardeiskaya, 443100 Samara, Russian Federation.
Fax: +7 (846) 332 2122. E-mail: orgchem@samgtu.ru

The published data of the last 15 years on the antiviral activity and the mechanism of action of cage compounds are integrated and described systematically. The considerable interest in the cage compounds as antiviral agents is related to the specific features of the spatial structure of this class of derivatives and high lipophilicity and rigidity of the carbon cage, which allows these molecules to easily penetrate through the lipid layer of biological membranes. Data on the ion channel structure of influenza A and hepatitis C viruses and docking data for some cage structures to these channels are presented. Data on the antiviral properties of cage compounds against RNA genome viruses, the influenza A virus and its mutant strains, hepatitis C virus, human immunodeficiency viruses, and other RNA-containing viruses, are presented. The efficiency of cage compounds against the DNA-genome viruses, herpes virus, cytomegalovirus and orthopoxviruses, is demonstrated. The proven participation of aminoadamantanes in the suppression of early stages of the influenza virus life cycle suggests that efficient inhibitors of not only the influenza virus but also other RNA- and DNA-containing viruses could be found among the cage molecules.

Key words: cage compounds, antiviral activity, adamantane, viral infections, docking.

The recent decades have witnessed a considerable increase in the number of antiviral drugs useful for the therapy of viral diseases that are either life-threatening or harmful to the health of population. These rather recent achievements are related to the development of molecular biology, technical breakthrough in culturing of many viruses in the laboratory, and identification of viral enzymes.[1] However, along with the therapeutic effect, the existing antiviral drugs possess drawbacks and, moreover, the range of antiviral drugs is obviously insufficient. This is evidenced by the Ebola outbreak in 2014, which became a large-scale epidemic threatening the world.

The emergence of new forms of viruses due to variability and mutations and the fact that efficient drugs for treating and preventing a considerable part of viral infections are still lacking dictate the necessity of permanent quest for novel antiviral compounds.

The enhanced interest in the cage compounds as antiviral agents is related to the spatial structure of these derivatives, high lipophilicity, and carbon cage rigidity, which

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1473—1496, July, 2015.

allow these molecules to easily penetrate through the lipid layer of biological membranes.[2,3]

Analysis of the cyclic moieties present in the molecules of drugs approved for use demonstrated that adamantane ranks in the 50th position among the 100 ring systems encountered most frequently in the drug molecules.[4]

The number of scientific publications and reviews of foreign and Russian researchers devoted to the medicinal chemistry of cage compounds,[3,5—14] in particular, their antiviral properties has considerably increased in recent years. Cage compounds proved to be active against RNA- and DNA-genome viruses of a very broad spectrum[14] including influenza, parainfluenza, avian sarcoma, rabies, herpes, tobacco mosaic, and hepatitis viruses; adenovirus, rhinovirus, orthopoxvirus, Newcastle disease virus, PC-virus, vesicular stomatitis virus, ECHO-6, poliomyelitis virus, Coxsackie virus, HIV-1 and HIV-2, and so on.

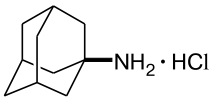
This review integrates the data on the antiviral activities and mechanisms of action of cage compounds published during the last 15 years, because the data up to 2000 have been covered in considerable detail.[14] The review includes only some of the earlier publications and patents that are of key significance. The antiviral activity is considered only for cage compounds containing no heteroatoms in the ring.

Antiviral activity of cage compounds against RNA-genome viruses

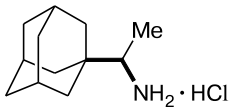
Among the wide diversity of RNA genome viruses that are pathogenic for humans and cause heavy infectious diseases, we consider the antiviral properties of cage compounds only for most abundant groups of viruses.

The first antiviral agents. Drug resistance

The history of cage compounds as potential inhibitors of virus replication started with the discovery of anti-influenza properties of amantadine (1-aminoadamantane hydrochloride) in 1964.[15] Amantadine (Symmetrel®) was the first adamantane derivative to be used in clinical practice. The discovery of the anti-influenza activity of 1-aminoadamantane stimulated intensive search for active compounds, which resulted in a new antiviral drug called rimantadine (α-methyl-1-adamantanemethylamine hydrochloride, Flumadine®). This drug proved to be more efficient and less toxic than amantadine.[16,17]



Amantadine



Rimantadine

The discovery of antiviral properties of amino derivatives of adamantane initiated the medicinal chemistry of adamantane derivatives. This resulted in the synthesis and investigation of biological properties of thousands of cage compounds, and these investigations continue till now.[8]

Studies of the metabolism of amantadine and rimantadine showed[14] 1-acetylaminoadamantane to be the key metabolite of amantadine. The second stage of biotransformation gives methylated and hydroxylated 1-aminoadamantane derivatives. In the case of rimantadine, metabolism follows a hydroxylation route.

In the late 1990s, the use of amantadine and rimantadine for treating and preventing influenza faced the problem of development of drug resistance[18—20] in response to uncontrolled use of the drugs. The resistance to aminoadamantanes has increased in the last 15 years from 0.8% in 1995 to 100% for the S31N mutant of H3N2[21,22] and pandemic H1N1 strain.[23,24] Meanwhile, most of oseltamivir-resistant seasonal H1N1 strains still remain sensitive to adamantane derivatives. Although currently aminoadamantanes are not recommended for use due to increase in the resistance, they still should be considered as possible agents against seasonal H1N1 viruses and highly pathogenic avian influenza H5N1 virus; nevertheless, discovery of new antiviral drugs with high activity and selectivity remains an important task.[20,25]

The results of the latest studies demonstrated that the virus resistance to adamantane-based drugs increases much more slowly than to neuraminidase inhibitors — oseltamivir and zanamivir.[26] Amantadine combined with oseltamivir demonstrated enhanced inhibitory effect on H3N2, H1N1, and H5N1 influenza viruses *in vitro*;[27,28] in *in vivo* experiments, they showed higher protection than monotherapy.[28,29] The synergistic effect *in vivo* was also found for rimantadine combined with oseltamivir.[30,31] Thus, the application of amantadine and rimantadine together with antiviral agents of a different chemical nature has high potential for treatment of some resistant strains of influenza viruses.[20,32]

The medicinal chemistry of adamantane derivatives and structural analogs gained a new impetus from the discovery of the mechanism of amantadine action on the replication of the influenza virus and viral proteins that form ion channels in some viruses. Subsequently these proteins were classified as a separate group and called viroporins.[33]

Viroporins are small proteins usually comprising about 100 or less amino acids and containing at least one hydrophobic transmembrane helical domain, which is to some extent amphiphilic as it separates the amino acid residues of hydrophobic and hydrophilic surfaces of the molecule. In view of the small size, these proteins have to oligomerize to larger structures to form an ion channel. This process is mainly due to hydrophobic interactions, although it can also be accompanied by formation of disulfide bonds. Oligomers ranging from tetramers (the ion

channel of M2 influenza virus)[34,35] to heptamers (P7 hepatitis C virus (HCV))[36—39] forming channels on cell and virion surfaces were identified.[33]

Small ion channels of this type were also found in other enveloped viruses, for example, BM2 (influenza B virus) and CM2 (influenza C virus) proteins and the Vpu protein in the human immunodeficiency virus of type 1 (HIV-1). Studies of the interactions of viroporins with ligands are important for the use of these proteins as drug targets.[40]

Activity of cage compounds against influenza A virus

The influenza virus is among the most abundant viruses having an ion channel on the lipoprotein envelope. This ion channel is called the M2 channel and serves for transporting hydrogen ions inside the viral envelope. A specific feature of the M2 ion channel is rather low proton conduction velocity (less than 10^4 ions per second) compared with typical ion channels.[33] The relatively low conduction velocity of the M2 channel is consistent with the small channel cavity[41] on the lipid membrane surface. The modern model of operation of the M2 channel implies that this protein plays an important role in two different stages of the influenza virus life cycle.[42,43] When the virus has penetrated into the cell, the low pH of endosome activates the M2 channel, which allows protons from the endosome to get into the virus. This results in the loss of the lipoprotein envelope and in uncoating of the viral RNA. The M2 protein also eliminates the pH gradient between the Golgi complex and the cytoplasm in order to prevent the untimely conformational changes of hemagglutinin at the stage of virus assembly.[44,45]

Structure and operation mechanism of the M2 ion channel. The M2 protein has an N-terminal extracellular domain (residues 1—23), transmembrane domain (residues 24—46) (TM), and C-terminal intracellular domain (residues 47—97). Four M2 molecules form a helical complex. The conserved histidine 37 (H37), tryptophan 41 (W41), and valine 27 (V27) residues are crucial for channel formation and proton conduction (Fig. 1).[46,47] The H37 tetramer cluster is important for the pH-activation of the channel,[48] whereas the W41 cluster forms the channel gate;[49] and the V27 cluster is located at the channel entrance and forms the second gate. The structures of the M2 channel of the influenza A virus were determined in amantadine and rimantadine complexes by X-ray crystallography[41] and NMR spectroscopy in solution,[50,51] respectively. The results of these studies confirm the tetrameric arrangement of the transmembrane helices forming the ion channel.

Mechanism of blocking of the M2 protein

During the last 10 years, numerous data concerning the mechanism of inhibition of the M2 protein were published. However, they are all contradictory; therefore, the ultimate mechanism of inhibition still remains obscure. The exact position of the binding site of adamantane-containing drugs is also a source of debate.[49] Two mechanisms were proposed relying on experimental data. The first one is blockage of the channel pore, which was revealed by X-ray diffraction,[41] and the second one is allosteric mechanism established by NMR spectroscopy.[52]

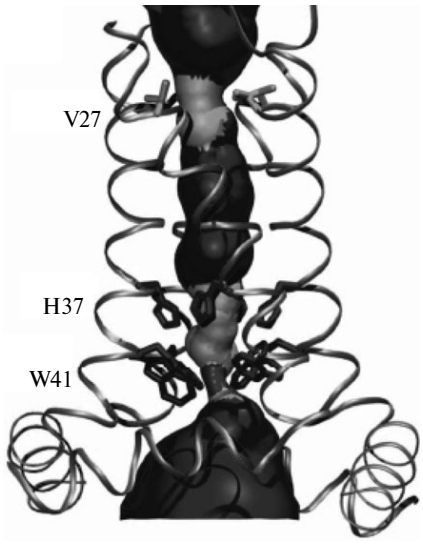


Fig. 1. Positions of the most important amino acid residues (histidine 37 (H37), tryptophan 41 (W41), and valine 27 (V27)) needed for M2 ion channel operation.[51]
Note. Figures 1—3 are available in full color in the on-line version of the journal (http://www.springerlink.com).

According to the blockage mechanism, amantadine physically plugs the pore by being arranged inside it. Valine (Val27), serine (Ser31), glycine (Gly34), and histidine (His37) residues are known to have a high affinity for adamantane and to be located in the close vicinity of the binding site (Fig. 2).[50]

According to the allosteric mechanism, inhibitors of the M2 protein efficiently stabilize the closed conformation of the C-terminal helices[50] and facilitate the orientation of the H37 residue. The possible binding sites of inhibitors in the M2 channel are Val27, Ser31, and Gly34. According to this mechanism, rimantadine binds to four equivalent units in the vicinity of the tryptophan gate on the lipid side of the channel and stabilize the pore closed conformation. It was concluded[52] that the lipid-facing pocket near the Phe54 gate is more significant for the virus inhibition mechanism by adamantane derivatives. In a study designed for the understanding of the mechanism of inhibition of the M2 channel, it was suggested[53] that the molecules of adamantane-derived drugs are likely to bind in any inner cavity (*e.g.*, near the H37 residue) or in the extracellular channel mouth (L26, A30, and S31 residues). The results of other investigations also confirmed

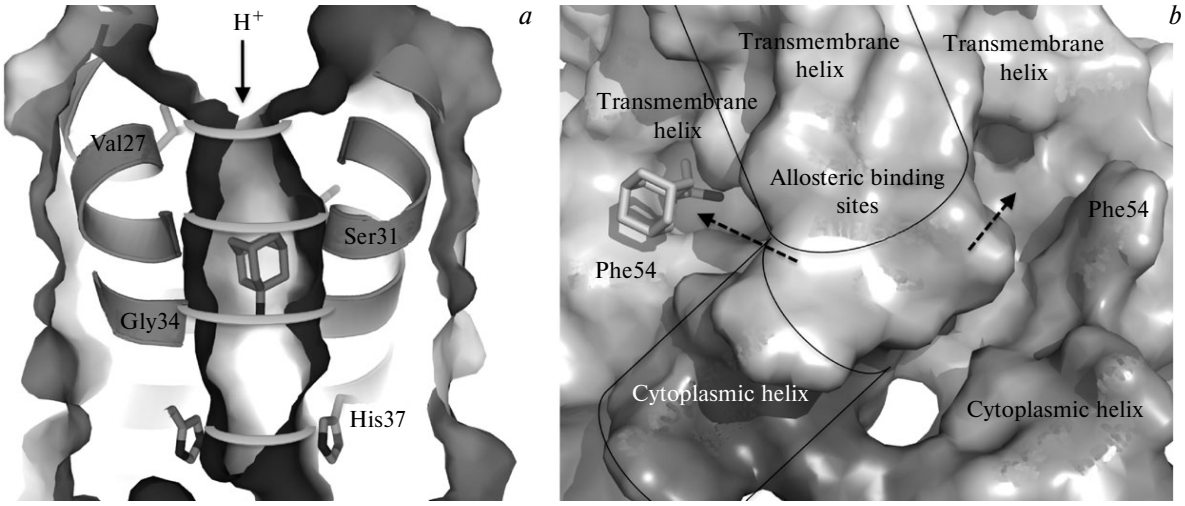


Fig. 2. Position of the amantadine molecule inside (*a*) and on the surface (*b*) of the ion channel.[50]

the assumption that the predominant binding site is located inside the M2 channel.[5,54,55] Currently it is commonly assumed that inhibitors of the M2 proteins block the channel *via* a series of binding interactions in the channel pore.[40,47,56–59] Currently, the progress in the development of M2 channel inhibitors with enhanced properties has been restricted by poor understanding of the inhibition mechanism and insufficient knowledge of the binding site position. It is noteworthy that the amino acid residues inside the M2 channel (the residues from V27 in G34) are especially important for the favorable binding of adamantane.[60–63]

Recently, most of influenza A virus strains have been resistant to amantadine and rimantadine; the most abundant mutation making the virus drug resistant is S31N. The V27A and L26F mutations also occur rather frequently;[52] however, a larger part of resistant virus sybtypes represent the S31N mutant of the M2 protein.[53,54] It was suggested[64] that this mutation leads to indirect increase in the M2 protein mobility and thus prevents the inhibition. All of the above-listed mutations considerably weaken the hydrophobic packing between the N-terminal ends of the transmembrane helices, and this results in looser and more flexible tetramer structure. Loosening of the channel structure may hamper binding of the drug by destabilizing the rimantadine binding pocket in the case of allosteric inhibition mechanism or upon weakening of hydrophobic contacts with amantadine in the pore in the case of pore blocking model.[65]

New M2 ion channel blockers. Owing to the increase in the number of drug resistant strains of the avian influenza H5N1 virus and the H1N1 virus that are resistant both against adamantane derivatives and neuraminidase inhibitors, it is necessary to find and develop new anti-influenza agents. For this reason, considerable effort was invested into the development of new drugs that would be able to affect a wider range of influenza virus strains. The most efficient approach to address this problem is virtual screening, including molecular docking. Currently molecular docking is applied to study binding of ligands to natural macromolecules. It is a useful tool for the understanding of the dynamic structure of proteins and can also serve to study the effect of solvent molecules on the protein structure.[66]

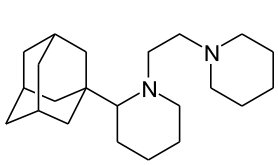
Currently, intensive research of cage structures for identification of the most active M2 ion channel inhibitors is in progress. In one of the studies,[5] more than 200 compounds were tested for binding to the M2 protein. The docking was performed for two drug binding sites of amino acid residues, including S31 and A30, inside and outside the channel, respectively. As a result, 10 structures exhibiting the strongest binding inside the cavity and 10 structures with the strongest binding outside the channel were selected.

Later,[67] docking of 1447 compounds to the M2 ion channel was carried out. The free binding energies were determined for all structures and three ligands were found having lower free binding energy than the standard ligands (amantadine and rimantadine) and stronger interaction with the M2 channel (the last three ligand structures among the structures located on the channel surface).

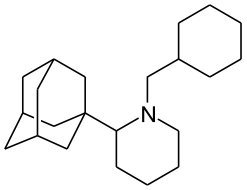
The results of studies of the inhibitory action of amino adamantane derivatives towards the H7N1 influenza virus *in vitro* demonstrated[68] that most compounds surpass amantadine in the selectivity index. Noteworthy is *N*-(1-adamantyl)ethylenediamine dihydrochloride whose selectivity index is almost twice as high as that of amantadine.

Almost all of the existing M2 channel inhibitors have only one pharmacophore group and, in most cases, it is the amino group. As shown in Fig. 2, adamantane-based inhibitors with one pharmacophore group can bind only to one helix of the M2 channel. Nevertheless,

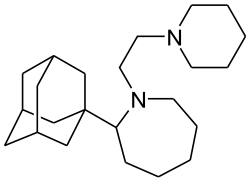
Ligands located inside the M2 channel cavity (see Ref. 5)*



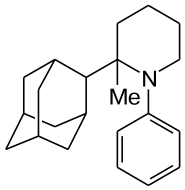
−12.13



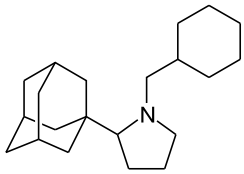
−12.10



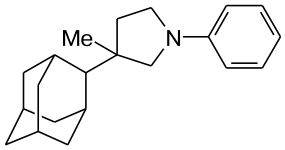
−12.00



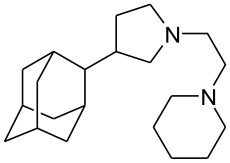
−11.97



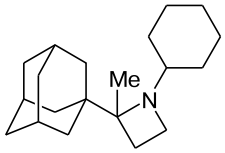
−11.76



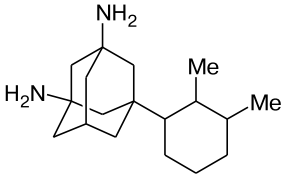
−11.31



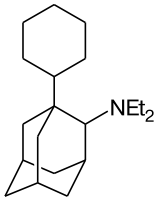
−11.23



−10.95

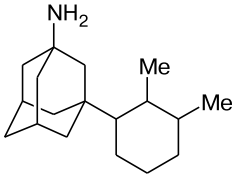


−10.84

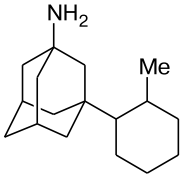


−10.77

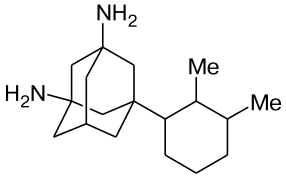
Ligands located on the M2 channel surface (see Refs 5, 67)*



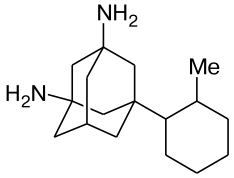
−7.68



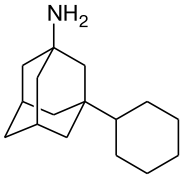
−7.62



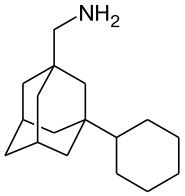
−7.50



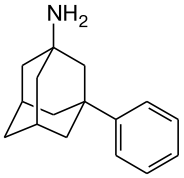
−7.30



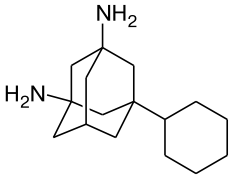
−7.27



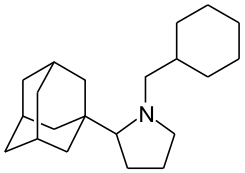
−7.20



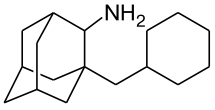
−6.96



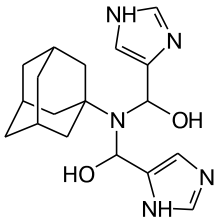
−6.92



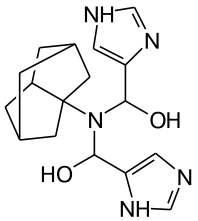
−6.72



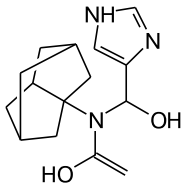
−6.72



−6.6766



−5.7709



−4.9738

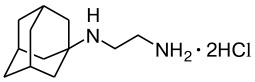
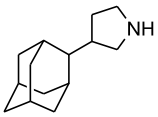
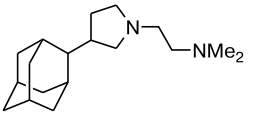
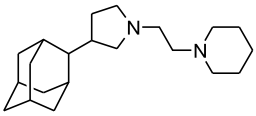
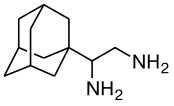
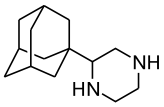
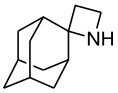
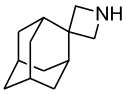
* The numbers below the structures are binding energies/kcal mol^{-1}.

compounds having higher activity than amantadine and rimantadine were obtained from these multifunctional derivatives.[69]

A series of adamantane derivatives with various substituents, including amino and hydroxy groups, cyclohexane and aromatic residues, which were more active than the traditional agents, were developed.[69—78] All compounds of these series were tested for the activity *in vitro*. In 2011,[79] a series of compounds based on isopinene possessing high activity against the influenza H3N2 virus were obtained. A number of azoloadamantane compounds more active against the influenza A virus than amantadine were synthesized in 2010.[80] Adamantanecarboxylic acid derivatives exhibiting higher activity against H3N2 virus than zanamivir were found in 2012.[81] 2,2′-Substituted amantadine analogs proved[82] to be much more active. Higher activity as compared with amantadine was found for its N-benzylated derivatives.[83] some derivatives of D_3-trishomocubane[84] also exhibited activity against the influenza H2N2 virus comparable with the activity of amantadine. The structures of the most active compounds are shown in Table 1.

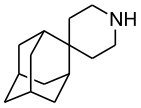
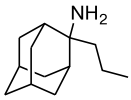
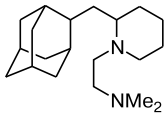
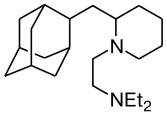
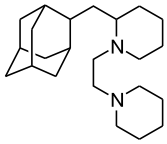
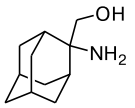
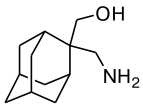
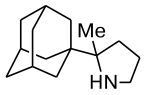
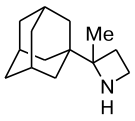
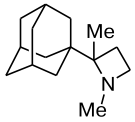
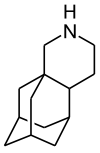
In recent years, researchers have expressed increasing interest in the search for new M2 ion channel blockers, because the M2 channel is more conserved than other influenza virus components. The potential inhibitors are designed using not only the adamantane cage but also trishomocubane, isopinene, and other cage compounds.

Table 1. Anti-influenza activity of cage compounds (IC_{50} is the inhibitory concentration 50%)

Compound	IC_{50} /μmol L^{-1}	Influenza strain	Activity referred to		Ref.
			amantadine	rimantadine	
	0.1	H7N1	2.5	—	68
	0.60	H2N2	4.3	—	69
	5.0	H3N2	2.6	—	69
	0.38	H2N2	6.8	—	69
	9.4	H3N2	1.3	—	69
	0.35	H3N2	36.5	—	69
	1.7	H2N2	1.7	—	69
	18.3	H3N2	2.7	1.0	70
	24.1	H3N2	2.03	0.8	70
	0.36	H3N2	5.5	1.0	71
	0.33	H3N2	6	1.1	71

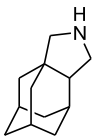
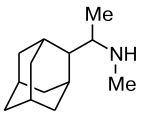
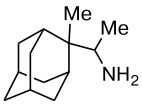
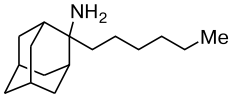
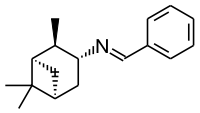
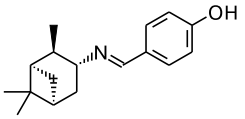
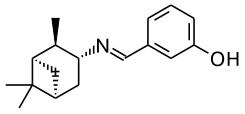
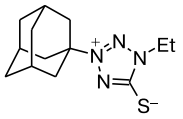
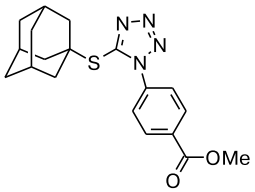
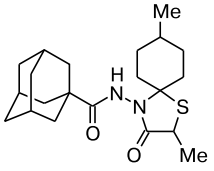
(*to be continued*)

Table 1 (*to be continued*)

Compound	IC_{50} /μmol L^{-1}	Influenza strain	Activity referred to		Ref.
			amantadine	rimantadine	
	0.16	H3N2	12.4	2.3	71
	<1.7	H2N2	0.65	—	72
	<1.7	H3N2	0.53	—	72
	5.9	H3N2	8.3	3.2	73
	7.2	H3N2	6.8	2.7	73
	3.6	H3N2	13.6	5.3	73
	1.46	H3N2	1.4	0.25	74
	0.34	H3N2	5.9	1.1	74
	1.56	H2N2	26.9	9	75
	1.8	H3N2	3.3	0.22	75
	1.96	H2N2	21.4	7.1	75
	2.3	H3N2	2.6	0.17	75
	4.1	H2N2	10.2	3.41	75
	11	H3N2	0.55	0.04	75
	0.6	H3N2	3.3	0.6	76

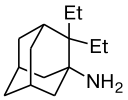
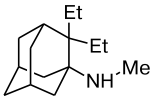
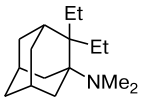
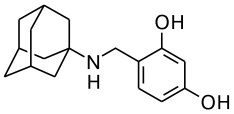
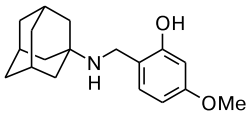
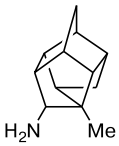
(*to be continued*)

Table 1 (*continued*)

Compound	IC_{50} /μmol L^{-1}	Influenza strain	Activity referred to		Ref.
			amantadine	rimantadine	
	0.5	H3N2	4	0.7	76
	1.7 51.0	H2N2 H3N2	8.8	4.2 0.4	77 77
	4.1 5.2	H2N2 H3N2	3.7	1.7 3.7	77 77
	0.13 1.5 1.1	H1N1 H2N2 H3N2	1846 0.23 2.5	846 1.1 0.48	78 78 78
	7.78	H3N2	2.7	—	79
	0.088	H3N2	240	—	79
	5.99	H3N2	3.5	—	79
	3*	H1N1	—	1.7	80
	2*	H1N1	—	2.5	80
	1.6	H3N2	140	28.1	81

(*to be continued*)

Table 1 (*continued*)

Compound	IC_{50} /μmol L^{-1}	Influenza strain	Activity referred to		Ref.
			amantadine	rimantadine	
	2.0	H1N1	26.5	31.5	82
	4.0	H1N1	13.3	15.8	82
	4.0	H1N1	13.3	15.8	82
	35.2	S31N	5.7	—	83
	59	WT	0.27	—	83
	43.1	S31N	4.6	—	83
	79	WT	0.2	—	83
	30	H2N2	0.8	—	84

* In μg mL^{-1}.

Activity of cage compounds against the human hepatitis C virus

The human hepatitis C virus (HCV) contains viroporin p7, which is attractive target for the therapy, as it plays a certain role in the virus particle assembly and affects its exit from the cell.[85] However, the exact function of p7 is still unknown. The action of the p7 channel may be to suppress the decrease in the pH of cell organelles and to protect the emerging virions from acid-induced conformational changes.[86] Furthermore, there is a set of data indicating that p7 has a crucial influence on the virus assembly and exit from the cell.[85]

The p7 protein consists of 67 amino acid residues. Six such proteins are combined to form an ion channel selective to Na^+, K^+, and Ca^{2+} ions. More recent studies showed that the p7 channel indirectly affects the H^+-conduction. Recently, the structure of the p7 channel in solution was determined by NMR spectroscopy.[87] The top and bottom views of the p7 channel are shown in Figs 3, *a* and *b*, respectively. In the p7 channel, there are six equivalent hydrophobic channels between the peripheral and pore-forming helices, which consist of Leu52, Val53, Leu55, and Leu56 from H3 and Phe20, Val25, and Val26 from H2. The molecules of a drug occupy several pockets in the p7 channel located at the outer edge of the channel funnel (see Fig. 3, *c*). In this state, the channel cannot expand and, hence, it does not transmit ions.[86,87]

Studies of the antiviral activity of amantadine and its derivatives[85] at the stage of clinical trails for hepatitis C virus showed limited efficiency.

Since the p7 channel is necessary for replication of the hepatitis C virus, it is a potential target for the design of new drugs.

Virtual screening of more than 250 thousand compounds[88] with high predicted affinity for the adamantane binding site of the p7 protein was carried out. Some structures demonstrated a substantially (1000-fold) higher activity compared with amantadine. Structure—activity relationship measurements showed even a lower inhibiting concentration and activity against several strains of the hepatitis C virus. These inhibitors are of considerable interest for the development of efficient drug candidates against hepatitis C virus.

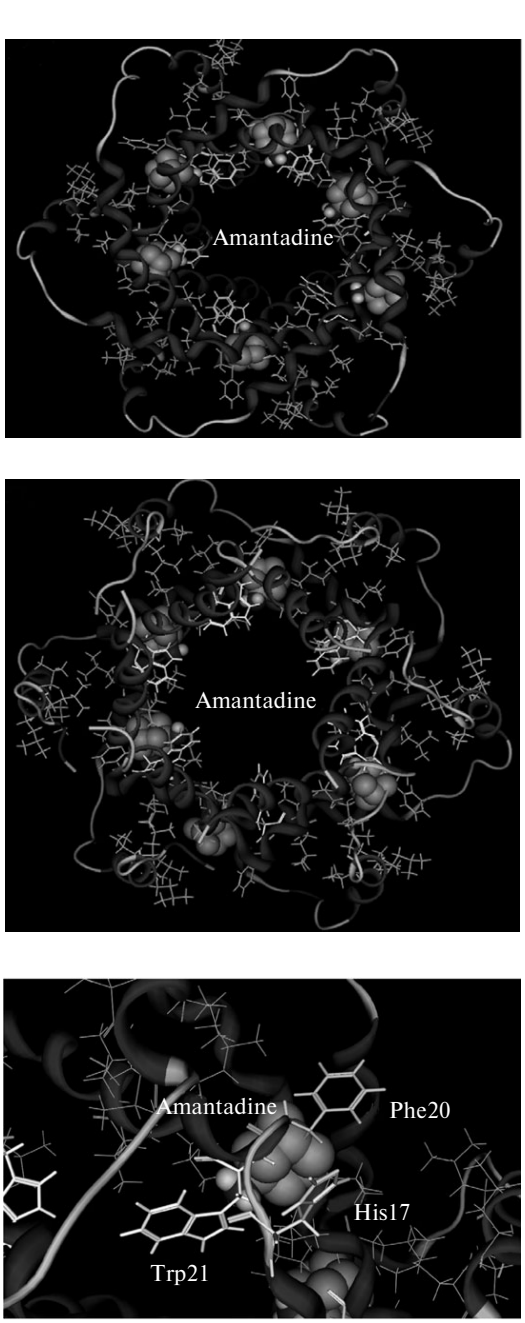


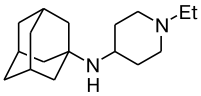
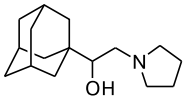
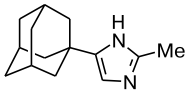
Fig. 3. Structure of the p7 ion channel of the hepatitis C virus:[87] top view (*a*) and bottom view (*b*) and the pocket on the ion channel surface binding the amantadine molecule (*c*).

The molecular docking of ligands to the p7 protein with subsequent *in vitro* verification revealed three compounds having higher inhibitory activity than rimantadine[88] (Table 2).

Yet another target of drugs suppressing the replication of hepatitis C virus is RNA-dependent RNA polymerase. It was shown[89] that introduction of a cage substituent into 2-amino-3-(4-phenyloxyphenyl)acrylic acid markedly enhanced inhibition of this enzyme (Table 3). The introduction of the adamantane moiety into phenylaminoisothiazole[90] also enhances the inhibiting activity (see Table 3).

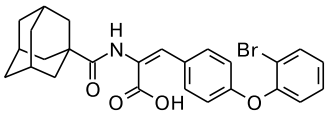
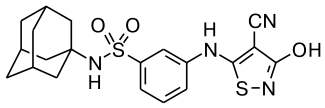
Adamantane derivatives show noticeable activity against the hepatitis C virus; therefore, it seems pertinent to continue the search for new inhibitors among compounds of this series.

Table 2. Compounds exhibiting inhibitory activity toward the p7 protein of the hepatitis C virus (see Ref. 88)

Compound	IC_{50}* /μmol L^{-1}	Viral strain	Activity**
	52 23	WT L20F	1.1 4.3
	39 53	WT L20F	1.4 1.8
	27	WT	2.1

* Here and below, the inhibitory concentration (50%).
** Relative to rimantadine.

Table 3. Compounds exhibiting antiviral activity against RNA-dependent polymerase of the hepatitis C virus

Compound	IC_{50}/μmol L^{-1}	Ref.
	0.07	89
	1.4	90

Activity of cage compounds against other human RNA-genome viruses

There is an enormous diversity of other pathogenic RNA-containing viruses. Some of them are also sensitive to cage compounds. For example, amantadine proved to be effective against the rhabdovirus[91] and the hepatitis A virus,[92] while rimantadine was effective against the dengue fever virus.[93] Some adamantylarylamine derivatives[94] exhibit inhibitory activity *in vitro* toward *N*-methyltrans-

ferase of the dengue fever virus. In 2013, it was found[95] that adamantylacetic acid derivatives are active against the Ebola virus.

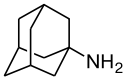
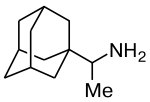
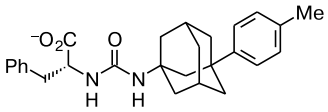
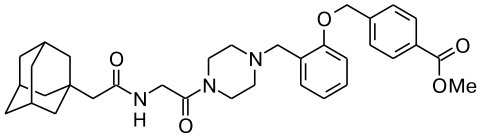
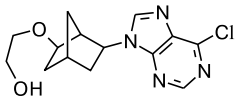
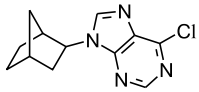
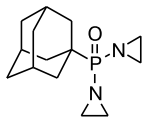
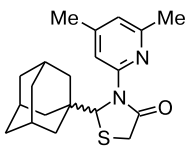
The Coxsackie viruses belong to the class of enteroviruses and affect various internal organs. Some norbornylpurine derivatives exhibit high activity against Coxsackie viruses of type B, which cause myocarditis, pericarditis, and hepatitis.[96,97]

N,*N*´-Bis(ethylene)-*P*-(1-adamantyl)phosphonic diamide (NYPD) was found to suppress the Rous sarcoma virus *via* inhibition of the early stage of virus replication after adsorption on the cell membrane. The data derived from experiments on RSV-transformed non-producing cells indicate that NYPD cannot affect the expression of oncogens by the embedded virus genome.[98]

There is quite a lot of information about the activity of cage compounds against the human immunodeficiency virus (HIV). Most often, the activity is observed for adamantane-containing heterocyclic compounds.[99—103] Pentacycloundecane derivatives also show a fairly good activity.[104] Adamantane-containing polymers are unusual HIV inhibitors.[105] Considerable activity against HIV-1 was found for the synthetic analogs of glycosphingolipids as specific inhibitors of glycolipid receptors.[106] The structures of the most efficient compounds are summarized in Table 4.

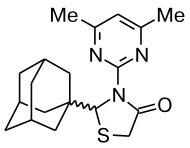
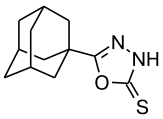
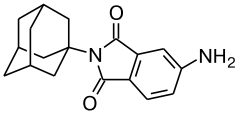
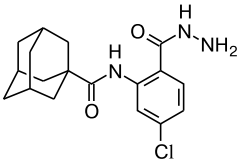
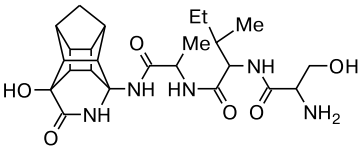
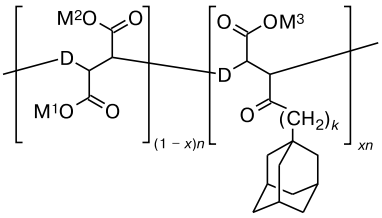
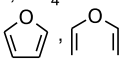
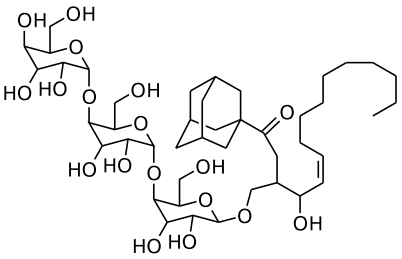
Compounds containing a cage moiety are active against a broad spectrum of RNA-genome viruses. This is apparently due to the fact that the bulky cage moiety can enter the ion channel cavity of the virus and thus block the viral activity.

Table 4. Compounds exhibiting antiviral activity against various RNA genome viruses

Compound	IC_{50}/μmol L^{-1}	Virus	Ref.
	256 330	Rhabdovirus Hepatitis A	91 92
	72.5	Dengue	93
	60.5	Dengue	94
	0.02	Ebola	95
	13	Coxsackie B virus	96
	0.81	Coxsackie B3 virus	97
	25*	Rous sarcoma virus	98
	0.350	HIV-1	99

(*to be continued*)

Table 4 (*continued*)

Compound	IC_{50}/μmol L^{-1}	Virus	Ref.
	0.67	HIV-1	100
	10*	HIV-1	101
	16 27	HIV-1 HIV-2	102 102
	15.1	HIV-1	103
	0.5	HIV-1	104
 M^1, M^2, M^3 = H, Na^+, K^+, NH_4^+ n = 15—20, $k \geq 1$, D = 	6	HIV-1	105
	—	HIV-1	106

* In μg mL^{-1}.

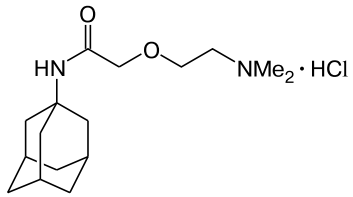
Antiviral activity of cage compounds against DNA-genome viruses

DNA-containing viruses form more than 20 families among which poxvirus, herpesvirus, adenovirus, papillomavirus, hepadnavirus, parvovirus, and some other are most toxic for humans. The genetic material of the DNA-genome viruses represents a single- or double-stranded DNA molecule.[107] Among the DNA-genome viruses, herpes viruses are globally occurring polytropic agents caus-

ing a variety of clinical forms of the disease. The poxvirus family is most dangerous as regards the epidemic characteristics and case fatality rate.

Activity of cage compounds against herpes virus and cytomegalovirus

Many adamantane derivatives exhibit activity against some DNA-genome viruses, in particular, the herpes simplex virus. The drug tromantadine, 2-(2-dimethylaminoethoxy)-*N*-(1-adamantyl)acetamide hydrochloride, which is effective against herpes simplex viruses of types 1 and 2, was developed by Merz company[108] and approved for clinical use since 1973. This agent commercialized under the trade name Viri-merz is used to treat the herpetic skin and mucosa lesions.[109,110]



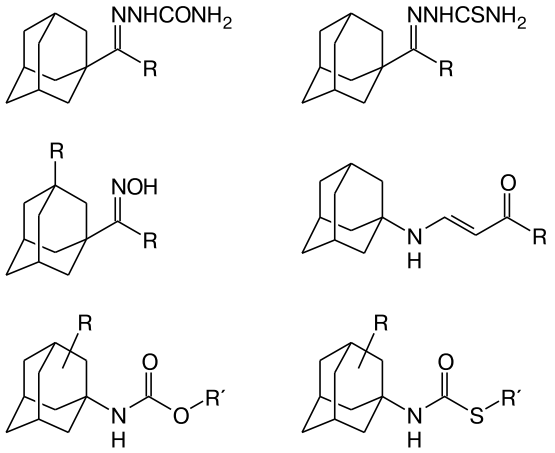
Tromantadine

It is believed that tromantadine affects early stages of interaction of the virus with the cell before the synthesis of macromolecules and the stage of assembly of virions. The sizes of the hydrophobic and hydrophilic parts of the tromantadine molecule are balanced, unlike those of amantadine, which accounts for the possibility of more intense prevention of membrane merging and inhibition of the herpes virus.[111,112]

Subsequently, antiherpetic activity was established for other adamantane derivatives: 3-ethyl-1-adamantanol and ethyl (3-ethyl-1-adamantyl)carbamate.[113–115] The ethyl (3-ethyl-1-adamantyl)carbamate activity against the herpes virus was demonstrated in experiments with different virus strains including the type resistant to acycloguanosine (ACG). Upon the combined use of ethyl (3-ethyladamantan-1-yl)carbamate and ACG, the inhibition of the herpes virus reproduction in cell culture is enhanced and the case fatality rate among the laboratory animals with experimental herpes viral neuroinfection is reduced compared with the separate use of these agents.[114]

A study of the anti-herpetic properties of (3-hydroxy-1-adamantyl)-1-ethylamine hydrochloride (oxyrimantadine) in cell culture demonstrated that this compound is a highly selective inhibitor of HSV-1.[116,117]

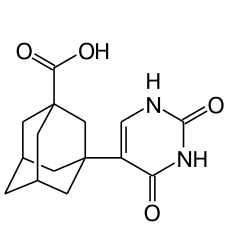
The antiviral properties of numerous adamantane derivatives were studied in relation to the herpes virus.[113,117–123] Among these compounds, the activity was found for adamantane-derived semicarbazones, thiosemicarbazones, and β-aminoketones; adamantyl methyl ketone oxides; adamantyl carbamates; adamantylpyrrolidines; amino adamantane derivatives; and adamantane-containing heterocycles.



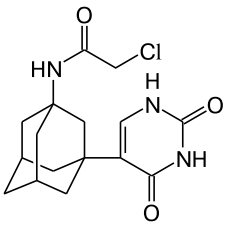
Adamantane derivatives exhibiting anti-herpetic activity

The virus-inhibiting action of thiosemicarbazones and thiocarbohydrazones was studied for different types of herpes virus (HSV-1, thymidine kinase-deficient HSV-1 and HSV-2).[124] Among the recently synthesized adamantane derivatives, note 2-aminopyridine *N*-substituted adamantylthiourea with anti-herpetic properties.[125]

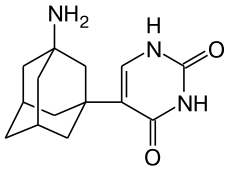
A study of the antiviral activity of 5-(3-R-1-adamantyl)uracils[126] in the *vero* cell culture demonstrated that most of the synthesized compounds are active against herpes viruses of types 1 and 2 (HSV-1 and HSV-2). The selectivity indices (SI) for 5-(3-R-1-adamantyl)uracils are presented below.



SI = 20 (HSV-1)



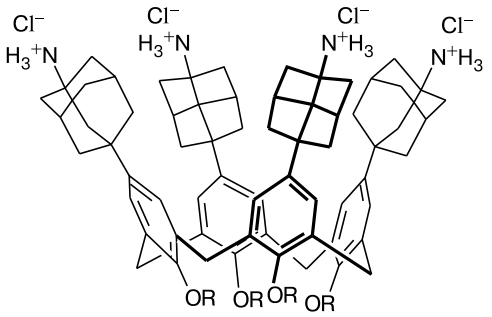
SI = 10 (HSV-2)



SI = 20 (HSV-1)

In relation to the preparation of 1-aminoadamantane conjugates with calix[4]arenes — *p*-(3-amino-1-adamantyl)calix[4]arenes — it was demonstrated that the antiviral activity of 1-aminoadamantane can be combined with that of some calix[*n*]arenes that also possess antiviral activities.[127] The aminoadamantane derivative de-

monstrated a clear-cut antiviral action against HSV-2 in cell culture.



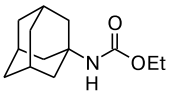
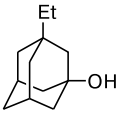
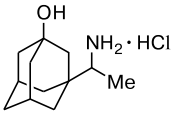
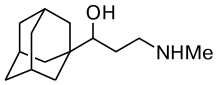
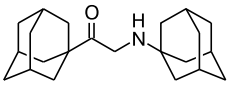
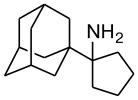
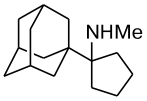
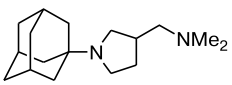
R = H, Bu

It is known that upon introduction into molecules of biologically active compounds, the bulky adamantane moiety can substantially modify their pharmacological action. The antiviral activity of new 2-substituted phenylbenzimidazoles and 2-phenylimidazopyridines, including compounds containing adamantane moiety, has been investigated.[128] Among the tested compounds, some were found to efficiently suppress replication of the herpes simplex virus (HSV-2). Diadamantyl-substituted 2-phenylimidazopyridine also showed high activity in the animal model of the herpetic infection. It is believed[128] that discovery of antiviral agents of this type could provide an alternative approach to the treatment of herpetic infections, especially useful in the case of drug resistant strains.

The activity against the herpes virus was also identified in *N*-substituted adamantylhydroxamic acid.[129]

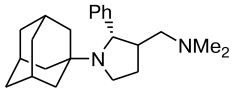
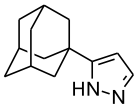
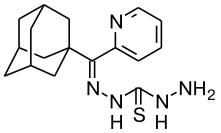
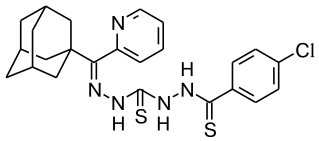
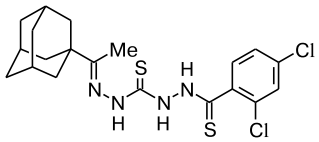
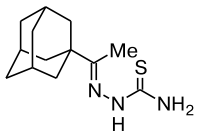
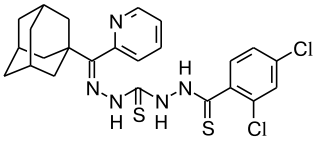
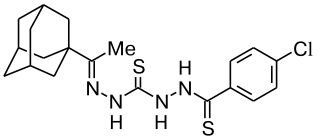
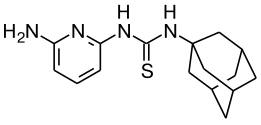
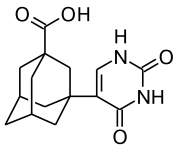
The data on the antiviral activities of various cage compounds against herpes virus (HSV) and cytomegalovirus (CMV) are summarized in Table 5.

Table 5. Antiviral activity of cage compounds against herpes simplex virus (HSV) and cytomegalovirus (CMV)

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	HSV-1	0.62	113, 114
	HSV-1	5.21	115
	HSV-1	15.6	116, 117
	HSV-1	2.71	120
	HSV-1	2.54	120
	HSV-1 TK-HSV-1 HSV-2 CMV	>10 >10 >10 >20	122 122 122 122
	HSV-1 TK-HSV-1 HSV-2 CMV	>10 >10 >10 >20	122 122 122 122
	HSV-1 TK-HSV-1 HSV-2 CMV	>10 >10 >10 >20	122 122 122 122

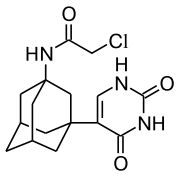
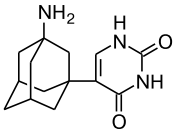
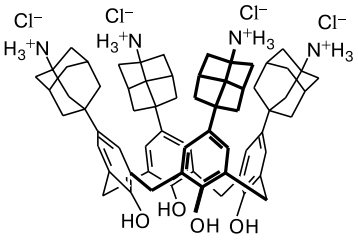
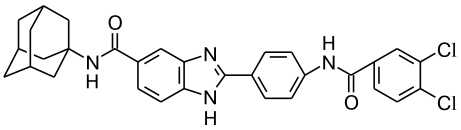
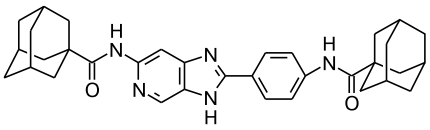
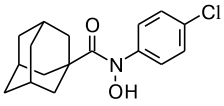
(*to be continued*)

Table 5 (*continued*)

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	HSV-1	>10	122
	TK-HSV-1	>10	122
	HSV-2	>10	122
	CMV	>5	122
	HSV-1	8.29	123
	HSV-1	>16	124
	TK-HSV-1	>16	124
	HSV-2	>16	124
	HSV-1	>16	124
	TK-HSV-1	>16	124
	HSV-2	>16	124
	HSV-1	>16	124
	TK-HSV-1	>9.6	124
	HSV-2	>9.6	124
	CMV	>2	124
	CMV	>2	124
	CMV	>2	124
	CMV	>2	124
	HSV-1	6.2	125
	HSV-1	50	126

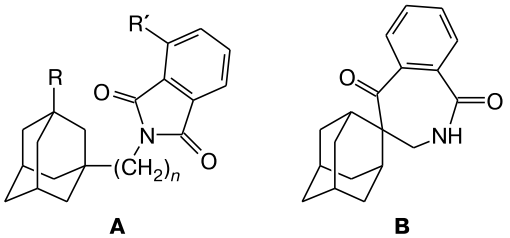
(*to be continued*)

Table 5 (*continued*)

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	HSV-2	50	126
	HSV-1	50	126
	HSV-2	10	127
	HSV-2	20*	128
	HSV-2	5*	128
	HSV-1 HSV-2 CMV	>16 >16 7	129 129 129

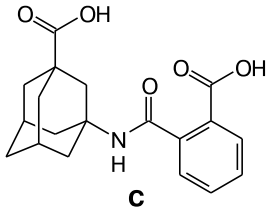
* In nmol L^{-1}.

Three libraries of adamantane derivatives were synthesized: adamantylphthalimides **A**, azaheterocyclic adamantane derivatives **B**, and adamantyl amino acid derivatives **C**. The antiviral properties of these compounds against herpes viruses (HSV-1, thymidine kinase-deficient HSV-1 and HSV-2) were estimated.[130] However, these compounds showed little antiviral activity in cell culture.



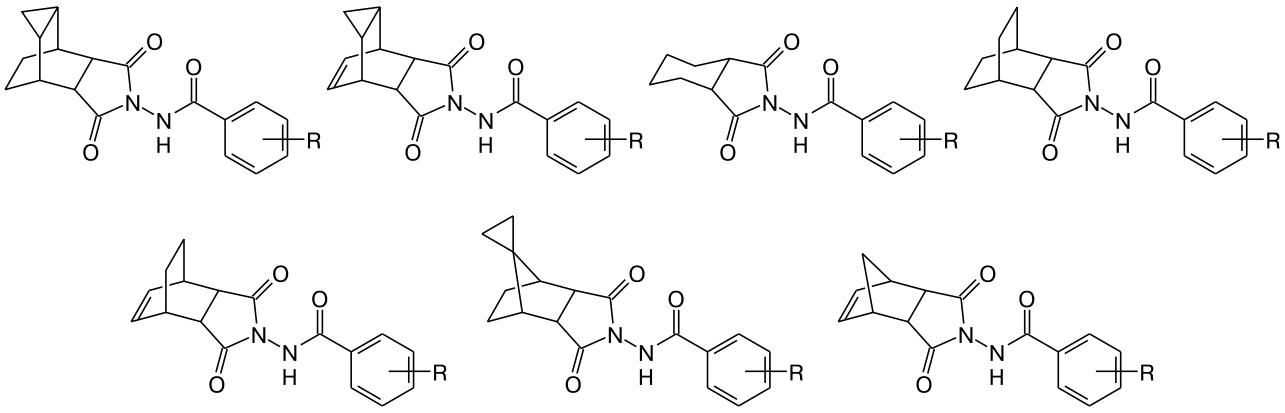
A

B



C

The cage compounds are of interest as potential agents also for the therapy of the cytomegalovirus infection. Cytomegalovirus is a virus with a double-stranded DNA from the family of herpes viruses. Among viral infections, cytomegalovirus is the most frequently occurring pathology. A considerable number of papers were devoted to the virus-inhibiting action of cage compounds. The activity against



Polycyclic cage structures tested against orthopoxviruses by SIGA Technologies

CMV was found for a wide range of adamantane derivatives. The data on virus-inhibiting action of these compounds are summarized in Table 5.

Activity of cage compounds against poxviruses

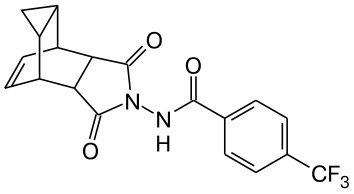
Poxviruses occupy a special place among DNA-genome viruses. The variola (smallpox) virus, which belongs to the genus orthopoxvirus of the poxvirus family, is considered to be most dangerous due to its pathogenic and epidemic behavior and represents a menace as a biological agent that can be used for bioterrorism. Poxviruses are largest and most complicated among all known human and animal viruses.[131] Their genome is represented by a two-stranded DNA, which bears information about the amino acid sequences of several tens of polypeptides. The reproductive cycle of the variola virus is very complicated. The poxvirus maturing and exit from the cell as well as penetration into the cell are multistage processes involving intermediate forms.[131]

The high throughput screening of a large array of compounds (more than 350,000) performed by SIGA Technologies (USA) resulted in identification of a new class of low-molecular-weight agents exhibiting high anti-orthopoxvirus activity.[132]

It was found that some polycyclic imides containing a benzamide ring inhibit the formation of extracellular forms of the virus. These compounds target the F13L gene, which encodes the main enveloped protein (p37) needed for the virus particle formation and exit from the cell, thus preventing virus propagation.[133–135]

For many tricyclononane carboxamides, the concentration providing inhibition of 50% of viruses varies from 20 nmol L^{-1} to >20 μmol L^{-1}.[134,136] The most active agent out of this group is tecovirimat[137,138] (ST-246) whose oral bioavailability is 31%.

The drug ST-246 (4-trifluoromethyl-*N*-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocyclopropa[*f*]-isoindol-2(1*H*)-ylbenzamide) is efficient against a series



Tecovirimat

of orthopoxviruses, including the vaccinia virus, monkeypox, cowpox, camelpox, and mousepox viruses, and variola virus.[136,139]

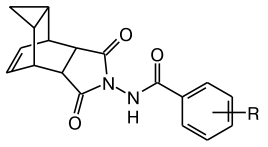
During the study, a number of ST-246 analogs with different substituents in different positions of the benzene ring were synthesized; most of these compounds showed activity against the vaccinia and cowpox viruses.[134]

Higher activity was found for 4-nitro-, 4-bromo-, and 4-chloro-substituted analogs. The researchers of SIGA Technologies found that the activity of compounds of this series is substantially affected by the presence of an electron-withdrawing group in the benzene ring. For example, 4-nitrophenyl derivatives were 100 times more active than 4-dimethylaminophenyl analogs. Furthermore, the inhibitory activity was markedly affected by the position of the electron-withdrawing substituent in the benzene ring. Compounds with an electron-withdrawing group in the *para*- or *meta*-position have a higher activity, which markedly decreases for the *ortho*-substituted derivatives.

The antiviral activities of tecovirimat analogs against the vaccinia and cowpox viruses *in vitro* are presented in Table 6.

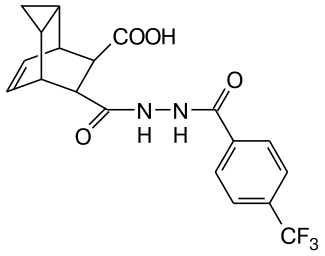
The efficiency of tecovirimat against variola virus was measured in nonhuman primate experiments.[140] Tecovirimat was approved as a drug for treating smallpox and is the most efficient chemotherapeutic agent against all orthopoxviruses. Currently, about 1.7 million courses of tecovirimat can be manufactured in the USA in case of emergency (*www.siga.com*).

Table 6. Antiviral activity of tecovirimat analogs against vaccinia and cowpox viruses[134]



R	EC_{50}/μmol L^{-1}	
	vaccinia	cowpox
4-NO_2	0.02	0.15
4-NH_2	7.7	>20
4-NMe_2	2.0	15.5
4-Cl	0.02	0.77
3-Cl	0.04	0.6
2-Cl	3.0	>20
4-Br	0.02	1.6
3-Br	0.05	0.6
2-Br	2.3	>20
4-OMe	2.2	>20
4-Pyridyl	0.5	17.2
3-Pyridyl	0.74	>20
2-Pyridyl	>20	>20
CF_3 (ST-246)	0.04	0.6

Yet another analog of ST-246 was developed by joint effort of researchers from the Vorozhtsov Novosibirsk Institute of Organic Chemistry and the State Research Center of Virology and Biotechnology VECTOR (Koltsovo).[141—143] The agent NIOC-14, 7-[*N*′-(4-trifluoromethylbenzoyl)hydrazinocarbonyl]tricyclo[3.2.2.$0^{2,4}$]non-8-ene-6-carboxylic acid, efficiently suppresses the replication of orthopoxviruses in cell cultures in concentrations of 0.005—0.051 μg mL^{-1}.[141]



NIOC-14

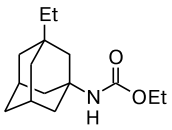
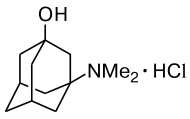
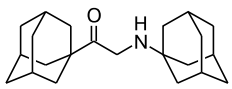
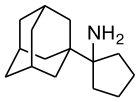
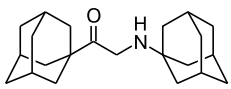
The antiviral activity found for NIOC-14 proved to be comparable with that of ST-246 (0.003 μg mL^{-1}) in all of the parameters measured *in vitro*.[141]

The synthesis and antiviral activity of a number of polycyclic analogs of the orthopoxvirus inhibitor, tecovirimat (ST-246), were reported.[144] It was assumed that replacement of the tricyclononane ring in ST-246 by another polycyclic cage can give rise to new compounds with a potential antipoxviral activity. Some of them were active against the vaccinia virus.

Antiviral properties against orthopoxviruses (vaccinia virus and cowpox, mousepox, and monkeypox viruses) were detected for adamantane-derived azidoketone hydrazones.[145]

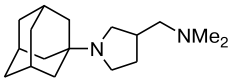
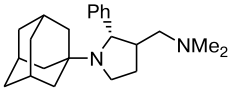
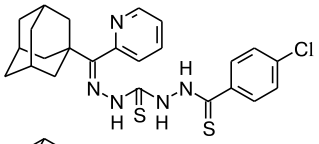
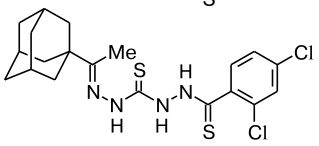
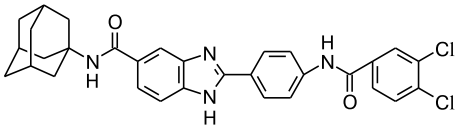
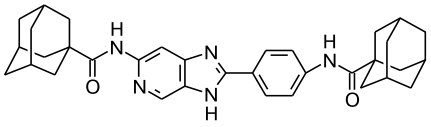
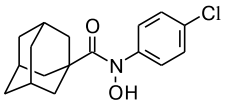
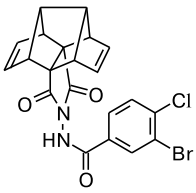
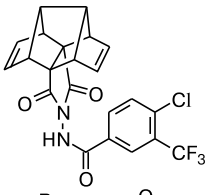
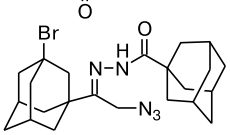
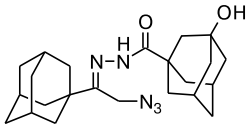
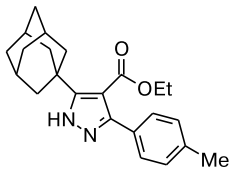
Screening of a multitude of cage compounds with respect to orthopoxviruses resulted in identification of compounds with clear-cut antiviral activities. Highly active compounds were found among adamantane-based pyrazoles, 1,2,4-triazoles, pyrrolidines, and amino- and

Table 7. Antiviral activity of cage compounds against orthopoxviruses

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	Vaccinia	5.15	113, 114
	Vaccinia	9.4	115
	Vaccinia	0.7	120
	Vaccinia	>10	122
	Vaccinia	>10	122

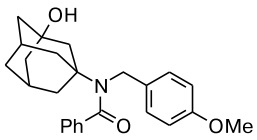
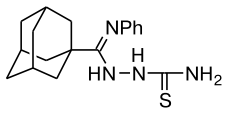
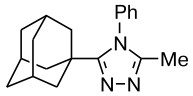
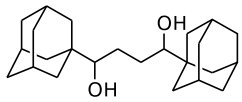
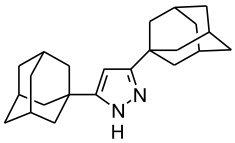
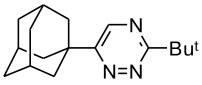
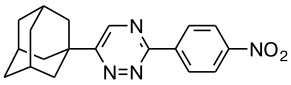
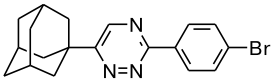
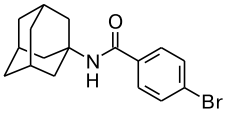
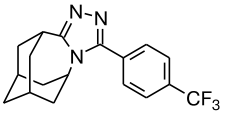
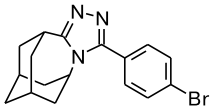
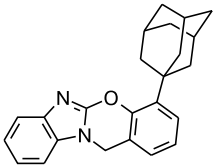
(*to be continued*)

Table 7 (*continued*)

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	Vaccinia	>10	122
	Vaccinia	>10	122
	Vaccinia	>16	124
	Vaccinia	>16	124
	Vaccinia	20*	128
	Vaccinia	10*	128
	Vaccinia	>16	129
	Vaccinia	0.16**	144
	Vaccinia	0.8**	144
	Vaccinia Cowpox Mousepox Monkeypox	1.28 28.3 9.8 4.2	145 145 145 145
	Vaccinia Cowpox Mousepox Monkeypox	0.96 10.8 14.4 3.8	145 145 145 145
	Vaccinia	0.83	146

(*to be continued*)

Table 7 (*continued*)

Compound	Virus	IC_{50}/μg mL^{-1}	Ref.
	Vaccinia	1.41	146
	Vaccinia	4.18	146
	Vaccinia	4.7	146
	Vaccinia Cowpox Mousepox	0.75 3.8 1.84	146, 147 146, 147 146, 147
	Vaccinia	3.26	146, 147
	Vaccinia	0.12	148
	Vaccinia	0.054	148
	Vaccinia	0.36	148
	Vaccinia	0.005	148
	Vaccinia	3.6	149
	Vaccinia	22.2	149
	Vaccinia	0.012**	150

* In nmol L^{-1}.
** In μmol L^{-1}.

hydroxy derivatives as well as among benzoylaminoadamantanes and unsymmetrical adamantyltriazines.[113,115,120,122,146–148] The activity against vaccinia virus was found for heterocyclic derivatives based on 4-azahomoadamantane[149] and adamantane-containing benzimidazobenzoxazine.[150] Data on the virus inhibitory properties targeting the vaccinia virus reproduction were reported for adamantyloxamides, adamantylcarbamates,[113,114] 2-substituted phenylbenzimidazoles, 2-phenylimidazopyridine derivatives, containing an adamantane moiety,[128] adamantane-based thiosemicarbazones and thiocarbohydrazones,[124] and adamantyl-1-*N*-(4-chlorophenyl)hydroxamic acid.[129]

Data on the antiviral activities of cage compounds against orthopoxviruses are summarized in Table 7.

Thus, the noticeable activity of cage compounds against herpes virus, cytomegalovirus, and orthopoxviruses implies that an important role belongs to the polycyclic cage. The presence of the lipophilic moiety in the known ST-246 drug suggests that replacement of the tricyclononane cage by the adamantane or some other cage could give rise to adequate drug candidates for inhibition of orthopoxviruses. Only few cases of activity of cage compounds are known against other DNA-containing viruses such as adenovirus, papillomavirus, hepatitis B virus, and other. Nevertheless, it can be assumed with a reasonable degree of confidence that more intensive research in the medicinal chemistry of cage compounds would bring about satisfactory antiviral drug candidates.[151]

The structural features of cage compounds correspond in the best way to the view that the nucleus functions as the transport part of the molecule and the side chain (substituent) is the attaching part in the antiviral behavior. The initial and final (pre- and post-synthetic) stages of the reproduction of all enveloped viruses occur in the hydrophobic phase of the bilayer membranes of living cells.

The value of cage compounds, including adamantane derivatives, as antiviral agents is generally their ability to be immersed into hydrophobic components of the cell membrane to a certain depth owing to the presence of the hydrocarbon cage in the molecule. The proven participation of aminoadamantanes in the suppression of the early stages of the influenza virus life cycle suggests the possibility of finding effective cage inhibitors for not only influenza virus but also other RNA- and DNA-containing viruses.

This work was financially supported by the Russian Science Foundation (Project No. 15-13-0084) and the Ministry of Education and Science of the Russian Federation in terms of the State Order No. 4.1440.2014/K.

References

1. E. Littler, B. Oberg, *Antivir. Chem. Chemother.*, 2005, **16**, 155.
2. W. J. Geldenhuys, S. F. Malan, J. R. Bloomquist, A. P. Marchand, C. J. Van der Schyf, *Med. Res. Rev.*, 2005, **25**, 21.
3. J. Liu, D. Obando, V. Liao, T. Lifa, R. Codd, *Eur. J. Med. Chem.*, 2011, **46**, 1949.
4. R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845.
5. L. Tran, S. B. Choi, B. O. Al-Najjar, M. Yusuf, H. A. Wahab, L. Le, *Molecules*, 2011, **16**, 10227.
6. D. W. Oliver, S. F. Malan, *Med. Chem. Res.*, 2008, **17**, 137.
7. M. D. Duque, E. Torres, E. Valverde, M. Barniol, S. Guardiola, M. Rey, S. Vázquez, in *Recent Advances in Pharmaceutical Sciences*, Ed. D. Muñoz-Torrero, Transworld Research Network, India, 2011, 35.
8. L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.*, 2013, **113**, 3516.
9. E. De Clercq, *Nature Rev. Drug Discov.*, 2006, **5**, 1015.
10. E. De Clercq, J. Neyts, *Trends Pharmacol. Sci.*, 2007, **28**, 280.
11. A. A. Spasov, T. V. Khamidova, L. I. Bugaeva, I. S. Morozov, *Pharm. Chem. J. (Engl. Transl.)*, 2000, **34**, 1 [*Khim.-Farm. Zhurn.*, 2000, **34**, 3].
12. G. Lamoureux, G. Artavia, *Curr. Med. Chem.*, 2010, **17**, 2967.
13. J. Joubert, W. J. Geldenhuys, C. J. Van der Schyf, D. W. Oliver, H. G. Kruger, T. Govender, S. F. Malan, *Chem. Med. Chem.*, 2012, **7**, 375.
14. I. S. Morozov, V. I. Petrov, S. A. Sergeeva, *Farmakologiya Adamantanov* [*Adamantane Pharmacology*], Volgograd Medical Academy, Volgograd, 2001, 320 (in Russian).
15. W. L. Davies, R. R. Grunert, R. F. Haff, J. F. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, C. E. Hoffmann, *Science*, 1964, **144**, 862.
16. A. Tsunoda, H. F. Maassab, K. W. Cochran, W. C. Eveland, *Antimicrob. Agents Chemother.*, 1965, **5**, 553.
17. F. G. Hayden, J. M. I. Gwaltney, C. R. L. Van, K. F. Adam, B. Giordani, *Antimicrob. Agents Chemother.*, 1981, **19**, 226.
18. D. L. Mayers, in *Drug Resistance. Vol. 1. Mechanisms of Drug Resistance*, Eds S. A. Lerner, M. Ouellette, J. D. Sobel, Humana Press, 2009.
19. D. Y. Oh, A. C. Hurt, *Scientifica*, 2014, **2014**, ID 430629.
20. L. Simeonova, A. Galabov, *Biotechnol. Biotechnol. Eq.*, 2011, **25**, 8.
21. V. M. Deyde, X. Xu, R. A. Bright, M. Shaw, C. B. Smith, Y. Zhang, Y. Shu, L. V. Gubareva, N. J. Cox, A. I. Klimov, *J. Infect. Dis.*, 2007, **196**, 249.
22. M. I. Nelson, L. Simonsen, C. Viboud, M. A. Miller, E. C. Holmes, *Virology*, 2009, **388**, 270.
23. F. S. Dawood, S. Jain, L. Finelli, M. W. Shaw, S. Lindstrom, R. J. Garten, *N. Engl. J. Med.*, 2009, **360**, 2605.
24. H. Zaraket, H. Kondo, C. Tabet, R. Wakim, Y. Suzuki, G. S. Dbaiboc, R. Saito, H. Suzuki, *J. Clin. Virol.*, 2011, **51**, 170.
25. *17th Expert Committee on the Selection and Use of Essential Medicines*, March 2009, Geneva, http://www.who.int/selection_medicines/committees/expert/17/application/Section24.
26. V. Garcia, S. Aris-Brosou, *Mol. Biol. Evol.*, 2013, **31**, 355.
27. J. T. Nguyen, J. D. Hoopes, M. H. Le, D. F. Smee, A. K. Patick, D. J. Faix, P. J. Blair, M. D. de Jong, M. N. Prichard, G. T. Went, *PLOS One*, 2010, **5**, e9332.
28. D. F. Smee, B. L. Hurst, M. H. Wong, K. W. Bailey, J. D. Morrey, *Antimicrob. Agents Chemother.*, 2009, **53**, 2120.
29. K. N. Masihi, B. Schweiger, T. Finsterbusch, H. Henge, *J. Chemother.*, 2007, **19**, 295.

30. A. S. Galabov, L. Simeonova, G. Gegova, *Antivir. Chem. Chemother.*, 2006, **17**, 251.
31. I. A. Leneva, N. Roberts, E. A. Govorkova, O. G. Goloubeva, R. G. Webster, *Antivir. Res.*, 2000, **48**, 101.
32. J. T. Nguyen, J. D. Hoopes, D. F. Smee, M. N. Prichard, E. M. Driebe, D. M. Engelthaler, M. H. Le, P. S. Keim, R. P. Spence, G. T. Went, *Antimicrob. Agents Chemother.*, 2009, **53**, 4115.
33. M. E. Gonzalez, L. Carrasco, *FEBS Letters*, 2003, **552**, 28.
34. Q.-S. Du, R.-B. Huang, S.-Q. Wang, K.-C. Chou, *PLOS One*, 2010, **5**, e9388.
35. J. Wang, Y. Wu, C. Ma, G. Fiorin, J. Wang, L. H. Pinto, R. A. Lamb, M. L. Klein, W. F. DeGrado, *PNAS*, 2013, **110**, 1315.
36. S. Griffin, *Fut. Med. Chem.*, 2014, **6**, 1893.
37. B. O. Yang, S. Xie, M. J. Berardi, X. Zhao, J. Dev, W. Yu, B. Sun, J. J. Chou, *Nature*, 2013, **498**, 7455.
38. S. D. C. Griffn, L. P. Beales, D. S. Clarke, O. Worsfold, S. D. Evans, J. Jaeger, M. P. G. Harris, D. J. Rowlands, *FEBS Lett.*, 2003, **535**, 34.
39. K. Gaedigk-Nitschko, M. X. Ding, M. A. Levy, M. J. Schlesinger, *Virology*, 1990, **175**, 282.
40. A. Kolocouris, C. Zikos, R. W. Broadhurst, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3947.
41. A. L. Stouffer, R. Acharya, D. Salom, A. S. Levine, L. Di Costanzo, C. S. Soto, V. Tereshko, V. Nanda, S. Stayrook, W. F. DeGrado, *Nature*, 2008, **451**, 596.
42. R. A. Lamb, L. H. Pinto, *Virology*, 1997, **229**, 1.
43. M. Kelly, J. A. Cook, P. Brown-Augsburger, M. C. Smith, L. H. Pinto, *FEBS Lett.*, 2003, **552**, 61.
44. A. Agirre, A. Barco, L. Carrasco, J. L. Nieva, *J. Biol. Chem.*, 2002, **277**, 40434.
45. J. V. Melton, G. D. Ewart, R. C. Weir, P. G. Board, E. Lee, P. W. Gage, *J. Biol. Chem.*, 2002, **277**, 46923.
46. L. H. Pinto, R. A. Lamb, *J. Biol. Chem.*, 2006, **281**, 8997.
47. C. Wang, R. A. Lamb, L. H. Pinto, *Biophys. J.*, 1995, **69**, 1363.
48. Y. Tang, F. Zaitseva, R. A. Lamb, L. H. Pinto, *J. Biol. Chem.*, 2002, **277**, 39880.
49. J. R. Schnell, J. J. Chou, *Nature*, 2008, **451**, 591.
50. D. Kalyan, *J. Med. Chem.*, 2012, **55**, 6263.
51. M. Sharma, M. Yi, H. Dong, H. Qin, E. Peterson, D. D. Busath, H. X. Zhou, T. A. Cross, *Science*, 2010, **330**, 509.
52. R. M. Pielak, J. R. Schnell, J. J. Chou, *Proc. Natl Acad. Sci. Am.*, 2009, **106**, 7379.
53. C. Laohpongspaisan, T. Rungrotmongkol, P. Intharathep, M. Malaisree, P. Decha, O. Aruksakunwong, P. Sompornpisut, S. Hannongbua, *J. Chem. Inf. Model.*, 2009, **49**, 847.
54. L. Simonsen, C. Viboud, B. T. Grenfell, *Mol. Biol. Evol.*, 2007, **24**, 1811.
55. R. A. Bright, D. K. Shay, B. Shu, N. J. Cox, A. I. Klimov, *J. Am. Med. Assoc.*, 2006, **295**, 891.
56. Q. S. Du, R. B. Huang, C. H. Wang, X. M. Li, K. C. Chou, *J. Theor. Biol.*, 2009, **259**, 159.
57. P. Intharathep, C. Laohpongspaisan, T. Rungrotmongkol, A. Loisruangsin, M. Malaisree, *J. Mol. Graph. Model.*, 2008, **27**, 342.
58. T. H. Nguyen, D. Hoang, L. Le, *IFMBE Proc.*, 2013, **49**, 384.
59. N. Tran, L. Tran, L. Le, *Med. Chem. Res.*, 2013, **22**, 6078.
60. J. Hu, T. Asbury, S. Achuthan, C. Li, R. Bertram, J. R. Quine, R. Fu, T. A. Cross, *Biophys. J.*, 2007, **92**, 4335.
61. M. Yi, T. A. Cross, H. X. Zhou, *J. Phys. Chem. B*, 2008, **112**, 7977.
62. S. D. Cady, K. Schmidt-Rohr, J. Wang, C. S. Soto, W. F. Degrado, M. Hong, *Nature*, 2010, **463**, 689.
63. T. A. Cross, H. Dong, M. Sharma, D. D. Busath, H. X. Zhou, *Curr. Opin. Virol.*, 2012, **2**, 128.
64. L. Tran, L. Le, *Med. Chem. Res.*, 2014, **23**, 3607.
65. J. Du, T. A. Cross, H. X. Zhou, *Drug Discov. Today*, 2012, **17**, 1111.
66. R. M. Pielak, J. J. Chou, *Biochem. Biophys. Res. Commun.*, 2010, **401**, 58.
67. U. S. F. Tambunan, M. R. Rahdiansyah, A. A. Parikesit, *On Line J. Biol. Sci.*, 2013, **13**, 1.
68. Pat. RF 2401263; *Byul. Izobret.* [*Invention Bull.*], 2010, 28 (in Russian).
69. G. Stamatiou, A. Kolocouris, N. Kolocouris, G. Fytas, G. B. Foscolos, J. Neyts, E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2137.
70. D. Tataridis, G. Fytas, A. Kolocouris, C. Fytas, N. Kolocouris, G. B. Foscolos, E. Padalko, J. Neyts, E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 692.
71. N. Kolocouris, G. Zoidis, G. B. Foscolos, G. Fytas, S. R. Prathalingham, J. M. Kelly, L. Naesens, E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4358.
72. A. Kolocouris, P. Spearpoint, S. R. Martin, A. J. Hay, M. Lypez-Querol, F. X. Sureda, E. Padalko, J. Neyts, E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6156.
73. D. Setaki, D. Tataridis, G. Stamatiou, A. Kolocouris, G. B. Foscolos, G. Fytas, N. Kolocouris, E. Padalko, J. Neyts, E. De Clercq, *Bioorg. Chem.*, 2006, **34**, 248.
74. G. Zoidis, N. Kolocouris, J. M. Kelly, S. R. Prathalingam, L. Naesens, E. De Clercq, *Eur. J. Med. Chem.*, 2010, **45**, 5022.
75. G. Zoidis, C. Fytas, I. Papanastasiou, G. B. Foscolos, G. Fytas, E. Padalko, E. De Clercq, L. Naesens, J. Neyts, N. Kolocouris, *Bioorg. Med. Chem.*, 2006, **14**, 3341.
76. G. Zoidis, N. Kolocouris, L. Naesens, E. De Clercq, *Bioorg. Med. Chem.*, 2009, **17**, 1534.
77. G. Zoidis, N. Kolocouris, G. B. Foscolos, A. Kolocouris, G. Fytas, P. Karayannis, E. Padalko, J. Neyts, E. De Clercq, *Antivir. Chem. Chemother.*, 2003, **14**, 153.
78. A. Kolocouris, C. Tzitzoglaki, F. B. Johnson, R. Zell, A. K. Wright, T. A. Cross, I. Tietjen, D. Fedida, D. D. Busath, *J. Med. Chem.*, 2014, **57**, 4629.
79. X. Zhao, C. Li, S. Zeng, W. Hu, *Eur. J. Med. Chem.*, 2011, **46**, 52.
80. V. V. Zarubaev, E. L. Golod, P. M. Anfimov, A. A. Shtro, V. V. Saraev, A. S. Gavrilov, A. V. Logvinov, O. I. Kiselev, *Bioorg. Med. Chem.*, 2010, **18**, 839.
81. F. Goktas, E. Vanderlinden, L. Naesens, N. Cesur, Z. Cesur, *Bioorg. Med. Chem.*, 2012, **20**, 7155.
82. E. Torres, R. Fernández, S. Miquet, M. Font-Bardia, E. Vanderlinden, L. Naesens, S. Vázquez, *ACS Med. Chem. Lett.*, 2012, **3**, 1065.
83. J. Wang, C. Ma, J. Wang, H. Jo, B. Canturk, G. Fiorin, L. H. Pinto, R. A. Lamb, M. L. Klein, W. F. DeGrado, *J. Med. Chem.*, 2013, **56**, 2804.
84. D. W. Oliver, T. G. Dekker, F. O. Snyckers, *Arzneim. Forsch. Drug. Res.*, 1991, **41**, 549.
85. L. W. Meredith, N. Zitzmann, J. A. McKeating, *Antivir. Res.*, 2013, **100**, 636.

86. A. L. Wozniak, S. Griffin, D. Rowlands, M. Harris, M. K. Yi, S. M. Lemon, S. A. Weinman, *PLOS Pathog.*, 2010, **6**, e1001087.
87. Q.-S. Du, S.-Q. Wang, D. Chen, J.-Z. Meng, R.-B. Huang, *PLOS One*, 2014, **9**, e93613.
88. T. L. Foster, M. Verow, A. L. Wozniak, M. J. Bentham, J. Thompson, E. Atkins, S. A. Weinman, C. Fishwick, R. Foster, M. Harris, S. Griffin, *Hepatology*, 2011, **54**, 79.
89. J. A. Pfefferkorn, R. Nugent, R. J. Gross, M. Greene, M. A. Mitchell, M. T. Reding, L. A. Funk, R. Anderson, P. A. Wells, J. A. Shelly, R. Anstadt, B. C. Finzel, M. S. Harris, R. E. Kilkuskie, L. A. Kopta, F. J. Schwende, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2812.
90. S. Yan, T. Appleby, E. Gunic, J. H. Shim, T. Tasu, H. Kim, F. Rong, H. Chen, R. Hamatake, J. Z. Wu, Z. Hong, N. Yao, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 28.
91. F. Superti, L. Seganti, A. Panà, N. Orsi, *Drugs Exp. Clin. Res.*, 1985, **11**, 69.
92. T. Kanda, O. Yokosuka, F. Imazeki, K. Fujiwara, K. Nagao, H. Saisho, *Biochem. Biophys. Res. Commun.*, 2005, **331**, 621.
93. W. C. Koff, J. L. Elm, Jr, S. B. Halstead, *Am. J. Trop. Med. Hyg.*, 1981, **30**, 184.
94. V. B. Luzhkov, B. Selisko, A. Nordqvist, F. Peyrane, E. Decroly, K. Alvarez, A. Karlen, B. Canard, J. Aqvis, *Bioorg. Med. Chem.*, 2007, **15**, 7795.
95. K. Lee, T. Ren, M. Cote, B. Gholamreza, J. Misasi, A. Bruchez, J. Cunningham, *ACS Med. Chem. Lett.*, 2013, **4**, 239.
96. M. Šála, H. Hřebabecký, P. Leyssen, M. Dejmek, M. Dračínský, A. M. De Palma, J. Neyts, R. Nenska, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1963.
97. M. Šála, A. M. De Palma, H. Hřebabecký, M. Dejmek, M. Dračínský, P. Leyssen, J. Neyts, H. Mertlíková-Kaiserová, R. Nenska, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4271.
98. T. L. McGraw, L. A. Cates, L. S. Daley, Y. C. Chen, *Antivir. Res.*, 1981, **1**, 269.
99. J. Balzarini, B. Orzeszko, J. K. Maurin, A. Orzeszko, *Eur. J. Med. Chem.*, 2007, **42**, 993.
100. J. Balzarini, B. Orzeszko-Krzesińska, J. K. Maurin, A. Orzeszko, *Eur. J. Med. Chem.*, 2009, **44**, 303.
101. A. A. El-Emam, O. A. Al-Deeb, M. Al-Omar, J. Lehmann, *Bioorg. Med. Chem.*, 2004, **12**, 5107.
102. J. Vamecq, K. Van Derpoorten, J. H. Poupaert, J. Balzarini, E. De Clercq, *Life Sci.*, 1998, **63**, 267.
103. M. A. El-Sherbeny, *Arch. Pharm.*, 2000, **333**, 323.
104. M. M. Makatini, K. Petzold, S. N. Sriharsha, M. E. S. Soliman, B. Honarparvar, P. I. Arvidsson, Y. Sayed, P. Govender, G. E. M. Maguire, H. G. Kruger, T. Govender, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2274.
105. M. E. Burstein, A. V. Serbin, T. V. Khakhulina, I. V. Alymova, L. L. Stotskaya, O. P. Bogdan, E. E. Manukchina, V. V. Jdanov, N. K. Sharova, A. G. Bukrinskaya, *Antivir. Res.*, 1999, **41**, 135.
106. R. Mahfoud, M. Mylvaganam, C. A. Lingwood, J. Fantini, *J. Lipid Res.*, 2002, **43**, 1670.
107. *Fundamental Virology*, Eds B. N. Fields, D. M. Knipe, Raven Press, New York, 1986, 768 pp.
108. D. Peteri, W. Sterner, *Arzneim. Forsch.*, 1973, **23**, 577.
109. K. E. Ostheimer, T. Busch, R. Gortelmeyer, K. D. Hahn, *Arzneim. Forsch.*, 1989, **39**, 1152.
110. W. Diezel, G. Michel, R. Gortelmeyer, K. E. Ostheimer, *Arzneim. Forsch.*, 1993, **43**, 491.
111. K. S. Rosenthal, M. S. Sokol, R. L. Ingram, R. Subramanian, R. C. Fort, *Antimicrob. Agents Chemother.*, 1982, **22**, 1031.
112. D. E. Ickes, T. M. Venetta, Y. Phonphok, K. S. Rosenthal, *Antivir. Res.*, 1990, **14**, 75.
113. Y. N. Klimochkin, I. K. Moiseev, E. I. Boreko, G. V. Vladyko, L. V. Korobchenko, *Pharm. Chem. J.* (*Engl. Transl.*), 1989, **23**, 304 [*Khim.-Farm. Zh.*, 1989, **23**, 418].
114. USSR Inventor´s Certificate 1721048; *Byul. Izobret.* [*Invention Bull.*], 1992, 11 (in Russian).
115. Yu. N. Klimochkin, M. V. Leonova, I. R. Korzhev, I. K. Moiseev, G. V. Vladyko, L. V. Korobchenko, E. I. Boreko, S. N. Nikolaeva, *Pharm. Chem. J. (Engl. Transl.)*, 1992, **26**, 616 [*Khim.-Farm. Zh.*, 1992, **26**, 58].
116. RF Patent 2269338; *Byul. Izobret.* [*Invention Bull.*], 2006, 4 (in Russian).
117. I. K. Moiseev, V. L. Andronova, V. V. Pozdnyakov, N. V. Makarova, G. A. Galegov, *Antibiotics Chemother.* (*Engl. Transl.*), 2002, **47**, 9 [*Antibiotiki i khimioterapiya*, 2002, **47**, 9].
118. N. V. Makarova, E. I. Boreko, I. K. Moiseev, N. I. Pavlova, M. N. Zemtsova, S. N. Nikolaeva, G. V. Vladyko, *Pharm. Chem. J. (Engl. Transl.)*, 2001, **35**, 308 [*Khim.-Farm. Zh.*, 2001, **35**, 18].
119. N. V. Makarova, E. I. Boreko, I. K. Moiseev, N. I. Pavlova, M. N. Zemtsova, S. N. Nikolaeva, G. V. Vladyko, *Pharm. Chem. J.* (*Engl. Transl.*), 2001, **35**, 480 [*Khim.-Farm. Zh.*, 2001, **35**, 17].
120. N. V. Makarova, E. I. Boreko, I. K. Moiseev, N. I. Pavlova, S. N. Nikolaeva, M. N. Zemtsova, O. V. Savinova, *Pharm. Chem. J. (Engl. Transl.)*, 2003, **37**, 8 [*Khim.-Farm. Zh.*, 2003, **37**, 8].
121. Yu. N. Klimochkin, I. K. Moiseev, G. V. Vladyko, L. V. Korobchenko, E. I. Boreko, *Pharm. Chem. J.* (*Engl. Transl.*), 1991, **25**, 485 [*Khim.-Farm. Zh.*, 1991, **25**, 46].
122. N. Kolocouris, A. Kolocouris, G. B. Foscolos, G. Fytas, J. Neyts, E. Padalko, J. Balzarini, R. Snoeck, G. Andrei, E. De Clercq, *J. Med. Chem.*, 1996, **39**, 3307.
123. N. V. Makarova, E. I. Boreko, I. K. Moiseev, N. I. Pavlova, S. N. Nikolaeva, M. N. Zemtsova, G. V. Vladyko, *Pharm. Chem. J.* (*Engl. Transl.*), 2002, **36**, 5 [*Khim.-Farm. Zh.*, 2002, **36**, 5].
124. A. Kolocouris, K. Dimas, Ch. Pannecouque, M. Witvrouw, G. B. Foscolos, G. Stamatiou, G. Fytas, G. Zoidis, N. Kolocouris, G. Andrei, R. Snoeck, E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 723.
125. N. Mibu, K. Yokomizo, T. Miyata, K. Sumoto, *Chem. Pharm. Bull.*, 2007, **55**, 1406.
126. A. Shmailov, L. Alimbarova, E. Shokova, V. Tafeenko, I. Vatsouro, V. Kovalev, *Tetrahedron*, 2010, **66**, 3058.
127. A. E. Motornaya, L. M. Alimbarova, E. A. Shokova, V. V. Kovalev, *Pharm. Chem. J.* (*Engl. Transl.*), 2006, **40**, 68 [*Khim.-Farm. Zh.*, 2006, **40**, 10].
128. H. Banie, A. Sinha, R. J. Thomas, J. C. Sircar, M. L. Richards, *J. Med. Chem.*, 2007, **50**, 5984.
129. M. Barbaric, S. Uršić, V. Pilepić, B. Zorc, A. Hergold-Brundić, A. Nagl, M. Grdiša, K. Pavelić, R. Snoeck, G. Andrei, J. Balzarini, E. De Clerq, M. Mintas, *J. Med. Chem.*, 2005, **48**, 884.

130. N. Basari, M. Sohora, N. Cindro, K. Mlinari-Majerski, E. De Clercq, J. Balzarini, *Arch. Pharm. Chem. Life Sci.*, 2014, **347**, 334.
131. M. N. Prichard, E. R. Kern, *Antivir. Res.*, 2012, **94**, 111.
132. WO Pat. 2004/112718; *Chem. Abstr.*, 2004, **142**, 86610.
133. S. Duraffour, S. Vigne, K. Vermeire, A. Garcel, E. Vanstreels, D. Daelemans, G. Yang, R. Jordan, D. E. Hruby, J. M. Crance, D. Garin, G. Andrei, R. Snoeck, *Antivir. Ther.*, 2008, **13**, 977.
134. R. Jordan, J. M. Leeds, S. Tyavanagimatt, D. E. Hruby, *Viruses*, 2010, **2**, 2409.
135. D. W. Grosenbach, R. Jordan, D. E. Hruby, *Future Virol.*, 2011, **6**, 653.
136. G. Yang, D. C. Pevear, M. H. Davies, M. S. Collett, T. Bailey, S. Rippen, L. Barone, C. Burns, G. Rhodes, S. Tohan, J. W. Huggins, R. O. Baker, R. L. Buller, E. Touchette, K. Waller, J. Schriewer, J. Neyts, E. De Clercq, K. Jones, D. Hruby, R. Jordan, *J. Virol.*, 2005, **79**, 13139.
137. T. R. Bailey, S. R. Rippin, E. Opsitnick, C. J. Burns, D. C. Pevear, M. S. Collett, G. Rhodes, S. Tohan, J. W. Huggins, R. O. Baker, E. R. Kern, K. A. Keith, D. Dai, G. Yang, D. Hruby, R. Jordan, *J. Med. Chem.*, 2007, **50**, 1442.
138. D. W. Grosenbach, A. Berhanu, D. S. King, S. Mosier, K. F. Jones, R. A. Jordan, T. C. Bolken, D. E. Hruby, *Proc. Natl Acad. Sci.*, 2010, **107**, 838.
139. K. Sliva, B. Schnierle, *J. Virol.*, 2007, **4**, 8.
140. E. M. Mucker, A. J. Goff, J. D. Shamblin, D. W. Grosenbach, I. K. Damon, J. M. Mehal, R. C. Holman, D. Carroll, N. Gallardo, V. A. Olson, C. J. Clemmons, P. Hudson, D. E. Hruby, *Antimicrob. Agents Chemother.*, 2013, **57**, 6246.
141. RF Patent 2412160; *Byul. izobret.* [*Invention Bull.*], 2011, 5 (in Russian).
142. A. S. Kabanov, Al. A. Sergeev, L. E. Bulychev, N. I. Bormotov, L. N. Shishkina, Ar. A. Sergeev, S. A. Bodnev, M. O. Skarnovich, A. R. Shevtsov, B. A. Selivanov, A. Ya. Tikhonov, A. P. Agafonov, A. N. Sergeev, *Problemy osobo opasnykh infektsii* [*Problems of Especially Dangerous Infections*], 2013, **2**, 54 (in Russian).
143. A. S. Kabanov, Al. A. Sergeev, L. N. Shishkina, L. E. Bulychev, M. O. Skarnovich, Ar. A. Sergeev, N. I. Bormotov, O. V. P´yankov, O. A. Serova, S. A. Bodnev, B. A. Selivanov, A. Ya. Tikhonov, A. P. Agafonov, A. N. Sergeev, *Voprosy Virusologii* [*Virology Issues*], 2013, **4**, 39 (in Russian).
144. E. Torres, M. D. Duque, P. Camps, L. Naesens, T. Calvet, M. Font-Bardia, S. Vazquez, *Chem. Med. Chem.*, 2010, **5**, 2072.
145. RF Patent 2376283; *Byul. izobret.* [*Invention Bull.*], 2009, 35 (in Russian).
146. I. K. Moiseev, S. A. Kon´kov, K. A. Ovchinikov, N. M. Kilyaeva, K. M. Bormasheva, O. N. Nechaeva, M. V. Leonova, Yu. N. Klimochkin, S. M. Balachin, N. I. Bormotov, O. A. Serova, E. F. Belanov, *Pharm. Chem. J.* (*Engl. Transl.*), 2012, **45**, 588 [*Khim.-Farm. Zh.*, 2011, **45**, 9].
147. Yu. Klimochkin, V. Osyanin, E. Golovin, M. Leonova, S. Konkov, N. Kilyaeva, N. Bormotov, O. Serova, S. Balakhnin, E. Belanov, *Antivir. Res.*, 2010, **86**, A59.
148. USSR Inventor´s Certificate 1568481; *Byul. izobret.* [*Invention Bull.*], 1990, 20 (in Russian).
149. Yu. Klimochkin, M. Baymuratov, E. Knayzeva, N. Baleeva, M. Leonova, M. Skomorohov, E. Belanov, S. Balakhnin, *Antivir. Res.*, 2011, **90**, A71.
150. Yu. Klimochkin, V. Osyanin, N. Sidorina, M. Leonova, E. Belanov, O. Serova, S. Balakhin, N. Bormotov, *Antivir. Res.*, 2011, **90**, A50.
151. E. I. Boreko, Yu. N. Klimochkin, A. K. Shiryaev, G. V. Vladyko, M. N. Zemtsova, S. N. Nikolaeva, P. L. Trakhtenberg, N. I. Pavlova, N. V. Makarova, O. V. Savinova, I. K. Moiseev, in *Uspekhi Khimii Adamantana* [*Advances in the Adamantane Chemistry*], Ed. N. S. Zefirov, Khimiya, Moscow, 2007, 70 (in Russian).

Received January 23, 2015;
in revised form May 19, 2015