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Mono- and sesquiterpenes as a starting platform for the development of antiviral drugs

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The revies focuses on low-molecular-weight plant metabolites (mono- and sesquiterpenes) exhibiting antiviral activity. Data on antiviral action of both essential oils and plant extracts and their components are provided. Structures of biologically active natural mono- and sesquiterpenoids as well as their derivatives showing a pronounced antiviral activity are presented. A special attention is given to the description of targets for antiviral therapy. The mechanisms of action of antiviral agents are considered.
The bibliography includes 163 references.

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1. Introduction

Viruses are the most abundant biological entities on Earth; they coexist with other living organisms such as bacteria, plants, and animals, including humans. The virus (virus, translated from Latin, means 'poison') is a non-cellular infectious agent that can only reproduce inside living cells. To date, more than 6000 viral species have already been identified, and this number is still growing; virologists suggest that there are more than 100 million of them.[1] Almost all living organisms are susceptible to viral infection. Once inside the host cells, some viruses can remain latent and be inactive[2] for a long period of time, which is the cause of chronic infections. However, most often viruses cause various structural and biochemical changes in infected cells, referred to as cytopathic effects. Most viral infections lead to cell death as a result of changes in the cytoplasmic (cell) membrane, lysis, or apoptosis. Moreover, the cell might die because of suppression of its normal activity, which is caused by viral proteins, and not all of them are part of the virus particle itself.

The commonly accepted classification of viruses is based on the type of nucleic acid, the size, and symmetry of the nucleocapsid, and includes the presence or absence of an outer envelope. Viruses of the same family have a similar type of genome and morphological characteristics. The genus of the virus indicates its biological and epidemiological characteristics, and also takes into account the degree of homology between the nucleotide sequences of the genome. The specific name of a human virus is usually associated with the type of its pathological effect or with the circumstances of the discovery and is officially assigned by an International Committee on Taxonomy of Viruses (ICTV).†

Human viruses cause a large number of especially dangerous [smallpox, bird flu, atypical pneumonia, acquired immunodeficience syndrome (AIDS), hemorrhagic fever, *etc.*] and common infectious diseases [common cold, acute respiratory viral infections (ARVI), influenza, rubella, *etc.*]. A person can be also infected with many animal viruses, and some of them acquire this ability under certain conditions. Noteworthy among them are avian and swine viruses widely known in recent years, as well as the new coronavirus SARS-CoV-2. Table 1 presents the most common viruses infecting humans.

In 2016, De Clercq and Lia[3] presented the history of the discovery of drugs that have shown their efficiency against the most dangerous viral infections. Although notable advances have been made in recent years in the development of antiviral drugs for the treatment of HIV, herpes, hepatitis, and acute respiratory infections, there remain many severe viral infections against which chemotherapy is virtually powerless. Thus, a particularly dangerous virus

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† See site https://talk.ictvonline.org

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Table 1. Human viruses and diseases caused by them.

Latin name of the family	Full name of the virus	Abbreviated name of the virus	Diseases	Availability of antiviral therapy
Ortomyxoviridae	Influenza A and B viruses	A/H1N1, H3N2, H5N1, H7N9	ARVI, influenza	Yes
Picornavirales	Rhinoviruses		Rhinovirus infection, common cold	No
Adenoviridae	Adenoviruses		The same	No
Coronaviridae	Coronaviruses	HCoV	"	No
	SARS coronaviruses [a]	MERS-CoV	SARS, atypical pneumonia	No
		SARS-CoV-2	COVID-19	No
Retroviridae	Human Immunodeficiency virus (HIV)	HIV-1, HIV-2	HIV infection, AIDS	Yes
Togaviridae	Chikungunya virus	CHIKV	Chikungunya virus infection	No
Flaviviridae	Yellow fever virus	Yellow fever	Yellow fever [b]	No
	Dengue virus	DENV	Dengue fever	No
	Zika virus	ZIKV	Zika fever	No
	Tick-borne encephalitis virus	TBEV	Tick-borne encephalitis	No
Bunyaviridae	Hantaan hantavirus	HTNV	Hemorrhagic fever with renal syndrome (HFRS)	No
Herpesviridae	Herpes simplex virus 1	HSV-1	Oral (herpetic stomatitis, herpes on lips) or genital herpes virus	No
	Herpes simplex virus 2	HSV-2	Oral and genital or vaginal herpes virus	Yes
	Varicella-zoster virus	VZV	Chicken pox, herpes zoster	No
	Epstein – Barr virus	EBV	Infectious mononucleosis	No
	Human cytomegalovirus	CMV	The same	No
Filoviridae	Ebola virus	EBOV	Ebola hemorrhagic fever	No
	Marburg virus	MARV	Marburg hemorrhagic fever	No
Papillomaviridae	Papillomaviruses	HPV	Anogenital warts infection [c]	No (see [d])

[a] SARS is severe acute respiratory syndrome; [b] acute hemorrhagic transmissible disease; [c] disease probably relating to breast cancer; [d] surgical resection.

SARS-CoV-2 caused a pandemic in 2019 – 2020 — a catastrophic increase in the number of affected by the new coronavirus infection (COVID-19).‡

Due to the ever-growing interest of researchers in the challenges of modern virology and the development of novel antiviral drugs, several works summarizing the data on specific antiviral activity have been published recently. Thus, recent advances in the influenza virus chemotherapy [5 – 9] and in the development of the specific inhibitors of flavivirus infections [10, 11] were presented; strategies for developing drugs aimed at the treatment of hepatitis,[12, 13] herpes simplex virus,[14, 15] filoviral infections,[16, 17] and Chikungunya virus [18] were analyzed. Reviews have been published that analyzed data on natural compounds exhibiting activity against the hepatitis B virus (HBV),[19, 20] on the study of metabolites of the higher plants used as HIV inhibitors [21 – 23] and showed antiviral action against herpes simplex viruses of types 1 and 2.[24, 25] Some reviews [26, 27] summarize data on the search for antiviral drugs using the molecular modelling approaches.

Despite the numerous reviews on the antiviral activity, no analysis of the results of the study of terpenoids and their functionalized derivatives as antiviral agents has been provided so far. The last consolidated articles on the antiviral activity of natural compounds date back to 2000 (see Ref. 28) and 2014,[29] with a significant part of the material in these works being focused on the properties of alkaloids, flavonoids, and coumarins, and only fragmentary information was given for terpene compounds. The present review examines the literature data on the study of antiviral action of mono- and sesquiterpenoids, and of their new derivatives. References on available original publications are provided that were published mainly between 2010 and 2020, as well as on earlier reports if they are critical for the discussion.

Naturally occurring compounds and their analogues are essential components in a wide range of potent drugs.[30, 31] They are of crucial importance to the development of the world pharmaceutical industry since the list of medicines based on natural compounds and their derivatives or analogues includes about one-half of all currently known medical preparations. Among them, mention should be made of pain relievers based on morphine derived from the opium poppy (*Papaver somniferum*), cardiotropic drugs based on digitalis glycosides (*Digitalis*), anti-inflammatory drugs based on steroid hormones. antibiotics and many others.[32, 33] For this reason, the search for antiviral agents based on naturally occurring compounds is of particular interest to researchers.

The selectivity index (SI) is a key parameter in determining antiviral properties. This parameter is a ratio of the concentration of a compound that causes the death of half of viable cells (CC_{50}) to the concentration required to achieve half-maximum inhibition (IC_{50}) of viral reproduction and is characteristic of its safety and efficiency. To be used in viral therapy, the drug must effectively (in low doses) prevent virus replication and show no toxicity, that is, it must be safe for normal cells at higher concentrations. Promising as an antiviral drug, a candidate compound

‡ Detailed information on SARS-CoV-2 virus see, *e.g.*, a review.[4]

should have the highest CC_{50} value and the lowest IC_{50} value. The selectivity index of a test compound reflects its ability to kill the virus as compared to cells. It is generally believed that compounds whose selectivity index value exceeds 8 are active.

In the present review, the antiviral activity index of all compounds is presented as their concentration of half-maximum inhibition (IC_{50}), expressed in μmol mL^{-1} (μM). It should be noted that the most proper is the comparison of the physiological action of compounds towards a particular virus within one library and under similar test conditions. At the same time, activity and toxicity indices can vary considerably since they are affected by various parameters including the type of the cells in use, virus titer, and a testing method. If the authors of the original publication provided only data on the activity of an antiviral agent, it was not possible to calculate the selectivity index.

2. Antiviral action of plant extracts

Since ancient times, people have used essential oils of aromatic plants to treat diseases of the upper respiratory tract, despite the fact that their active components were not yet known. According to estimates by the World Health Organization (WHO) and for the treatment of infectious diseases, most people (~80%) currently use traditional medicine based on water and aqueous ethanol extracts of medicinal herbs and other plant raw materials. In 2003, the review [34] was published summarizing data on the antiviral activity of the extracts of medicinal plants. Sohail *et al.* [35] presented the results of a study of extracts of more than 100 plant species as antiviral agents and emphasized that several plant extracts turned out to be most active against herpes simplex virus. The 2013 review [36] provided similar but less detailed data.

The studies on the antiviral action of plant extracts and herbal preparations are moving in various directions. For example, in some cases, the said activity is examined for extracts of a plant of the same class or the same family. Sometimes the authors follow the territorial principle and choose various plants that are found in the same region. Another line of research includes a detailed examination of the chemical composition of extracts of the plants of the same species and the activities of their components. Also, in some studies, certain biological properties of various water and organic extracts have been analyzed.

For instance, extracts of several plant species of the composite family (*Asteraceae*) have been studied as antiviral agents.[37] Among them, fractions obtained by extraction of an aerial part of *Baccharis gaudichaudiana* plant with ethyl acetate proved to be most active against herpes simplex virus. Water extracts of more than 140 plants were tested for herpes simplex virus 1 and influenza A virus.[38] Vijayan *et al.*[39] identified three samples showing high activity against herpes simplex virus 1 among the extracts of 18 native Indian medicinal plants.

Quite a few works are focused on the antiviral action of plants of a certain species. Thus, it was highlighted that the extract of Columbian plant *Achyrocline bogotensis* exhibits anti-rotavirus and anti-retrovirus activities;[40] the former activity is also shown by *Myracrodruon urundeuva* tree extract.[41] A high activity of an extract from a perennial thoroughwort (*Eupatorium perfoliatum*) against the influenza virus was found.[42] Shang *et al.* [43] reported on the antiviral properties of extracts from *Lonicera japonica*, which were studied on a wide range of viruses. The antiviral activity of a perennial essential-oil-bearing lemon balm (*Melissa officinalis*) has been studied in great detail.[44] It should be noted that Lalali *et al.*[45] observed the synergistic effect of the antiviral drug oselmamivir (known in Russia as tamiflu) when used together with the lemon balm extract. Phytochemical analysis was carried out, and antiherpetic activity was found in the extract of the Lebanese cedar coniferous tree (*Cedrus libani*).[46]

The listed publications devoted to the antiviral activities of plant extracts are but a tiny part of the extensive material on this topic. However, these data allow the conclusion to be drawn about the effective application of essential oils and extracts in antiviral therapy, although it is not always clear which of their components exhibit the desired type of activity. Nevertheless, the aforementioned materials provide a vivid illustration of prospects of the search for novel antiviral agents among the natural substances.

3. Monoterpenoids and their derivatives possessing antiviral activity

For the development of novel drugs based on plant metabolites, the availability of raw materials and their components, exhibiting a certain type of activity, is of great importance. One of the most popular trends is the search for natural compounds exhibiting high native activity and their use as building blocks for various chemical modifications.[47] This requires knowledge of which structural units of a natural compound are responsible for the desired type of activity. Analysis of available literature data helps to answer the questions of which modifications of a specific class of compounds were carried out previously and which structure – activity relationships have already been identified. In this Section, data on the antiviral activity of monoterpenoids and their analogues are given. With rare exceptions, we will not discuss details of chemical modifications and reaction conditions; if necessary, the reader can find them in original publications.

The modern scientific literature is represented by only a few reports focused on the antiviral activity of monoterpenoids. Most likely this is because compounds of this class do not show notable activity against most viruses. However, Orhan *et al.*[48] demonstrated that acyclic monoterpene aldehydes such as citral (**1**) (exists as a mixture of two geometric isomers, namely, geranial and neral), citronellal (**2**), and citronellol (**3**) (Fig. 1) are active against herpes simplex virus 1. The activity of terpinen-4-ol (**4**) in the individual state and as the part of the tea tree oil (*Melaleuca alternifolia*) against Influenza A H1N1/Puerto Rico/8/34 virus,[49] and against West Nile virus (WNV) in the *in vitro* and *in vivo* tests has been revealed.[50] Bicyclic terpenes (−)-α- (**5**) and (−)-β-pinens (**6**) turned out to be active against avian infectious bronchitis virus (IBV), which belongs to the family of α-coronaviruses,[51] with selectivity indices of 10 and 7.5 respectively.

In vitro studies of antiviral activity against the tobacco mosaic virus have been carried out for 29 essential oils, as well as for 10 net basic components of their extracts.[52] Among monoterpenes, citronellal (**2**), D-limonene (**7**), and 1,8-cineol (**8**) exerted high antiviral activity. The activity of the latter compound against herpes simplex virus 2 was also tested *in vitro* and *in vivo*.[53] Using an animal model of viral infection, Hu and co-workers [54] demonstrated that bicyclic ether **8** can enhance the protection against the influenza

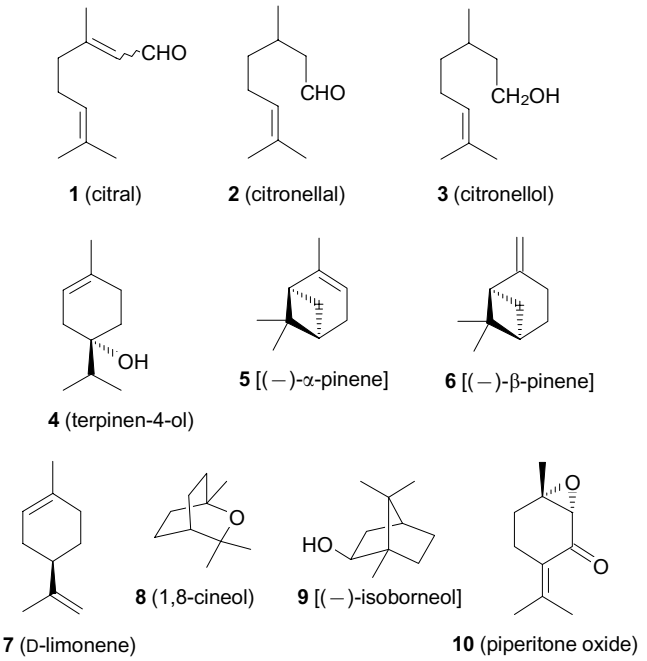


Figure 1. Structures of monoterpenoids **1** – **10** possessing antiviral activity.

virus, and studied its dose-related effect. Isoborneol (**9**) was found to inhibit the replication of herpes simplex virus 1.[55] The main component of the essential oil derived from *Mentha suaveolens*, the monoterpenic cyclic epoxide piperitone oxide (**10**), for which the values of IC_{50} = 0.6 μM and SI = 700 have been detected, also showed high activity against this virus.[56]

With the use of a pseudovirus system based on vesicular stomatitis virus with surface proteins E1/E2 of hepatitis C virus (HSVpp), the high antiviral activity of the aqueous extract of the flowering tops of *Lamium album* of Labiatae family has been identified.[57] An iridoid glucoside lamiridoside (**11**) was isolated from a methanol extract of this plant. The aglycone of this compound, monoterpenoid lamiridosin (**12**), was obtained as a diastereomeric mixture (Fig. 2). While glycoside **11** did not show activity in question, the mixture of isomeric monoterpenes demonstrated specific activity against hepatitis C virus entry C [IC_{50} = 2.3 μM (HSVpp)] and was inactive against vesicular stomatitis virus. Iridoid genipin (**13**) obtained from compound **11** also exhibited moderate antiviral activity with IC_{50} = 20 μM (HSVpp). The monoterpene moiety is probably responsible for the activity of the said extract against the hepatitis C virus.

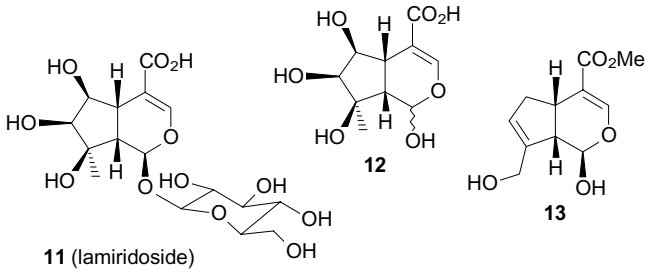


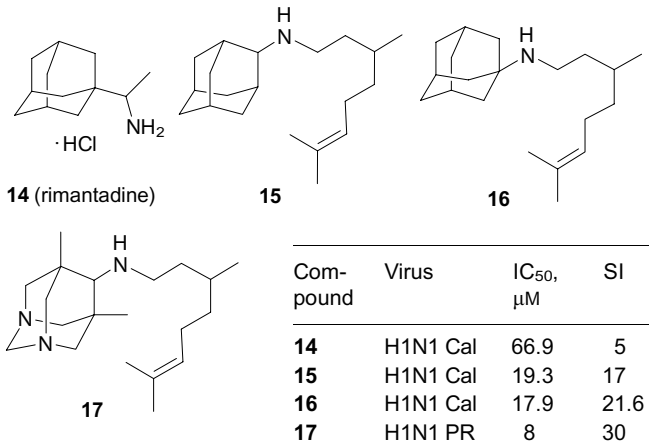
Figure 2. Structures of lamiridoside (**11**), lamiridosine (**12**), and genipin (**13**).

The above examples show that monoterpenoids are most active against herpes simplex viruses.

Usually, chemical modification of a natural molecule with additional functionalities capable of specific binding to certain biological targets can significantly alter its physiological properties, including an increase in antiviral activity. In medicinal chemistry, a strategy for the synthesis of novel derivatives with a targeted physiological activity using the 'concept of privileged scaffolds' has been successfully developed in recent years.[58 – 62] It consists in isolating the main structural motif of known biologically active compounds to obtain novel functional derivatives on its basis. This strategy is one of the main ways to develop effective drugs possessing the necessary physicochemical properties, improved pharmacological profile, and high biological activity.

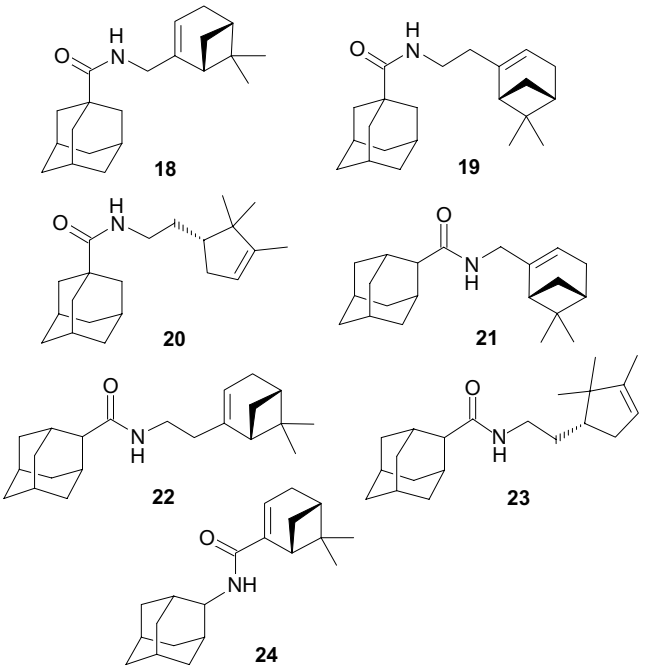
Adamantane derivatives possess various types of biological activities,[63, 64] therefore, the development of novel antiviral drugs based on adamantane scaffold is of great interest.[65] Teplov *et al.*[66] have demonstrated that 1-amino- and 2-aminoadamantanes readily react with natural monoterpene aldehydes [citronellal, citral, (+)- and (−)-myrtenal], and subsequent reduction of the C=N group with $NaBH_4$ provides the corresponding secondary amines. Among such products, maximum activity against the influenza A/California/07/09 (H1N1 pdm09) virus, far exceeding that of rimantadine (**14**) taken as a reference drug, was demonstrated by adamantanyl derivatives **15** and **16** bearing the citronellal moiety (Fig. 3). Besides the adamantane framework, 1,3-diazaadamantane scaffold was also used as a structural moiety to be applied in the synthesis of potent antiviral agents. Thus, diazoadamantanes have been reported,[67] possessing fragments of natural monoterpenoids in various positions. It was shown that only compound **17** bearing the citronellal moiety in the 6-position exhibited pronounced activity against the A/Puerto Rico/8/34 (H1N1) virus strain.

Adamantanes **18** – **24** exhibited unique activity against a wide range of viruses belonging to the poxvirus family. These compounds were obtained from monoterpene amines and adamantane-1(2)-carboxylic acids (Fig. 4).[68] Their antiviral activity was studied against variola vaccine virus



Compound	Virus	IC_{50}, μM	SI
14	H1N1 Cal	66.9	5
15	H1N1 Cal	19.3	17
16	H1N1 Cal	17.9	21.6
17	H1N1 PR	8	30

Figure 3. Structures and antiviral activity of rimantadine (**14**) and monoterpenic derivatives of adamantane (**15**, **16**) and diazaadamantane (**17**).



Compound	Virus VV		Virus CPXV		Virus ECTV	
	IC_{50}, μM	SI	IC_{50}, μM	SI	IC_{50}, μM	SI
18	1.7	1123	4.7	406	2.7	707
19	3.1	242	4.1	183	1.6	469
20	1.7	934	4.6	345	2.5	635
21	4.6	267	15.0	82	12.6	97
22	4.4	85	12.5	30	9.5	39
23	1.4	281	2.5	158	1.4	281
24	1.8	451	7.2	113	1.7	477

Figure 4. Hybrid structures of **18** – **24** based on monoterpenes and adamantane and their antiviral activity.

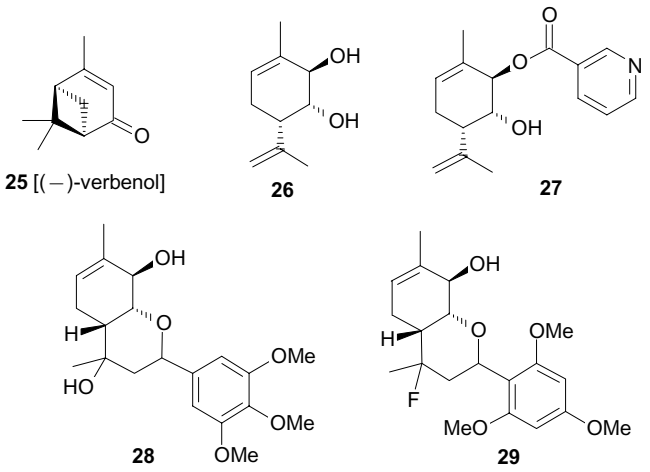
(strain Copenhagen, VV), cowpox (strain Grishak, CPXV), and mousepox (ectromelia, strain K-1, ECTV). The synthesis of compounds **18** – **24** comprised the prior preparation of monoterpene amines, which were then reacted with adamantane-(1 or 2)-carboxylic acid chlorides. Oxidation of myrtenal afforded the corresponding carboxylic acid whose chloride reacted with 2-aminoadamantane to give amide **24**. As is evident from the data presented in Fig. 4, compounds **18** – **20**, containing the amide bond in the 1-position of the adamantane moiety, showed higher activity than agents **21** – **23**, in which the amide linker is located in the 2-position of the cage. In general, it can be concluded that the authors succeeded to find a novel class of potent anti-poxviral agents exhibiting activity in the lower micromolar concentration range.

The global eradication program for the smallpox virus has eliminated it from the environment, and with the cessation of universal vaccination in 1980, more than half of the world's population currently lacks smallpox immunity. At the same time, the threat of smallpox exists. Moreover, for humans, the opthopoxviruses of animals, for example, cows and monkeys, are also dangerous. Such viruses circulate in animal populations, evolve, and periodically spread, causing outbreaks of disease among humans. Therefore, the search for novel drugs that are effective against orthopoxviruses, is currently an urgent challenge.

Starting from an available bicyclic ketone (−)-verbenone (**25**), derivatives **26** – **29** were synthesized and their antiviral activity was studied.[69, 70] Mononicotinic ester **27** with *p*-menthane moiety was obtained from (−)-verbenone (**25**) in several steps. The reaction sequence included epoxidation, the opening of an epoxide ring by an acid, and esterification of the resulting diol **26** with nicotinic acid chloride (Fig. 5). Compound **27** demonstrated its antiviral activity against influenza A/California/07/09 (H1N1) virus.[69] The absolute configuration of the compound was found to be critical for the appearance of antiviral activity; (+)-verbenone-derived isomer turned out to be inactive.

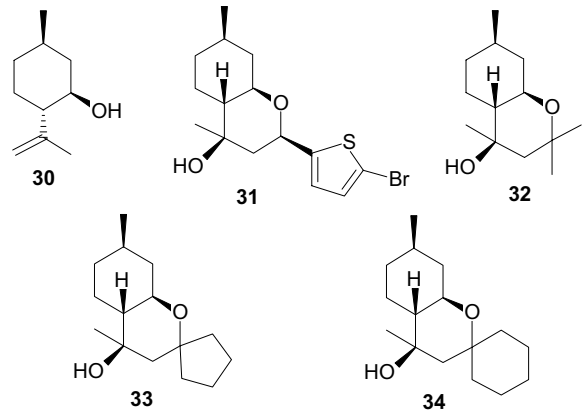
Ardashov *et al.*[69] synthesized 22 hexahydro-2*H*-chromene derivatives *via* reactions of diol **26** with various aromatic aldehydes. These reactions were carried out under acid-catalyzed conditions; in the presence of montmorillonite K-10 the corresponding alcohols were obtained, while catalysis with boron trifluoride etherate produced fluorinated products. This library of compounds was tested as inhibitors of influenza A virus subtype H1N1. Compounds **28** and **29** bearing three methoxy groups (in positions 3, 4, 5 or 2, 4, 6 respectively) in the benzene ring proved to be most active.[70] Based on this fact, the authors suggested that the presence of methoxy groups in the benzene ring improves the pharmacological profile of the compounds, while halogen atoms and nitro groups have the opposite effect.

Natural alcohol (−)-isopulegol (**30**) reacts readily with bromo-substituted thiophencarboxaldehydes under catalysis with clay K-10. This leads to products with octahydro-2*H*-chromene scaffold, among which compound **31** showed high activity against influenza A/California/07/09 (H1N1pdm09) virus (Fig. 6).[71] In the follow-up study, the reaction of isopulegol (**30**) with a wide range of ketones was studied providing a large library of octahydro-2*H*-chromene derivatives to examine their antiviral properties.[72]



Compound	IC_{50} (H1N1 Cal), μM	SI
27	32	17
28	63	26
29	5.1	54

Figure 5. Structures of (−)-verbenone (**25**) and its derivatives **26** – **29**, and antiviral activity of compounds **27** – **29**.



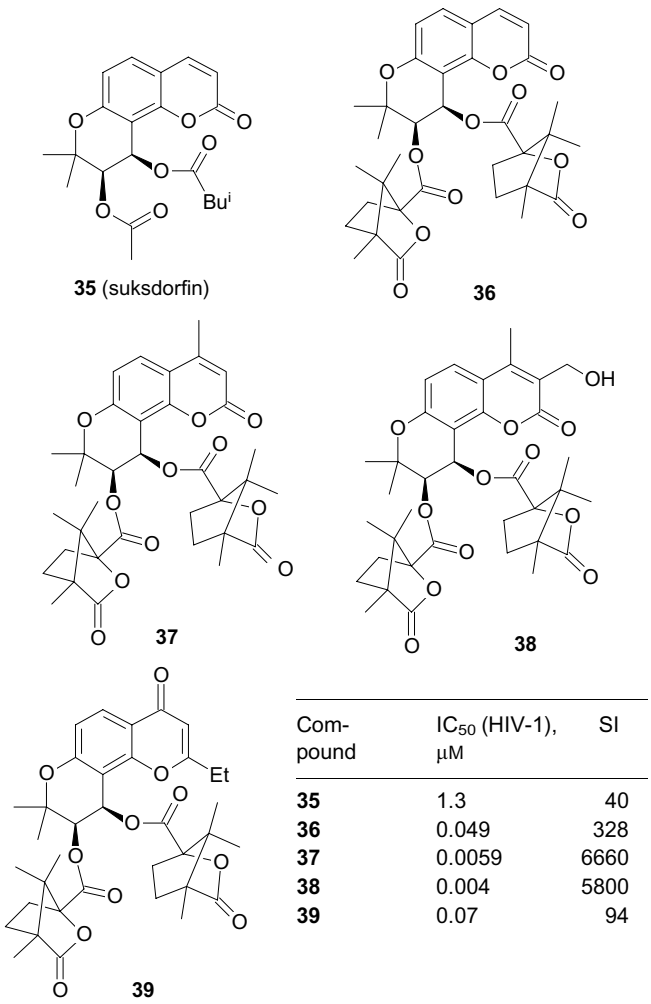
Compound	Virus	IC_{50}, μM	SI
31	H1N1 Cal	8.5	25
32	H1N1 Cal, H2N2	0.9	1570
	H1N1 PR	7.5	189
	B	17	83
33	H1N1 PR	8.4	96
34	H1N1 PR	18	33

Figure 6. Structures and antiviral activity of (−)-isopulegol (**30**) and its derivatives **31** – **34** based on octahydro-2*H*-chromene framework.

Among the tested compounds, agent **32** demonstrated extremely high activity (in the submicromolar range of concentrations) against influenza A/California/07/09 (H1N1)pdm09 and influenza A/Singapore/1/57 (H2N2) viruses. This compound also exerted pronounced activity against A/Puerto Rico/8/34 (H1N1) and B/Florida/04/06 viruses. Compounds **33** and **34**, containing spirocyclopentane and spirocyclohexane moieties, also proved to be highly active against influenza A/Puerto Rico/8/34 (H1N1) virus. The synthesis of biologically active chiral heterocyclic compounds derived from monoterpenoids has been detailed in a recent review. [73]

The design of hybrid molecules combining fragments of two natural compounds such as monoterpenes and coumarins has been described. The latter species can undoubtedly be called 'privileged structures', since coumarin derivatives demonstrate diverse biological activities including antiviral one.[74,75] Lee and co-workers [76–78] synthesized coumarin derivatives and studied their antiviral action towards HIV-1. Natural coumarin suksdorfin (**35**) was found to possess significant activity against the said virus (Fig. 7). This compound was isolated from a perrenial herbaceous plant *Lomatium suksdorfii*,[79] which is native to North America and was also found in the roots of *Phlojodicarpus sibiricus*, which is widely spread throughout the territory of Russia.

Suksdorfin analogues were obtained by the reactions of 3′,4′-dihydroxycoumarins and camphanic acid chloride.[76] [(−)-Camphanic acid is a terpenoid based on the 2-oxabicyclo[2.2.1]octane cage and is used in the synthesis of various chiral catalysts.] For example, (3′*R*,4′*R*)-dicamphanoyl-*cis*-khellactone (DCK, **36**) and its 4-methyl derivative (4-MDCK, **37**) were prepared in this way. While establishing the structure – activity relationships for these compounds and their analogues, the highest virus-inhibiting potency was found in the case of *R*-oriented substituents in positions 3′ and 4′ of coumarin and planar configuration

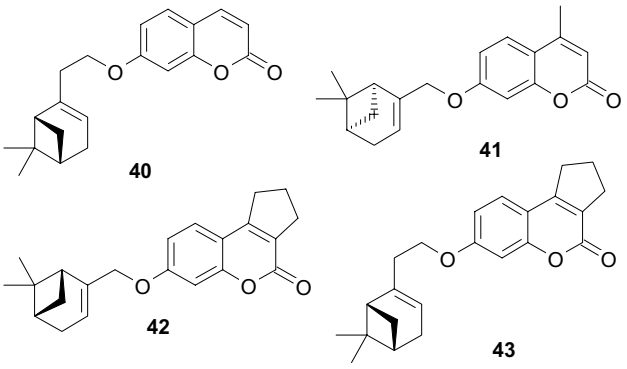


Compound	IC_{50} (HIV-1), μM	SI
35	1.3	40
36	0.049	328
37	0.0059	6660
38	0.004	5800
39	0.07	94

Figure 7. Structures and antiviral activity of suksdorfin (**35**) and diacylcoumarins **36** – **39**.

of the coumarin framework. Also, the effect of substituents in positions 3′, 4′, 5′, and 6′, as well as the nature of a heteroatom (oxygen or sulfur) in the position 1′ were studied in details (see Ref. 80). It was shown that the replacement of a camphane bicycle with adamantane or camphor-10-sulfonic acid moiety leads to the loss of activity against HIV-1. A water-soluble analogue of DCK, compound **38**;[81] has been obtained and studied, and its pharmacokinetic properties were identified. A derivative **39** containing an oxo group in position 4′ of coumarin also proved itself as a potent anti-HIV agent.[82] Therefore, it can be concluded that the strategy of combining the coumarin backbone with the natural monoterpenoid scaffold is an effective approach to the design of compounds possessing high antiviral activity.

Starting from hydroxycoumarins, ethers bearing a monoterpene moiety and a coumarin ring were also synthesized (Fig. 8).[83] Such products, *e.g.*, compounds **40** – **43**, are formed in the reaction of coumarin with the corresponding halosubstituted terpenoids. Maximum potency against influenza A/California/07/09 (H1N1)pdm09 virus was demonstrated by compounds containing fragments of (−)-nopol (**40**, **43**) and also (+)- and (−)-myrtenols (**41** and **42** respectively). Salakhutdinov and co-workers [83] carried out a detailed study of the structure – activity relation-

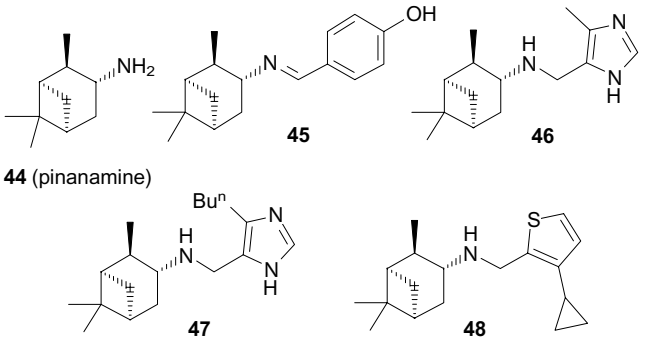


Compound	IC_{50} (H1N1 Cal), μM	SI
40	0.5	20
41	10	13
42	36	28
43	21	41

Figure 8. Structures and antiviral activity of monoterpene – coumarin hybrid molecules **40** – **43**.

ship and showed that the substitution of the coumarin backbone with acyclic natural moieties is less promising for the appearance of the desired antiviral activity than the use of bicyclic monoterpenoids.

Bicyclic terpenoids have also found application as building blocks for designing novel antiviral agents. For example, (1*R*,2*R*,3*R*,5*S*)-pinan-3-amine (pinanamine, **44**) proved to be a more potent inhibitor of influenza A (H3N2) virus compared to the known drug amantadine (1-aminoadamantane) (Fig. 9).[84] It was subsequently established that Schiff base **45**, containing pinanamine and 4-hydroxybenzylidene moieties, inhibits rimantadine-susceptible



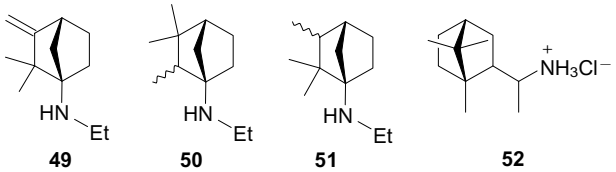
Compound	Virus	IC_{50}, μM	SI
45	H3N2 HK	0.08	
46	H3N2 HK	3.2	78
47	H3N2 HK	2.5	80
	H1N1 Guangzhou	3.4	58
48	H1N1 Guangzhou	0.3	83
	H1N1 PR	2.2	11
	H3N2 HK	5.3	5
	H7N3	4.5	5
	H9N2	6.8	4

Figure 9. Structures and antiviral activity of pinanamine (**44**) and its derivatives **45** – **48**.

strain of influenza A/Hong Kong/8/68 (H3N2) virus.[85] Compound **45** is active in the nanomolar concentration range, however, the authors provided no data on the toxicity of the compound, which made it impossible to assess the safety of this agent. Compound **46** substituted with 4-methylimidazole ring acts as a potent inhibitor of rimantadine-susceptible strain of influenza A/Hong Kong/8/68 (H3N2 virus, but is inactive against rimantadine-resistant strains of influenza A (H1N1) virus.[86] Further studies led to the production of its analogue **47**, containing n-butyl substituent in the heterocycle, which had an inhibitory effect both on H3N2 and H1N1 serotypes of influenza A virus.[87] Later, the same authors [88] synthesized a library of 40 compounds bearing heterocyclic aromatic moieties. Among such derivatives, 3-cyclopropyl-2-thienylmethyl-substituted pinanamine **48** showed activity in the micromolar range against a wide spectrum of strains of influenza virus such as A/Guangzhou/GIRD/07/2009 (H1N1), A/PR/8/34 (H1N1), A/HK/68 (H3N2), A/duck/Guangdong/1/1996 (H7N3), and A/duck/HK/Y280/97 (H9N2). At the same time, the rather high toxicity of the said compound results in relatively low values of its selectivity index.

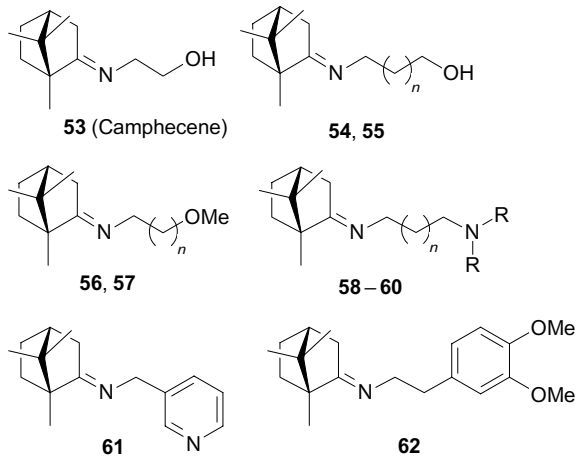
Special attention was given to the synthesis and study of antiviral activity of compounds based on natural monoterpenes containing bicyclo[2.2.1]hept-2-ene (norbornane) cage. Such compounds are known as promising precursors for antiviral agents. In 1995, Martinez *et al.*[89] reported the synthesis of substituted 1-aminonorbornanes **49** – **51** (Fig. 10) from (±)-camphor. The products possessed high activity against rimantadine-susceptible strain of influenza A virus (the authors did not specify the strain) and moderate activity against African swine fever virus (ASFV). Significantly later it was revealed [90] that ammonium salt **52** based on the (+)-camphor scaffold inhibits rimantadine-susceptible strain of influenza A/Hong Kong/68 (H3N2) virus and probably blocks the M2 ion channel. It is noteworthy that the authors provided no data on the toxicity of compounds with the bornane scaffold; the safety of these agents thus could not be assessed.

A large library of camphor imino derivatives [91] has been synthesized, and their antiviral activity was tested. A convenient procedure to obtain such products was elaborated based on the solvent-free reaction of (+)-camphor with various amines under the action of anhydrous $ZnCl_2$ under



Compound	Virus	IC_{50}, μM	SI
49	A	0.55	1000
	ASFV	160	13
50	A	0.55	1000
	ASFV	170	10
51	A	55	10
	ASFV	160	12
52	H3N2 HK	0.1	

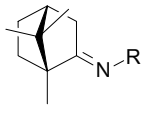
Figure 10. Structures and antiviral activity of camphor-derived norbornyl-1-amines **49** – **51** and ammonium salt **52**.



Compound	*n*	R_2N	IC_{50} (H1N1 Cal), μM	SI
53	–	–	5.1	503
54	1	–	6.7	357
55	3	–	18.6	113
56	1	–	23	61
57	2	–	17.5	128
58	1	morpholino	5.0	91
59	1	Me_2N	21	100
60	0	Et_2N	10	81
61	–	–	7.4	295
62	–	–	8.3	186

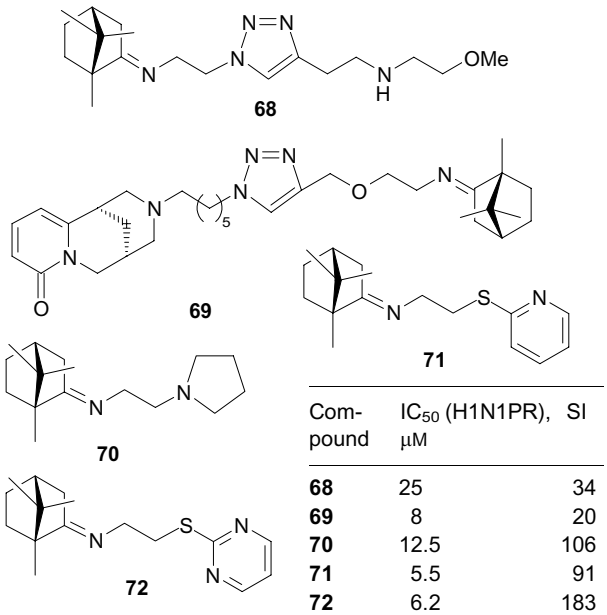
Figure 11. Structures and antiviral activity of imine derivatives of (+)-camphor **53** – **62** bearing a functionalized pendant group.

reflux. A variety of (+)-camphor imino derivatives was thus obtained, having a bicyclic cage and various substituents at the nitrogen atom. As substituents, alcohol, ether, and amino groups as well as nitrogen-containing moieties and aromatic rings were used (Figs 11 – 13). The length of the spacers between imino groups and heteroatoms, the nature of substituents at the nitrogen atoms, types of (hetero)aromatic rings, *etc*, were varied. Among the products, mention should be made of camphor-2-imino derivatives of alcohols (**53** – **55**), methyl ethers (**56**, **57**), amines (**58** – **60**), pyridine (**61**), and 4,5-dimethoxybenzene (**62**) (Fig. 11).



Compound	R	Virus	IC_{50}, μM	SI
63	Pr^n	H1N1 Cal	19.7	131
		H1N1 PR	4.1	632
64	Bu^n	H1N1 Cal	7.7	312
		H1N1 PR	5.8	417
65	n-C_5H_{11}	H1N1 Cal	7.7	104
		H1N1 PR	12.2	66
66	n-C_7H_{15}	H1N1 Cal	1.4	171
		H1N1 PR	4.8	49
67	cyclo-C_6H_{11}	H1N1 Cal	55.4	23
		H1N1 PR	15.5	83

Figure 12. Structures and antiviral activity of (+)-camphor alkylimino derivatives **63** – **67**.



Compound	IC_{50} (H1N1PR), μM	SI
68	25	34
69	8	20
70	12.5	106
71	5.5	91
72	6.2	183

Figure 13. Structures and antiviral activity of camphecene heterocyclic derivatives **68** – **72**.

Antiviral activity of these compounds against rimantadine-resistant strain of influenza virus A/California/07/09 (H1N1)pdm09 has been studied. The highest activity with minimal toxicity was shown by the product of the reaction of (+)-camphor and ethanolamine, compound **53**, which the authors called Camphecene. It possessed a wide spectrum of antiviral activities against the most epidemiologically dangerous strains of influenza A/Puerto Rico/8/34 (H1N1), A/Aichi (H3N2), A/mallard/Pennsylvania/10218/84 (H5N2), and B/Lee/40 viruses, with selectivity indices of 645, 75, 97, and 116, respectively. The activity of camphecene has been confirmed in a model of lethal influenza pneumonia.[92]

In the case of readily volatile amine reactant, the authors proposed to carry out the reaction in a closed system under microwave irradiation. Such optimization of the reaction conditions made it possible to avoid a decrease in the amine concentration in the reaction mixture and helped to improve the product yields. Using this procedure with titanium isopropoxide as a dehydrating agent, alkylimino derivatives of (+)-camphor **63** – **67** were obtained (Fig. 12).[93] Antiviral activity of these compounds against two strains of rimantadine-resistant influenza A/California/07/09 (H1N1)pdm09 and A/Puerto Rico/8/34 (H1N1) viruses was tested, the results are given in Fig. 12. As can be seen from these data, the highest activity against both strains was observed for compounds **63** and **64**, bearing n-propyl and n-butyl groups.

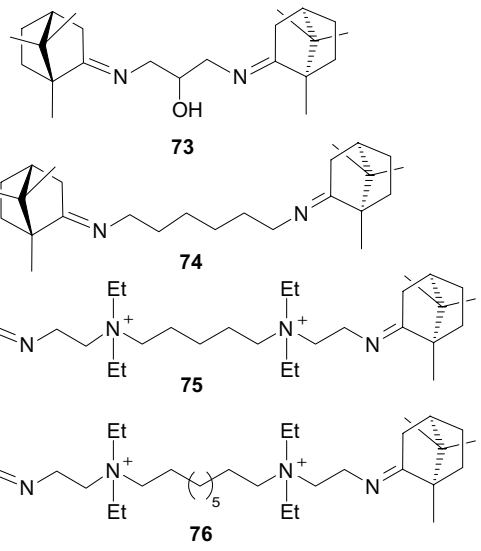
Following up on this area of research, a series of works on chemical modification of the lead compound camphecene (**53**) were published. A library of its derivatives bearing a triazole ring in the pendant chain was synthesized using click chemistry. Among these compounds, maximum activity against influenza A/Puerto Rico/8/34 (H1N1) virus was demonstrated by the (+)-camphor-derived agent **68**.[94] Conjugates of camphecene with (–)-cytisine (quinolizidine alkaloid) were obtained, among which agent **69** proved to be the most active.[95] Modification of the primary hydroxyl

group of camphecene gave rise to a variety of compounds containing camphor scaffold together with aliphatic and aromatic cyclic moieties.[96] It was shown that derivatives bearing pyrrolidine (**70**), pyridine (**71**), and pyrimidine (**72**) rings (Fig. 13) are highly active against influenza A/Puerto Rico/8/34 (H1N1) virus.

(+)-Camphor reacts with aliphatic and aromatic diamines affording the corresponding symmetric diimines.[97] Maximum activity against influenza A/California/07/09 (H1N1)pdm09 virus was observed for symmetric diimine **73**, containing a hydroxyl substituent in the linker, and aliphatic diimine **74** (Fig. 14). Despite high toxicity against influenza A viruses demonstrated by symmetric *exo*,*exo*-diamines after being reduced, they are characterized by higher toxicity. This accounts for a significant decrease in the therapeutic index.

The reactions of imine **60** with alkyl and aryl dihalides yielded diimino derivatives of camphor whose four quaternary nitrogen atoms were connected by linkers of various lengths and rigidity.[98] The elongation of a linker was shown to enhance the toxicity of the resulting dimers. Compounds **75** and **76** exhibited the most pronounced antiviral activity and rather low toxicity. Accordingly, it can be concluded that the authors demonstrated an extremely high potential of camphor imino derivatives as influenza A virus inhibitors.[94–97]

Camphor-based compounds turned out to be active not only against influenza A and B viruses. Thus, Sokolova *et al.*[99] used (+)-camphor thiosemicarbazone **77** to obtain substituted thiazoles substituted in the 4-position with *p*-chloro- (**78**) and *p*-bromophenyl groups (**79**). These compounds display antiviral activity against the vaccinia virus (VV) in the micromolar range. The values of IC_{50} were 2.7 and 2.4 μM, and those of IS were 24 and 32 for agents **78** and **79** respectively (Fig. 15).



Compound	IC_{50} (H1N1 Cal), μM	SI
73	2	88
74	15	89
75	14	87
76	6.9	82

Figure 14. Structures and antiviral activity of (+)-camphor dimeric derivatives **73**–**76**.

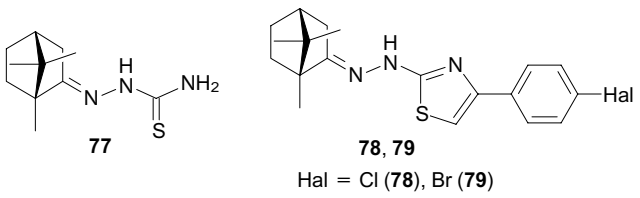
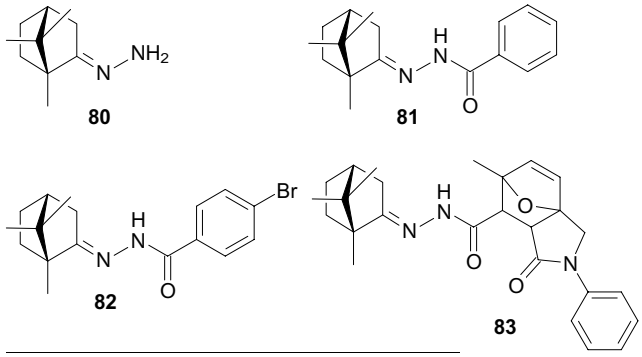


Figure 15. Structures of (+)-camphor thiosemicarbazone **77** and thiazoles **78** and **79** derived therefrom.

The use of (+)-camphor hydrazone **80** as a starting compound allowed the synthesis of a series of the corresponding *N*′-acyl hydrazones, which were tested for antiviral activity.[100] The highest activity against vaccinia virus was detected for benzoyl hydrazide **81** and its *p*-bromo derivative **82**, as well as their analogue **83** bearing epoxyisoindole moiety (Fig. 16). It should be noted that the latter compound also showed moderate activity against influenza A/Puerto Rico/8/34 (H1N1) virus.

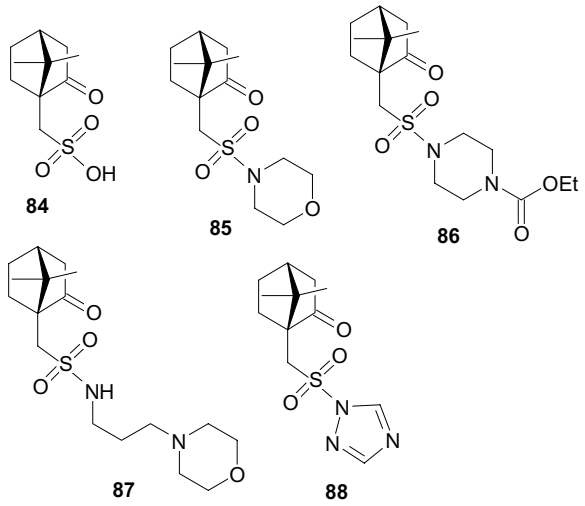


Compound	IC_{50} (VV), μM	SI
81	5.1	280
82	11.1	26
83	6.2	97

Figure 16. Structures of (+)-camphor hydrazone **80**, *N*′-acyl derivatives **81** –**83**, and their antiviral activity.

Salakhutdinov and co-workers[101] synthesized a series of *N*-heterocyclic camphor derivatives from commercially available (1*S*)-(+)-camphor-10-sulfonic acid (**84**). With the use of a panel of pseudoviruses (p-EbV-GP) containing on their surfaces a glycoprotein (GP) of the Ebola virus, the activity of the above-mentioned agents was studied. Compounds **85**–**87** bearing a saturated *N*-heterocycle (Fig. 17) were shown to exhibit high activity against the ability of the Ebola virus to enter into the cell. Compound **88** containing 1,2,4-triazole ring also demonstrated high activity and had the lowest toxicity under the test conditions. It should be emphasized that the use of pseudovirus systems allows for a search for inhibitors of highly pathogenic infections in BSL-2 laboratories.§ This modern methodology demonstrates high efficiency and is safe to use.

§ BSL-2 is a laboratory which meets the requirements of the 2nd biosafety level (for the work with microorganisms of III – IV pathogenicity groups).



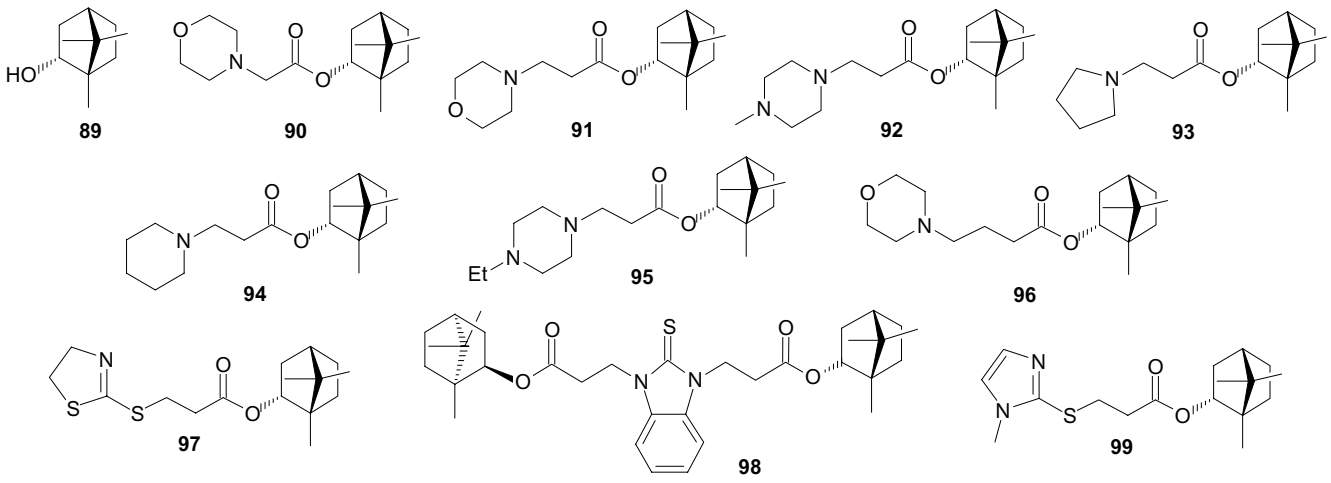
Compound	IC_{50} (p-EbV-GP), μM	SI
85	0.9	921
86	5	134
87	3	232
88	1	1764

Figure 17. Structures (1*S*)-(+)-camphor-10-sulfonic acid (**84**), *N*-heterocyclic derivatives **85**–**88**, and their antiviral activity.

(−)-Borneol (**89**) is one more available cage monoterpene. The presence of the reactive secondary hydroxyl group in the structure of this natural alcohol opened access to the synthesis of a large library of (−)-borneol ester derivatives, with both the length of an aliphatic chain and the type of the saturated *N*-heterocyclic moiety being varied.[102–108] It was found that compounds **90**–**93** show notable activity against influenza A/Puerto Rico/8/34 (H1N1) virus in the micromolar range Fig. 18).[102] With the use of a pseudovirus containing the Marburg virus GP protein (p-MarV-GP) on its surface, ester derivatives of (−)-borneol were tested, and the pronounced activity of compounds **93**–**95** was revealed.[103] Later, high antifilovirus activity of compound **94** and its hydrochloride was confirmed using the infectious Marburg virus (strain Popp) [104] and Ebola virus (strain Zaire).[105] Since compounds of this class showed a wide spectrum of biological activity, the same research team [106] studied the biological properties of similar ester derivatives towards the vaccinia virus. Among such agents, high activity together with low toxicity was observed for morpholine-substituted compounds **90**, **91**, **96**, and compound **97** bearing a 4,5-dihydrothiazole ring. It may also be noted that the ester derivatives of (−)-containing saturated heterocyclic moieties, exhibit pronounced anti-ulcerogenic properties.[107] Later it was found that symmetric compound **98**, containing two moieties of the natural skeleton, and agent **99**, containing *N*-methylimidazole ring, are active against influenza A/Puerto Rico/8/34 (H1N1) virus.[108]

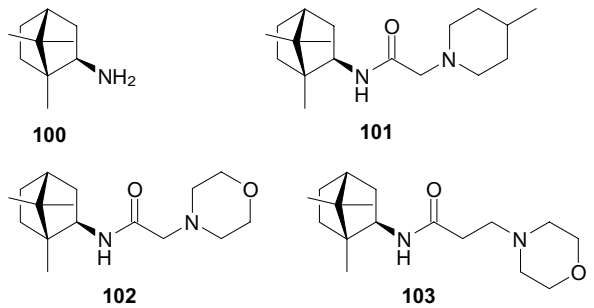
To elucidate the influence of the type of a linker between the bornane cage and saturated heterocyclic moiety on the activity, a procedure was developed to carry out the selective reduction of (+)-camphor oxime to produce isobornylamine **100**.[105] Based on this amine, a series of amides containing *N*-heterocyclic moieties were prepared (Fig. 19). It turned out that compounds **101**–**103** bearing 4-methylpiperidine and morpholine rings are potent vaccinia virus inhibitors.[108] Later, the activity of the said compounds was confirmed on a wide range of orthopoxviruses.[109]

Using camphoric acid (**104**), which is a product of exhaustive oxidation of camphor, as a starting molecule, and various diamines as reagents, Chernyshov *et al.*[110] found that nitrogen-containing polycyclic compounds



Compound	Virus	IC_{50}, μM	SI	Compound	Virus	IC_{50}, μM	SI
90	H1N1 PR	7	82	**94**	p-MarV-GP	9	35
	VV	18	56	**95**	p-MarV-GP	10	47
91	H1N1 PR	12	45	**96**	VV	7.9	23
	VV	3.4	48	**97**	VV	12.9	36
92	H1N1 PR	1.9	26	**98**	H1N1 PR	8	67
93	p-MarV-GP	12	59	**99**	H1N1 PR	14	24

Figure 18. Structures of *N*-heterocyclic esters **90**–**99** based on (−)-borneol (**89**) and their antiviral activity.



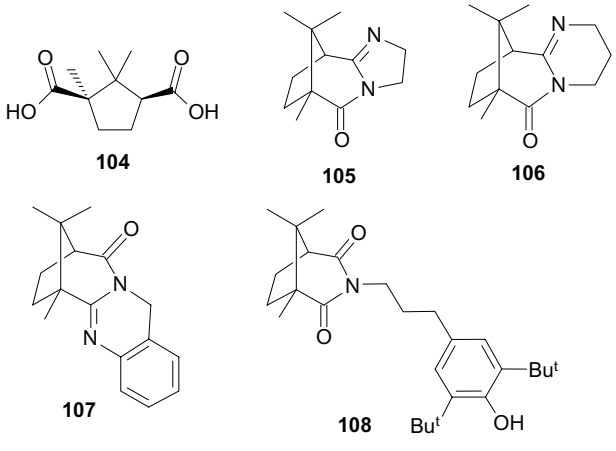
100 **101** **102** **103**

Compound	IC_{50} (VV), μM	SI
101	2.5	54
102	12.5	40
103	7.4	63

Figure 19. Structures of amides **101** – **103** based on isobornyl amine **100** and their antiviral activity.

105 – **107** (Fig. 20) could be obtained in one step. Tricyclic cage agents **105** and **106** exhibited activity against rimantadine-resistant strain of influenza A/Puerto Rico/8/34 (H1N1) virus, while tetracyclic compound **107**, being a formal analogue of quinozaline alkaloids, was active against a wide spectrum of influenza viruses such as A/Puerto Rico/8/34 (H1N1), A/Aichi (H3N2), and A/mallard/Pennsylvania/10218/84 (H5N2). Later, it was proved[111] that amide **108**, bearing 2,6-di(*tert*-butyl)phenol moiety, effectively inhibits flaviviruses such as Zika (ZV) and yellow fever (YF) viruses.

Summarizing the material of this Section, the high potential of monoterpenes as building blocks in the development of novel antiviral agents should be highlighted. The efficiency of the strategy for the synthesis of hybrid compounds containing along with the monoterpene moiety an adamantane scaffold or a coumarin ring was shown. Emphasis should be placed on bicyclic monoterpenoids as a basic pharmacophoric component of a biologically active molecule. In our opinion, the potential of available cage monoterpenes to be used as a starting platform in the synthesis of potent antiviral agents is very high. To date, such studies are one of the most rapidly developing and advanced areas in medical chemistry.



104 **105** **106** **107** **108**

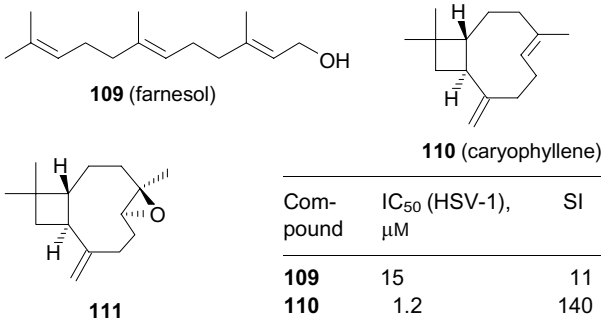
Compound	Virus	IC_{50}, μM	SI
105	H1N1 PR	51	28
106	H1N1 PR	36	37
107	H1N1 PR	17	62
	H3N2 Aichi	27	41
	H5N2 mallard	21	53
108	ZV	1.1	100
	YF	1.6	62

Figure 20. Structures of polycyclic derivatives **105** – **108** based on (+)-camphoric acid **104**.

4. Sesquiterpenoids and their derivatives possessing antiviral activity

In the modern scientific literature, one can find quite a few publications covering the studies of the direct virus-inhibiting activity of natural sesquiterpenoids. For example, Astani *et al.*[112] described the antiviral activity against HSV-1 for three most available sesquiterpenoids, namely, acyclic alcohol farnesol (**109**), bicyclic natural cycloalkene caryophyllene (**110**) and its 4β,5α-epoxy derivative **111** (Fig. 21). The authors compared antiviral activities of compounds **109** – **111** and anise oil, which, in addition to these components, contains eugenol (4-allyl-2-methoxyphenol), *trans*-anethole [4-(propen-1-yl) anisole], and β-eudesmol (sesquiterpene alcohol) in noticeable amounts. Caryophyllene (**110**) proved to be most active against HSV-1; compounds **109** and **111** also demonstrated noticeable antiviral activity. It can be assumed that it is the presence of these components in anise oil that is responsible for its high activity against herpes simplex virus 1 with a selectivity index of 160. It is noteworthy that natural anise oil isolated from the anise plant (*Pimpinella anisum*) is characterized by significantly lower toxicity than its individual components.

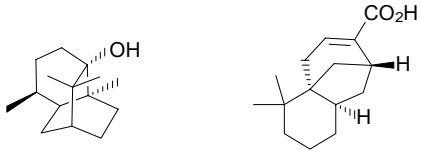
The patchouli oil (*Pogostemon cablin*), which is used in the perfumery industry, was tested for antiviral activity against the influenza virus.[113] A component of this tropical plant oil, tricyclic sesquiterpenoid pathouli alcohol (**112**), turned out to be active against influenza A/PR/8/34 (H1N1) and B/Ibaraki/2/85 viruses (the authors provided no data on the toxicity of this compound) (Fig. 22).[114] Wu *et al.*[115] studied the antiviral activity of patchouli alcohol against influenza A/Leningrad/134/17/1957 (H2N2) virus and carried out animal experiments supporting its antiviral effect.[116] Moderate activity against herpes simplex viruses 1 and 2 was also revealed in tricyclic sesquiterpenoid **113**, isolated from *Glyptopetalum sclerocarpum*.[117]



109 (farnesol) **110** (caryophyllene) **111**

Compound	IC_{50} (HSV-1), μM	SI
109	15	11
110	1.2	140
111	3.2	25

Figure 21. Structures and antiviral activity of farnesol (**109**), caryophyllene (**110**) and its 4β,5α-epoxy derivative **111**.



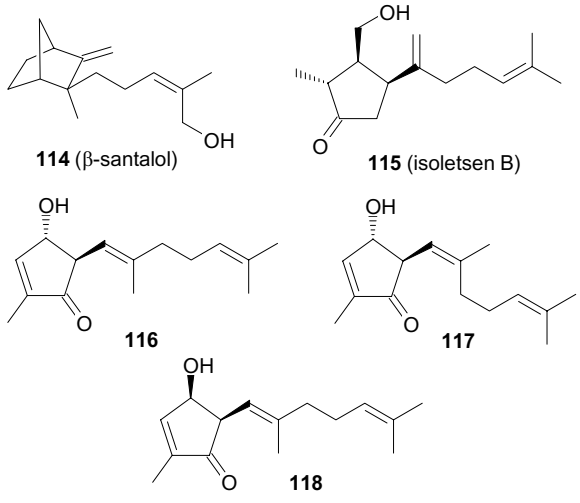
112 (patchouli alcohol) **113**

Compound	Virus	IC_{50}, μM	SI
112	H1N1 PR	2.6	
	B Ibaraki	40.8	
	H2N2 Leningrad	4.0	4.9
113	HSV-1	21	10
	HSV-2	51	4

Figure 22. Structures and antiviral activity of patchouli alcohol (**112**) and tricyclic sesquiterpenoid **113**.

Currently, sandalwood oil, which is an essential oil of tropical sandalwood (*Santalum album*), is widely used in medicine. It is particularly popular in cosmetology due to its medicinal and rejuvenating properties, which have been known since ancient times. Benencial and Courreges [118] described the antiviral effect of this essential oil against herpes simplex virus. Later, its main components were isolated, and β-santalol (**114**) (Fig. 23) was shown to display activity against influenza A/Hong Kong/8/68 (H3N2) virus which is comparable to that of the reference agent oseltamivir.[119]

Zhang *et al.*[120] extracted leaves and twigs of *Litsea verticillata* with chloroform, isolated a sesquiterpene alcohol isoletsen B (**115**) from the resulting extract, and examined the activity of this compound against human immunodeficiency virus. Secondary metabolites of the same plant, isomers **116**–**118**, differing in the location of the hydroxyl group and double bond configuration, exhibit moderate activity against HIV-1.[121]



114 (β-santalol) **115** (isoletsen B)

116 **117** **118**

Compound	Virus	IC_{50}, μM	SI
114	H3N2 HK	12	8
115	HIV-1	38	3
116	HIV-1	21.4	2.6
117	HIV-1	8.5	2.9
118	HIV-1	30.3	2.4

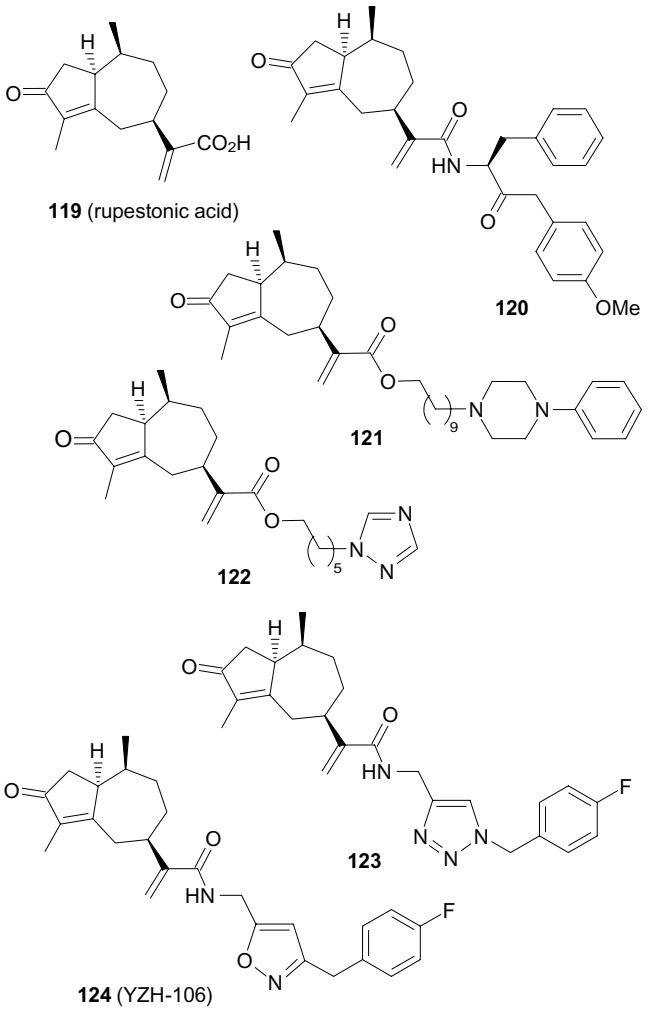
Figure 23. Structures and antiviral activity of natural alcohols β-santanol (**114**) and isoletsen B (**115**), and isomers of the latter (**116**–**118**).

Researches highlighted the modification of the major component of the wormwood (*Artemisia rupestris*) extract, namely, rupestonic acid (**119**), with the aim of developing agents that would be active against influenza viruses (Fig. 24).[122] The said wormwood tinctures have been anciently used in Chinese folk medicine for the treatment of this disease. Compound **119** has a bicyclo[5.3.0]decane backbone and is a guiaine-type sesquiterpenoid. It was originally established [122] that rupestonic acid is only active against influenza B/Beijing/97/13 virus, however, a later publication [123] reported the data on the activity of compound **119** against influenza A/Beijing/90/15 (H3N2) virus. This compound gave rise to a series of derivatives bearing amide moieties, *e.g.*, compound **120**, which exhibited moderate activity against influenza A/Beijing/90/15 (H3N2) virus and was inactive against influenza B virus. Phenylpiperazine analogue **121** demonstrated activity against the influenza virus H1N1 serotype but did not affect the H3N2 serotype.[123] At the same time, compound **122**, containing the 1,2,4-triazole ring, possessed moderate or high activity against a wide spectrum of influenza viruses.

To synthesize a variety of compounds comprising 1,2,4-triazole ring, nowadays, click chemistry is widely used. With the use of this technique, a library of such derivatives derived from rupestonic acid was obtained. All resulting compounds were tested for antiviral activity against influenza A/FM/1/47 (H1N1), oseltamivir-resistant influenza A/TianjinJinnan/15/2009 (H1N1), and influenza B viruses.[124] The highest activity against influenza B virus was detected in compound **123**; no potent agents against other strains were found. The follow-up studies showed[125] that compound **124** (trade code YZH-106), whose linker is substituted by an isoxazole moiety, exhibits a wide range of activities against various influenza strains, *e.g.*, A/FM1/1947 (H1N1), oseltamivir-resistant A/TianjinJinnan/15/2009 (H1N1), A/Wuhan/359/1995 (H3N2), rimantadine-resistant A/FujianTongan/196/2009 (H3N2), and B Fujian-Xinluo/54/2006 viruses. Preliminary pharmacokinetics and the mechanism of action have been studied for the said compound. Moreover, the introduction of a glycoside moiety to the carboxyl group can significantly improve the activity of a compound against influenza A virus serotype H3N2.[126]

Modification of the natural rupestonic acid (**119**) at the sesquiterpene moiety, including the five-membered ring,[127, 128] as well as at the carbonyl and carboxyl groups [129] did not cause a noticeable increase in antiviral activity.[130]

In recent years, natural sesquiterpene isoprenoids containing a lactone ring have attracted great interest from researches. This is a numerous class of compounds, most of which are secondary metabolites of plants of the composite family (*Asteraceae*). Sesquiterpene lactones are characterized by a great diversity of structures; their backbone can include one, two, or three aliphatic rings, as well as linear or branched alkyl substituents and oxygen-containing groups as substituents. Natural sources are known and spatial structures have been established for more than 400 compounds of this class. Sesquiterpene lactones typically exhibit various types of biological activity. Some compounds can be isolated from the plant raw materials in preparative



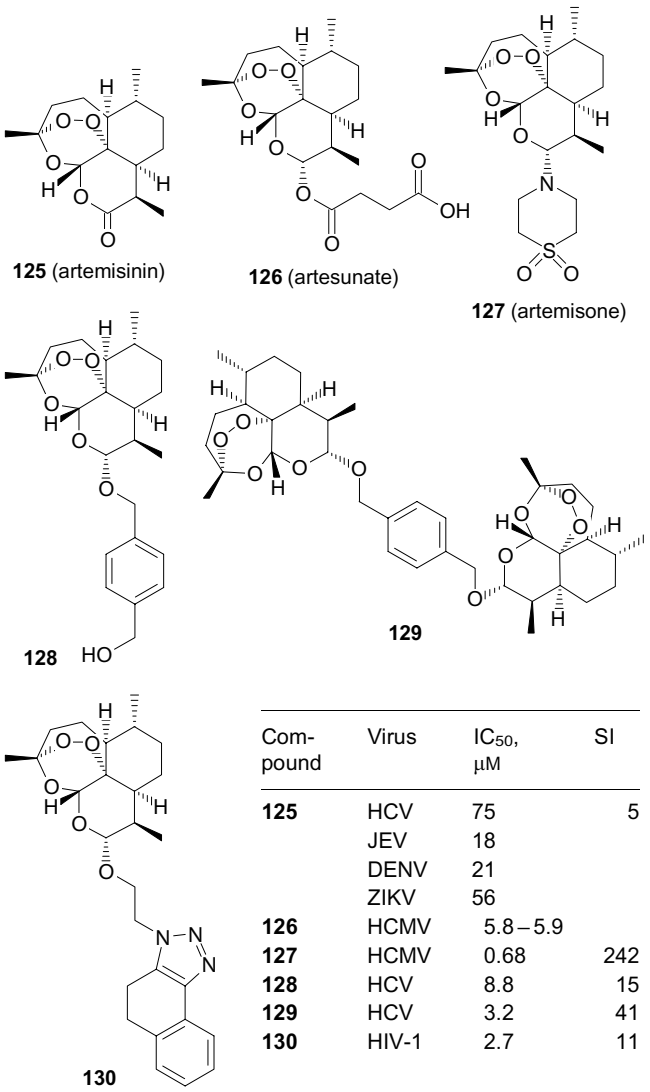
Compound	Virus	IC_{50}, μM	SI
119	H3N2	25	181
120	H3N2	56	1.9
121	H1N1	2.4	188
122	H1N1	7.2	28
	H3N2	5.2	38
	B	3.2	62
123	B	8.9	43
124	H1N1 FM	1.2	25
	H1N1 TJ	1.3	25
	H3N2 W	3.6	8.8
	H3N2 FT	3.2	10.1
	B	4.5	7.12

Figure 24. Structures and antiviral activity of rupestonic acid (**119**) and its derivatives **120** – **124**.

quantities, and the presence of various functionalities in the molecule allows for their easy modification to provide novel derivatives.[131] The methods of isolation from various natural sources, chemical transformations, and biological activities of sesquiterpene lactones are highlighted in several modern reviews (see, *e.g.*, publications [132 – 134]).

Artemisinin (**125**), a commercially available cadinane-type lactone known for its antimalarial effect, is considered to be one of the most studied representatives of this class. Compound **125** is isolated from the annual herbaceous wormwood (*Artemisia annua* L.), which is widely used in Chinese folk medicine for the treatment of various diseases (Fig. 25). The biological properties of artemisinin are described by Dai *et al.*,[135] and its total synthesis is reported by Wang *et al.*[136] Currently, artemisinin (**125**) *per se* and its derivatives have achieved world-wide recognition as agents against malaria pathogens (*Plasmodium* protozoans), which are resistant to conventional antimalarial drugs, as well as therapeutics for the treatment of cerebral and infantile malaria.[137]

The use of antimalarial drugs as antiviral agents is a promising trend in modern medicine.[138] It was shown that artemisinin and its analogue artesunate (**126**) are active against a wide spectrum of viruses of *Herpesviridae* family, namely, herpes simplex virus 1, Epstein – Barr virus, and human cytomegalovirus. The antiviral effect of artesunate against ganciclovir-susceptible and ganciclovir-resistant human cytomegalovirus (HCMV) has been established.[139] Artemisinin derivative, artemisone (**127**), exhibits activity against cytomegalovirus in a dose comparable to that for widely used ganciclovir.[140] For artemisone, a synergistic effect has been found, with its activity increasing when co-

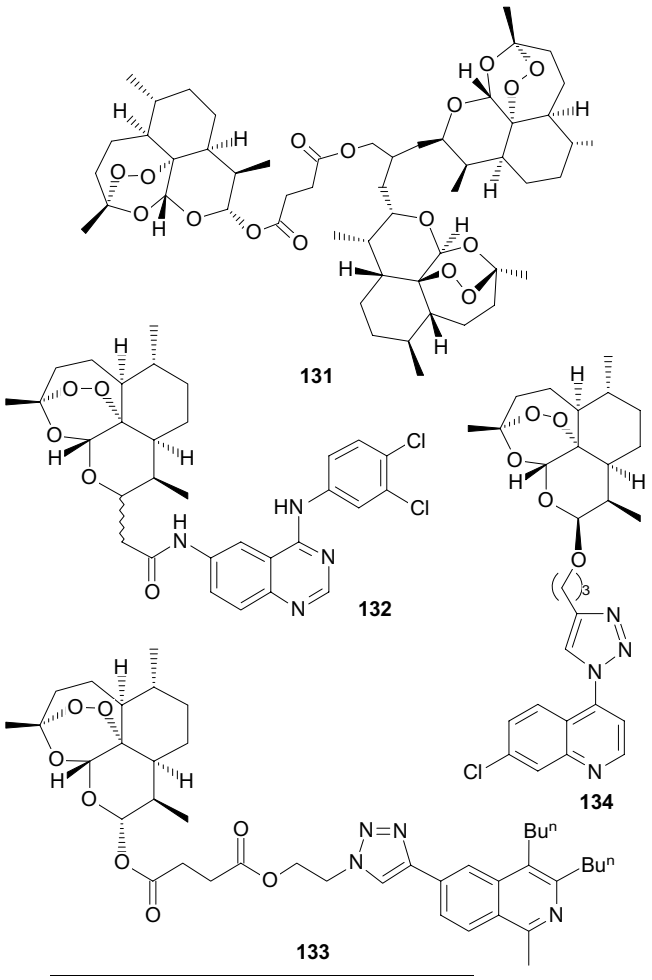


Compound	Virus	IC_{50}, μM	SI
125	HCV	75	5
	JEV	18	
	DENV	21	
	ZIKV	56	
126	HCMV	5.8 – 5.9	
127	HCMV	0.68	242
128	HCV	8.8	15
129	HCV	3.2	41
130	HIV-1	2.7	11

Figure 25. Structures and antiviral activity of artemisin (**125**) and its analogues **126** – **130**.

used with drugs intended for the treatment of cytomegalovirus.[141] Using an animal model, high antiviral potency of artemisinin and artesunate against Japanese encephalitis virus (JEV), a member of the flavivirus family, has been revealed.[142] Moreover, artemisinin as well as its ether derivatives such as monomer (**128**) and dimer (**129**) display pronounced activity against hepatitis C virus (HCV).[143] Compound **130** bearing an *N*-heterocyclic moiety, has an antiviral effect against human immunodeficiency virus type 1.[144]

Based on artesunate (**126**), a trimer **131** (Fig. 26) was obtained whose activity against human cytomegalovirus was two orders of magnitude higher than the activity of the starting compound.[145] The same research team[146] carried out extensive work on the synthesis of hybrids of artemisinin with quinazoline and quinoline rings. It was found that artemisinin – quinazoline hybrid **132**, obtained as a mixture of isomers, is a potent inhibitor of cytomegalovirus with activity in the nanomolar concentration range. Capci *et al.*[147] succeeded to obtain a large library of conjugates of artemisinin with quinazoline and quinoline moieties using click chemistry; compounds **133** and **134** proved to be most active.

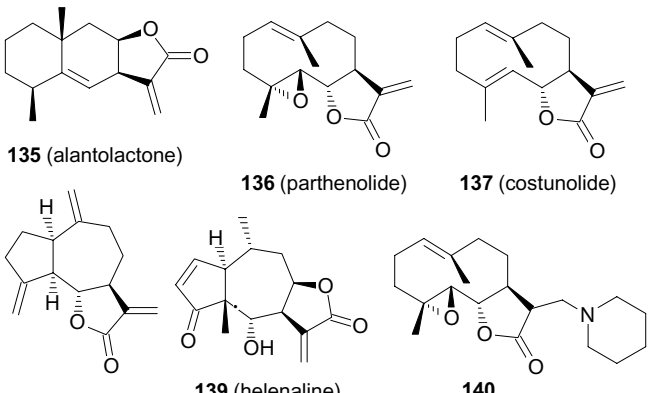


Compound	IC_{50} (HCMV), μM	SI
131	0.04	
132	0.15	
133	0.22	454
134	0.3	333

Figure 26. Structures and antiviral activity of artemisin derivatives **131** – **134**.

Besides artemisinin, natural sesquiterpene lactones with different types of carbon backbone also exert antiviral activity. For example, eudesmanolid alantolactone (**135**), isolated from the horseheal (*Inula helenium* L.), shows activity against herpes simplex virus type 1 (Fig. 27).[148] In addition to alantolactone, other lactones such as germacranolides, parthenolide (**136**) and costunolide (**137**), guayanolides, dehydrocostus lactone (**138**) and helenaline (**139**), were tested for their antiviral activity against the hepatitis virus.[149] Among the above-mentioned lactones, of particulate note is parthenolide (**136**), isolated from flowers and fruits of feverfew, or pyrethrum (*Tanacetum parthenium*), which has a variety of biological activities. Hwang *et al.*[149] found that the reduction of the *exo*-methylene double bond of a lactone ring results in the loss of antiviral activity. Various derivatives of parthenolide were obtained *via* chemical transformations, among which compounds possessing a higher virus-inhibiting effect than the initial lactone were found. The structure – activity relationship for such derivatives has been analyzed and it was revealed that the combination of a lactone ring with saturated *N*-heterocyclic motifs improves the target activity. Thus, lactone **140**, bearing a piperidine ring, demonstrated higher virus-inhibiting properties as compared to parthenolide. Also, a significant activity of compound **136** against herpes simplex virus 1 was detected.[150]

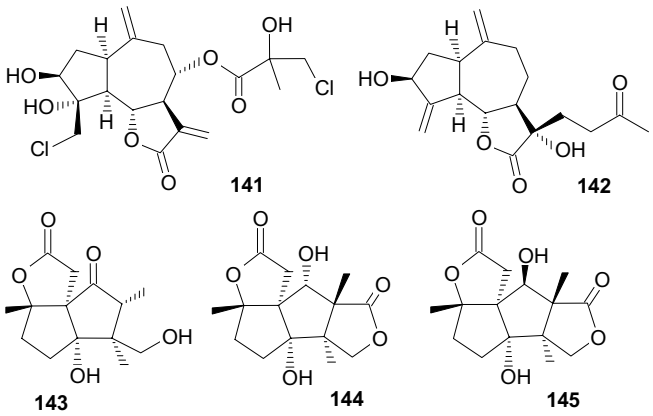
Guayane-type lactones **141** and **142** (Fig. 28), exhibiting antiviral activity against herpes simplex virus 1, were isolated from yellow centaury (*Centaurea solstitialis*).[151] As anti-hepatitis B virus agents, nor-sesquiterpene lactone henrylactone F (**143**) and isomeric tetracyclic lactones **144** and **145**, secondary metabolites of an anise tree (*Illicium henryi*), which is a Chinese endemic plant, were studied.[152]



Compound	Virus	IC_{50}, μM
135	HCV	2.03
	HSV-1	0.4
136	HCV	2.21
	HSV-1	1.2[a]
137	HCV	2.69
138	HCV	3.08
139	HCV	1.25
140	HCV	1.64

[a] SI = 11.9

Figure 27. Structures and antiviral activity of lactones **135** – **140**.



Compound	Virus	IC_{50}, μM	SI
141	HSV-1	0.28	16
142	HSV-1	0.001	10 000
143	HBV	0.5	6.6
144	HBV	0.09	25
145	HBV	0.007	43

Figure 28. Structures and antiviral activity of tri- and tetracyclic natural lactones **141** – **145**.

A review published in 2012 [153] covers the biological properties of natural sesquiterpene coumarins. Among such compounds, of special interest as antiviral agents are methyl galbanate (**146**) and farnesiferol C (**147**), isolated from an extract of fetis gum, or asafetida belonging to the Apiacea family (*Ferula assafoetida*, Apiacea family) (Fig. 29). The milky sap isolated from the roots of this herbaceous perennial is used as a spice, and other *Ferula* species provide galbanum, a gum resin, which has been used since ancient times in folk medicine. Compounds **146** and **147** were highly effective against influenza A virus H1N1serotype with IC_{50} = 0.6 and 0.8 μM respectively.[154]

Data presented in this Section demonstrated that among natural sesquiterpenoids, quite a few compounds which display pronounced activity against various viruses have been identified. At the same time, most of such compounds are found in plants in minor amounts, and multi-step procedures of their isolation make them not readily available. Therefore, it is difficult to use sesquiterpenoids as building blocks in the synthesis of large libraries intended for the search for potent antiviral agents. An exception is rupestonic acid (**119**) and artemisinin (**125**), whose chemical modifications provided access to novel sesquiterpene derivatives possessing significant antiviral activity.

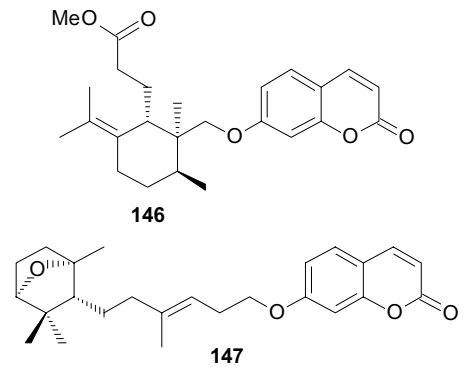


Figure 29. Structures of sesquiterpene coumarins **146** and **147**.

5. Targets for antiviral therapy

Two main 'targets' for the action of drugs, which the antiviral therapy is focused on, are the patient's body and the virus *per se*. To interact with the former, interferone and inhibitors of the host cell proteins are used, while the latter is directly targeted by the antiviral agents.

Stages of development of a viral infection in a human body define the mechanisms of action of the antiviral agents. At the initial stage, skin and mucous membranes are most susceptible to the viral infection; the virus can also enter the bloodstream through insect bites. The virus does not enter the host cell anywhere, only in a certain area of the cytoplasmic membrane does the virus bind to glycoproteins, which are its specific receptors. To control the viral infection, the following processes in a body can be inhibited:

— virus attachment (adhesion) to the membrane of host cells;

— fusion of the host cell membrane with the viral envelope;

— deproteinization (nucleic acid release) of the viral genome.

Once entering the cell, viruses proliferate inside it to form new viral particles and then spread throughout the body. At this moment, the virus circulating freely in the blood can be affected.

The life cycle (reproduction) of the virus includes several stages:¶

— attachment of the virus to the target cell,
— viral entry,
— disassembly of the virus capsid (envelope proteins),
— viral DNA or RNA replication,
— viral protein synthesis,
— assembly of the viral particle,
— virion release from the cell.

Each step can serve as a potential target for the development of an antiviral drug. A virion enters the cell due to the activity of the surface protein, which can cause the fusion between the cell lipid membrane and the protein envelope of the virus. For various types of viruses, there can be various surface glycoproteins. Then viruses enter the cell by immersing a part of the cell membrane at the site of their adsorption; this process is known as endocytosis. For enveloped viruses, the fusion between the viral envelope and the host cell membrane is promoted by an acidic medium. The virus first enters the cell in the endosome, and then it is released into the cytoplasm, at which time partial deproteinization of virions and modification of their nucleoproteid occurs. Once the deproteinization step is completed, the virus cannot be isolated from the cell culture since it no longer exists as an individual particle but causes many processes in the cells. This reproduction step, which is referred to as a shadow phase or an eclipse phase, includes the replication of viral nucleic acids and viral protein synthesis. Various groups of viruses are characterized by various energy demands for the shadow phase to occur, thus indicating the involvement in the process of various cellular pathways. The end of the shadow phase means the

¶ See site https://viralzone.expasy.org/936

formation of the viral components necessary for the assembly of daughter populations in the infected cell. This implies the need for three processes:

— expression of the genetic material of a virus through its transcription and the subsequent translation, which leads to the appearance of viral proteins;

— synthesis of the genetic material of the virus (replication);

— assembly of daughter populations from the genetic material and viral proteins.

Further, the paths of enveloped and non-enveloped viruses diverge. The enveloped viruses gradually bud off the host cell surface, and virions of non-enveloped viruses accumulate in the cell until it dies, and spill out like peas from the pod.

Viral replication can be inhibited in various stages. Thus, in early stages, it is possible to prevent the virus attachment and inhibit endocytosis, limit the transfer of viral DNA or RNA to the replication site, and inhibit the synthesis of viral proteins such as 'early' (enzymes) and 'late' ones. In the next stages, it is possible to inhibit the synthesis of viral DNA and DNA or proteins responsible for the detachment of the virus from the cell. And finally, to prevent the formation of new viruses, virus-infected cells can be killed.

In addition, cell signalling pathways can become the targets for antiviral agents. For example, a viral infection activates the intracellular signalling pathway, whose central component is the nuclear factor NF-kB, and which regulates the acute inflammation as the body's response to viral infection and induces apoptosis. At the end of this signalling pathway, the caspase cascade is activated, which causes the destruction of nuclear pores and in those cases where the virus replication occurs in a nucleus, this facilitates the diffusion of the viral RNP† from the nucleus.[155] The Raf/MEK/ERK signalling pathway is yet another cellular mechanism used by the virus to transfer new RNP to the plasma membrane.[156]

To have an insight into the mechanism of action of newly discovered antiviral compounds, special methods have been developed in virology.[157] To identify the stages of the antiviral action of the agents, the activity of a compound *versus* the time of its addition into an infected cell culture was tested.[158] Such studies help to determine the stage of viral replication that is affected by this compound. Based on the results obtained, which are represented in the form of graphs or bar charts, the potential targets of action of a specific compound can be assessed in advance. It is possible to produce virus strains that are resistant to the agent and to identify the mutation of resistance to them *via* the whole-genome sequencing. The location of mutations will indicate both the specific site of a viral protein that binds to the agent and the sites inducing the changes in the general protein conformation ('hidge mutations').

Moreover, methodologies have been developed for testing the lead compounds for their ability to inhibit specific viral proteins, to block binding to the receptor inside the cell, and for the polymerase and endonuclease activity of the polymerase complex, *etc*. These data can serve to identify a specific target for the agent under investigation.

Currently, not only conventional replication-competent viruses but also pseudoviral systems are widely used to identify compounds that specifically inhibit certain viral proteins.[159] Pseudoviral systems are recombinant particles consisting of a capsid of one virus (usually lentivirus or vesicular stomatitis virus), on the surface of which proteins of another virus are located. The binding and entering of such a particle into the cell is completely provided by the surface protein. Pseudoviruses are produced artificially by introducing various genetically engineered constructs into special production cells. Pseudotyping proceeds using plasmids that encode various surface proteins. The final stage of obtaining the viral particle includes its detachment from the surface of the production cell. The advantages of the pseudoviral system are the ability to immediately identify the stage of the life cycle of the virus in which inhibition occurs and its high biological safety. The use of pseudoviral system is of particular importance in the search for specific agents which are active against highly infectious viruses such as, *e.g.*, Ebola and Marburg viruses. Studies performed on pseudoviruses can be carried out in BSL-2 biolaboratories, whereas handling the infectious filovirus requires the maximum biosafety level, namely BSL-4‡ (see Ref. 160).

6. The mechanism of action of antiviral agents based on terpenoids

Significant attention of researchers engaged in the search for novel antiviral agents is devoted to the study of the mechanism of action of promising compounds. The analysis of publications shows that at present, agents displaying activity against various strains of the influenza A virus are the most studied from the point of view of the mechanism of action.

In some cases, to establish the antiviral mechanism of action of newly developed compounds, the results obtained by inhibition of various types and strains of the same virus or strains with known mutations in the key subunits of the virus are compared. Being based on the similarity of the adamantane and aza-adamantane scaffolds, Suslov *et al.*[67] suggested that compound **17** (see Fig. 3) exhibits activity as an inhibitor of the M2 ion channel of the influenza virus. Compounds **46** and **47** (see Fig. 9), representing imidazol-4-ylmethyl derivatives of pinanamine, demonstrated antiviral activity against both rimantadine-susceptible strain of influenza A/HK/69 virus and A/WSN/33 strain, which is resistant to rimantadine (**14**).[86] It was concluded that compounds **46** and **47** act as blockers of the M2 ion channel, which is responsible for the saturation of the cell with protons during endocytosis. To detect the activity of such derivatives as ionic blockers, studies were carried out using a two-electrode voltage clamp (TEVC).[161] However, the results obtained for A/M2-WT (wild type) and A/M2-S31N (rimantadine-resistant) virus proteins refuted this hypothesis.[87]

Experiments to identify the stage of viral replication were carried out for the isopulegol derivative **32** (see Fig. 6) based on the octahydro-2*H*-chromene backbone.[72] This compound was shown to be effective within 1 – 2 h after infection of cells with influenza virus. Its ability to directly inhibit the fusogenic activity of viral haemagglutinin (HA) *via* the extracellular system, as well as by detecting the dependence of the membranotropic action of haemaggluti-

† RNP is viral ribonucleoprotein, containing RNA and structuring proteins.

‡ BSL-4 is a laboratory which meets the maximum containment requirements of the 4th biosafety level (for the work with microorganisms of I pathogenicity group).

nin on the degree of destruction of erythrocytes and the release of free hemoglobin was studied. As a result, it was shown that compound **32** can directly suppress the fusogenic action of viral HA in a dose-dependent way, thereby providing a biochemical basis for its antiviral activity. Molecular modelling of active agents which are similar in structure to compound **32** and can interact with two possible haemagglutinin binding sites was performed. The first site represents the area of attachment of *tert*-butylhydroquinone (TBQH) (Fig. 30 *a*,*b*), a known HA inhibitor, while the second one is an active site, predicted on the basis of theoretical studies, which is located in the middle of the α-helix (see Fig. 30 *c*). Correlation between experimental results and theoretical calculations was only observed for the TBHQ-binding site. Therefore, it can be assumed that the mechanism of antiviral action of compound **32** is based on its interaction with two haemagglutinin monomers and the prevention of their conformational alterations during the development of a viral infection.

Compound **42**, which has a hybrid structure containing monoterpene and coumarin moieties (see Fig. 8), proved to be active in the early stages of influenza virus replication.[83] The use of the surface protein haemagglutinin as a target has also been proposed.

The mechanism of action of pinanamine derivative **48**, bearing 3-cyclopropyl-substituted thiophene ring, against influenza A virus H1N1 serotype was thoroughly studied (see Fig. 9).[88] Thus, it was shown that this compound demonstrated activity in the early stages of virus replication. The surface protein haemagglutinin and the virus M2 ion channel are responsible for the entry of the virus into the cell and saturation with protons at the step of endocytosis. With the use of TEVC technique, it was shown that agent **48** is not an ion channel blocker. Further, the virus strain resistant to the said agent was obtained and the viral haemagglutinin sequencing was performed. The identified mutation was found in the middle of the upper part of the HA protein. An amino-acid substitution HA2-E74D in the upper part of the α-helix for each of the trimers was

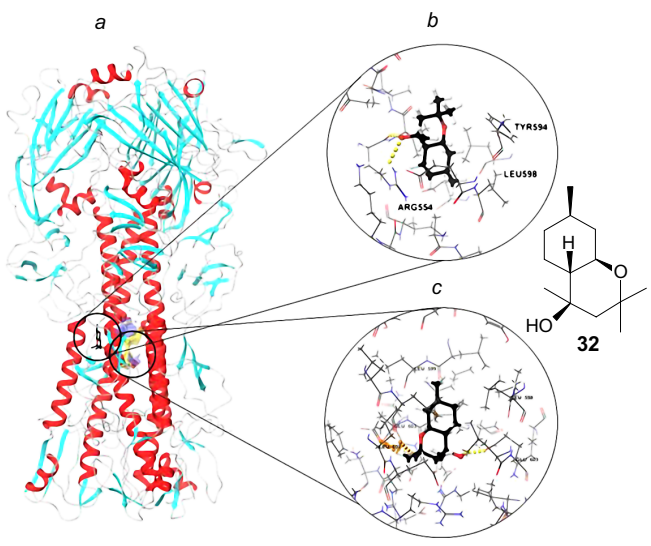


Figure 30. Interaction of compound **32** with active sites of the influenza gaemagglutinin (*a*) and enlarged images of the localization in the TBHQ binding site (*b*) and in the middle of the HA α-helix (*c*), obtained by the molecular modelling method.[72]

detected. Relatively small hydrophobic cavity was considered as a potential binding site for an inhibitor. The mapping of the binding site followed by the assessment of the affinity of compound **48** was complemented by the results of molecular simulations within 100 ns. According to the calculation results, agent **48** is located at the interface between the longest α-helix and β-loop, forming hydrophobic interactions with the surrounding amino acids. With a decrease in pH values, a conformation change occurs, in which the β-loop turns into the α-helix. At the same time, the HA2 unit is transformed into one extended α-helix whose ends attach to the virus envelope and cytoplasmic membrane (Fig. 31). According to the *in silico* results, compound **48** is located between the middle of the long α-helix and the place where the short α-helix passes into the β-loop, thereby blocking the turn. Zhao *et al.*[88] suggest that there are three possible binding sites and choose site 1 as the most probable.

Mechanisms of antiviral effect of camphecene (**53**) and other camphor-based imino derivatives have been investigated. Results of the study of an influenza virus inhibition with compounds **53** (see Fig. 11) and its analogues **60**, **63**, **72** (see Fig. 11 – 13) as a function of the time of addition suggest that these compounds are active in the early stages of viral replication. Camphecene-resistant strains of the influenza A virus were selected, and the V458(615)L mutation in the haemagglutinin HA providing the virus with a resistance phenotype was located.[162] It was shown that mutations in the surface haemogglutinin of the camphecene-resistant strain are located close to the fusion peptide of the HA2 subunit. In the same area, the proteolytic cleavage site intended for the haemagglutinin activation upon fusion is found. According to the spatial location of the substitution, the authors concluded that this substitution affects intersubunit interactions. This substitution can also hamper the conformational recognition of the 'host' of the proteolytic site by enzymes thereby decreasing the fusogenic activity of haemogglutinin. Simulation of the interaction of compound **53** with viral haemogglutinin using quantum mechanical calculations allowed two binding sites to be identified. The first site is located at the interface of HA1 and HA2 subunits (similar to the TBHQ binding site) in the area of the fusion peptide (Fig. 32 *a*), while the second one is located in the area of the proteolytic cleavage site in the lower part of the molecule (see Fig. 32 *b*). The change in the spatial arrangement of the said region results in appearance of various types of interaction between HA and camphecene, which turns round an amino acid at the V458(615)L mutant thereby hampering the formation of hydrogen bonds necessary for the generation of a strong complex. In this case, the bonding energy is -16.9 kcal mol^{-1} (see Fig. 32 *d*), whereas for the wild-type HA it is twice as high (-29.8 kcal mol^{-1}, see Fig. 32 *b*). Therefore, when resistance develops, V615L mutation occurs in the stem region of the HA2 subunit, which reduces the likelihood of the compound **53** binding to this haemogglutinin site. Hereinafter, the binding site of camphecene at the proteolytic cleavage site was referred to as camphecene binding site (CPH).[161]

The pathogenicity of the camphecene-resistant strain of the influenza A (H1N1) virus was studied in a mouse model of influenza infection, to obtain a comprehensive assessment of the virus properties.[162] The animals were infected with the wild-type camphecene-susceptible (Cf-S) and camphecene-resistant (Cf-R) strains. These studies provided

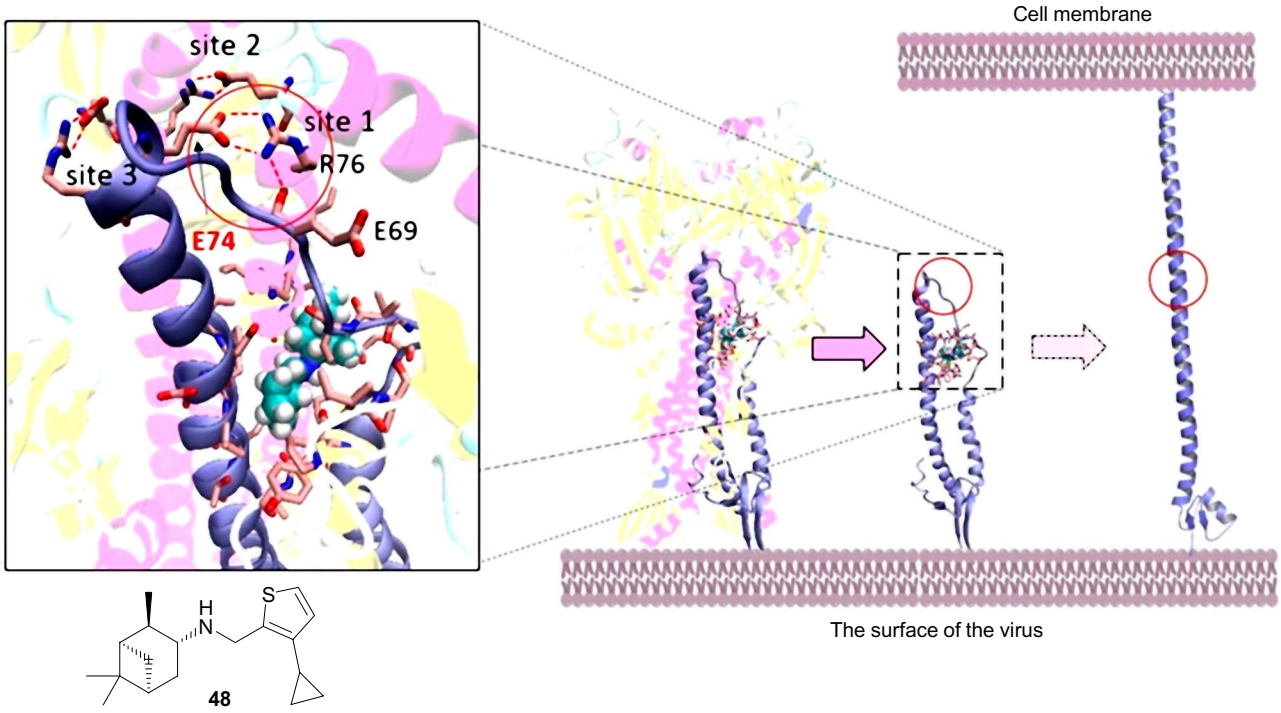


Figure 31. Simulatin the mechanism of action of agent **48**.[88]

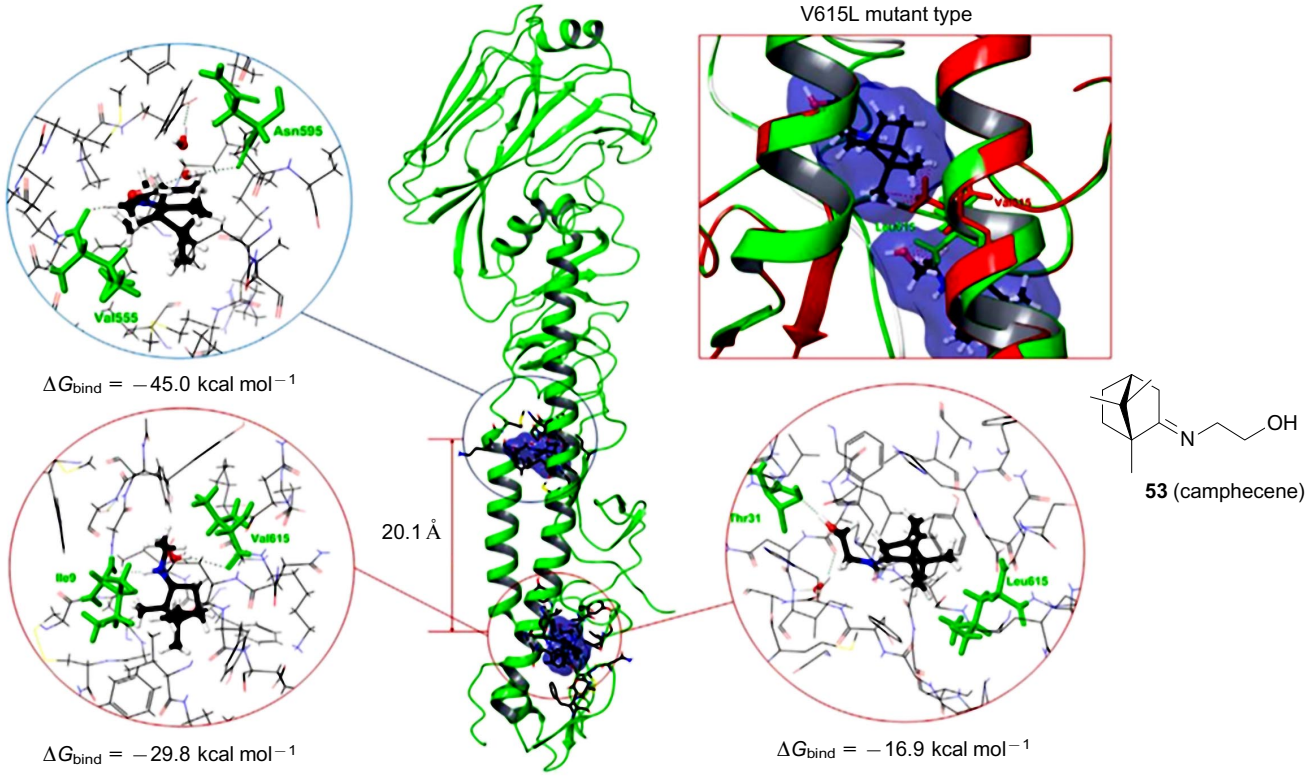


Figure 32. The results of binding camphecene (**53**) to active sites of influenza haemagglutinin (obtained by the molecular modelling method).[162]

evidence that such experiments induced fundamentally different processes. For all doses used, the animals infected with the Cf-S virus demonstrated weight loss and mortality, while the body weight of the animals infected with the Cf-R virus did not change during the experiment. Therefore, it can be concluded that the development of camphecene-resistance in the influenza virus decreases its pathogenicity in animals. This is a very important piece of information

that suggests that on using compounds **53** in clinical practice, viruses may become less pathogenic due to the development of drug resistance. Theoretical calculations showed the change in the energy of the protein complex of the HA surface protein of the influenza virus. According to the calculation results, V615L mutation decreases the internal energy of the subunit of the haemagglutinin trimer by 28 kcal mol^{-1}. Most likely, this leads to the stabilization of the protein as a whole and prevents the 'unfolding' of the haemagglutinin polypeptide chains, and also significantly decreases the pathogenicity of the camphecene-resistant influenza virus strain as compared to that for the wild-type virus. Consequently, the conformational rearrangements that occur when the virus enters the cell have much higher energy demands.

Analyzing the data on the antiviral activity of monoterpenes and their derivatives, mention should be made of the fact that with the use of pseudovirus system, activity of iridoids **12**, **13** (see Fig. 2) against hepatitis C virus, camphor-10-sulfonic acid derivatives **85**–**88** (see Fig. 17) against Ebola virus, and borneol-containing esters **93**–**95** (see Fig. 18) against Marburg virus was studied. According to these studies, the said agents are active in the initial stages of viral replication. Sokolova *et al.*[101] chose the surface protein GP of the Ebola virus as a target for antifiloviral agents **85**–**88** (see Fig. 17) and performed molecular modelling to reveal their active binding site.

In contrast to the above-described compounds showing direct virus-inhibiting properties, certain natural sesquiterpenoids exhibit their antiviral activity affecting the cell mechanisms and signal mechanisms of the host cell. Thus, it was found that bicyclic patchouli alcohol (**112**) (see Fig. 22) is involved in the RLN-signal pathway and inhibits the cytokine expression in the infected cell thereby lowering the influenza A virus replication.[163] Sesquiterpene lactone parthenolid (**136**) (see Fig. 27) decreases the accumulation of the NF-κB p65 subunit in the cell nucleus. Expression of the viral protein ICP0 confirmed the relationship between the NF-κB factor signalling pathway and antiviral activity. Parthenolide acts on the infected cells to decrease expression of ICP0 both in the nucleus and in cytoplasm and reduces expression of other surface glycoproteins of herpes simplex virus.[150]

Ma *et al.*[125] demonstrated that rupestonic acid derivative (YZH-106, **119**) (see Fig. 24) binds neither to the haemagglutinin and neuraminidase surface proteins of the influenza A virus nor to viral proteins. In the authors opinion, this agent exhibits its biological properties by acting on haemoxygenase *via* activation of MARK and ERK1/2 signalling pathways and further on the Nrf2 nuclear factor, and increases expression of the haemoxygenase HO, which is in turn regulated by the type 1 interferons. Therefore, compound YZH-106 is most likely to be active as an immunostimulant.

The mechanism of the antiviral action of artemisinin (**125**) and its analogues remains yet unclear. Nevertheless, the anticytomegaloviral activity of artemisinin is believed to result from the indirect inhibition of NF-κB cellular pathways and the Sp1 transcription factor.[138] It is known that artemisinin affects the malaria parasite through the formation of free radicals due to the presence of an *endo*-peroxide bridge in its structure.[135] The mechanism of antiviral action of artemisinin is probably based on the formation of reactive oxygen species, which in turn inhibit viral replication.

7. Conclusion

The provided material indicates that natural biologically active mono- and sesquiterpenoids are a matter of great interest among researchers both as lead compounds in the development of novel antiviral drugs and as key building blocks in the synthesis of various libraries of compounds. Difficulties of direct application of natural compounds in clinical practice are connected with their low availability since they form only a small part of plant material, and their isolation or industrial production is economically unsustainable. To date, the knowledge of the chemical nature and understanding of the relationship between the structure of a compound and a particular activity is a key purpose for chemists concerned with the modification of natural compounds.

As most available objects among mono- and sesquiterpenoids, monoterpene compounds are of special attention. Among them, bicyclic derivatives based on bornane, oxobornane, and pinabornane cages are the most promising as precursors in the design of novel potent antiviral agents. The synthetic strategy includes either the modification of the cage by introducing heterocyclic pharmacophoric moieties or a combination of two potentially active building blocks in a molecule.

Among sesquiterpenoids, sesquiterpene lactones are the most studied. Since plant sesquiterpene metabolites are far less elusive than monoterpenes, the synthesis of antiviral agents *via* chemical modification of such compounds is highlighted in relatively few studies.

Analysis of data on the mechanism of antiviral action of natural compounds suggests that it is just monoterpenoid derivatives that possess specific activity against the surface viral proteins, often being inhibitors of fusogenic activity. To date, most studied are mechanisms of action of monoterpenoid derivatives which are active against influenza viruses. Currently, available literature data support the hypothesis that sesquiterpene compounds display their activity affecting various cell signalling pathways.

To summarize, natural terpenoids have already proved to be promising objects for the synthesis of novel antiviral drugs. However, so that these compounds find wider application, one should not only focus on their intrinsic biological activity but also take into account the availability of the corresponding plant raw material as an economic component of their production process.

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8. List of acronyms

Following acronyms and designations are used in the review:

ASFV — African swine fever virus;

B Ibaraki — influenza B/Ibaraki/2/85 virus;

BSL-2 — a laboratory which meets the requirements of the 2nd biosafety level (for the work with microorganisms of III – IV pathogenicity groups);

BSL-4 — a laboratory which meets the maximum containment requirements of the 4th biosafety level (for the work with microorganisms of I pathogenicity group);

CC_{50} — concentration that causes death of 50% of viable cells;

Cf-R — camphecene-resistant influenza virus;

Cf-S — camphecene-susceptible influenza virus;

CPH-site — binding site of camphecene at the site of the HA protein proteolysis;
CPXV — cowpox virus;
DCK — (3′*R*,4′*R*)-dicamphanoyl-*cis*-khellacton;
DNA — desoxyribonucleic acid;
p-EbV-GP — pseudoviruses bearing the GP glycoprotein of the Ebola virus on the virion surface;
ECTV — ectromelia virus;
GP — surface glycoprotein of the Ebola virus;
H1N1 Cal — influenza A/California/07/09 (H1N1)pdm09 virus;
H1N1 FM — influenza A/FM/1/47 (H1N1) virus;
H1N1 PR — influenza A/Puerto Rico/8/34 (H1N1);
H1N1 TJ — influenza A/tianjinjinnan/15/2009 (H1N1) virus;
H3N2 aichi — influenza A/Aichi (H3N2) virus;
H3N2 FT — influenza A/FujianTongan/196/2009 (H3N2) virus;
H3N2 HK — influenza A/Hong Kong/8/68 (H3N2) virus;
H3N2 W — influenza A/Wuhan/359/1995 (H3N2) virus;
H5N2 mallard — influenza A/mallard/Pennsylvania/10218/84 (H5N2) virus;
HA — haemagglutinin (surface glycoprotein of the influenza virus);
HCMV — human cytomegalovirus;
HIV-1 — human immunodeficiency virus 1;
HBV — hepatitis B virus;
HSV — hepatitis C virus;
HSV-1 — herpes simplex virus 1;
HSV-2 — herpes simplex virus 2;
IBV — avian infectious bronchitis virus;
IC_{50} — half-maximal inhibitory concentration;
JEV — Japanese encephalitis virus;
p-MarV-GP — pseudoviruses bearing the GP glycoprotein of the Marburg virus on the virion surface;
4-MDCK — 4-methyl-(3′*R*,4′*R*)-dicamphanoyl-*cis*-khellacton;
RNA — ribonucleic acid;
RNP — viral ribonucleoprotein containing RNA and structuring proteins;
SARS-CoV-2 — causative agent for COVID-19;
SI — selectivity index;
TBQH — *tert*-butyl hydroquinone;
TEVC — two-electrode voltage clamp;
VV — vaccinia virus;
WNV — West Nile fever virus;
YF — yellow fever virus;
ZV — Zika virus;
WHO — World Health Organization.

References

1. N.J.Dimmock, A.J.Easton, K.N.Leppard. *Introduction to Modern Virology*. (7th Edn). (Wiley-Blackwell, 2015)
2. H.N.Acheson. *Fundamentals of Molecular Virology*. (2nd Edn). (Wiley, 2011)
3. E.De Clercq, G.Lia. *Clin. Microbiol. Rev.*, **29**, 695 (2016)
4. F.N.Novikov, V.S.Stroylov, I.V.Svitanko, V.E.Nebolsin. *Russ. Chem. Rev.*, **89**, 858 (2020)
5. M.von Itzstein. *Nat. Rev. Drug Discov.*, **6**, 967 (2007)
6. A.C.Hurt, T.G.Besselaar, R.S.Daniels, B.Ermetal, A.Fry, L.Gubareva, W.Huang, A.Lackenby, R.T.C.Lee, J.Lo, S.Maurer-Stroh, H.T.Nguyen, D.Pereyaslov, H.Rebelo-de-Andrade, M.M.Siqueira, E.Takashita, M.Tashiro, D.Tilmanis, D.Wang, W.Zhang, A.Meijer. *Antiviral Res.*, **132**, 178 (2016)
7. U.Grienke, M.Schmidtke, S.von Grafenstein, J.Kirchmair, K.R.Liedl, J.M.Rollinger. *Nat. Prod. Rep.*, **29**, 11 (2012)
8. X.Wu, X.Wu, Q.Sun, C.Zhang, S.Yang, L.Li, Z.Jia. *Theranostics*, **7**, 826 (2017)
9. E.Król1, M.Rychlowska, B.Szewczyk. *Acta Biochim. Polonica*, **61**, 495 (2014)
10. V.Boldescu, M.Behnam, N.Vasilakis, C.Klein. *Nat. Rev. Drug Discov.*, **16**, 565 (2017)
11. A.F.C.S.Oliveira, R.R.Teixeira, A.S.Oliveira, A.P.M.Souza, M.L.Silva, S.O.Paula. *Molecules*, **22**, 505 (2017)
12. F.Zhang, G.Wang. *Eur. J. Med. Chem.*, **75**, 267 (2014)
13. L.Guangdi, E.De Clercq. *Antiviral Res.*, **142**, 83 (2017)
14. M.K.Kukhanova, A.N.Korovina, S.N.Kochetkov. *Biochemistry (Moscow)*, **79**, 1635 (2014)
15. G.Kleymann. *Expert Opin. Investig. Drugs*, **12**, 165 (2003)
16. N.Litterman, C.Lipinski, S.Ekins. *F1000Res.*, **4**, 38 (2015)
17. E.Picazo, F.Giordanetto. *Drug Discov. Today*, **20**, 277 (2015)
18. F.E.da Silva-Júnior, G.O.Leoncini, É.E.S.Rodrigues, T.M.Aquino, J.X.Araújo-Júnior. *Bioorg. Med. Chem.*, **25**, 4219 (2017)
19. Y.H.Wu. *World J. Gastroenterol.*, **22**, 188 (2016)
20. F.H.Qi, Z.X.Wang, P.P.Cai, L.Zhao, J.Gao, N.Kokudo, A.Li, J.Han, W.Tang. *Drug Discov. Ther.*, **7**, 212 (2013)
21. S.S.Yang, G.M.Cragg, D.J.Newman, J.P.Bader. *J. Nat. Prod.*, **64**, 265 (2001)
22. I.P.Singh, H.S.Bodiwala. *Nat. Prod. Rep.*, **27**, 1781 (2010)
23. K.R.Kurapati, V.S.Atluri, T.Samikkannu, G.Garcia, M.P.Nair. *Front Microbiol.*, **6**, 1444 (2016)
24. M.T.Khan, A.Ather, K.D.Thompson, R.Gambari. *Antiviral Res.*, **67**, 107 (2005)
25. S.T.Hassan, R.Masarcíková, K.Berchová. *J. Pharm. Pharmacol.*, **67**, 1325 (2015)
26. J.Kirchmair, S.Distinto, K.R.Liedl, P.Markt, J.M.Rollinger, D.Schuster, G.M.Spitzer, G.Wolber. *Infect. Disord. Drug Targets*, **11**, 64 (2011)
27. J.N.Makau, K.Watanabe, T.Ishikawa, S.Mizuta, T.Hamada, N.Kobayashi, N.Nishida. *PLoS One*, **12**, e0173582 (2017)
28. K.A.El Sayed. *Nat. Prod. Antiviral Agents*, **24**, 473 (2000)
29. A.E.D.Bekhit, A.A.Bekhit. *Stud. Nat. Prod. Chem.*, **42**, 195 (2014)
30. H.Yao, J.Liu, S.Xu, Z.Zhu, J.Xu. *Expert Opin. Drug Discov.*, **12**, 121 (2017)
31. N.F.Salakhutdinov, K.P.Volcho, O.I.Yarovaya. *Pure Appl. Chem.*, **89**, 1105 (2017)
32. D.J.Newman, G.M.Cragg. *J. Nat. Prod.*, **79**, 629 (2016)
33. G.M.Cragg, P.G.Grothaus, D.J.Newman. *J. Nat. Prod.*, **77**, 703 (2014)
34. S.A.A.Jassim, M.A.Naji. *J. Appl. Microbiol.*, **95**, 412 (2003)
35. M.N.Sohail, F.Rasul, A.Karim, U.Kanwal, I.H.Attitalla. *Asian J. Animal Veter. Adv.*, **6**, 1125 (2011)
36. R.Pushpa, R.Nishant, K.Navin, G. Pankaj. *Int. Res. J. Pharm.*, **4**, 8 (2013)
37. M.F.Visintini Jaime, F.Redko, L.V.Muschietti, R.H.Campos, V.S.Martino, L.V.Cavallaro. *Virol. J.*, **10**, 245 (2013)
38. M.Kurokawa, T.Shimizu, W.Watanabe, K.Shiraki. *Open Antimicrob. Agents J.*, **2**, 49 (2010)
39. P.Vijayan, C.Raghu, G.Ashok, S.A.Dhanaraj B.Suresh. *Indian J. Med. Res.*, **120**, 24 (2004)
40. M.A.Téllez, A.N.Téllez, F.Vélez, J.C.Ulloa. *BMC Complement. Alternat. Med.*, **15**, 428 (2015)
41. A.B.Cecílio, P.C.Oliveira, S.Caldas, P.R.V.Campana, F.L.Francisco, M.G.R.Duarte, L.A.M.Mendonça, V.L.Almeida. *Rev. Bras. Farmacogn.*, **26**, 197 (2016)

42. A.Derksen, J.Kühn, W.Hafezi, J.Sendker, C.Ehrhardt, S.Ludwig, A.Hensel. *J. Ethnopharm.*, **188**, 144 (2016)
43. X.Shang, H.Pan, M.Li, X.Miao, H.Ding. *J. Ethnopharm.*, **138**, 1 (2011)
44. A.Shakeri, A.Sahebkar, B.Javadi. *J. Ethnopharm.*, **188**, 204 (2016)
45. P.Jalali, A.Moattari, A.Mohammadi, N.Ghazanfari. *Asian Pac. J. Trop. Dis.*, **6**, 714 (2016)
46. M.R.Loizzo, A.Saab, R.Tundis, G.A.Statti, I.Lampronti, F.Menichini, R.Gambari, J.Cinatl, H.W.Doerr. *Phytomedicine*, **15**, 79 (2008)
47. R.Paduch, M.Kandefer-Szerszeå, M.Trytek, J.Fiedurek. *Arch. Immunol. Ther. Exp.*, **55**, 315 (2007)
48. I.E.Orhan, B.Ozcelik, M.Kartal, Y.Kan. *Turk. J. Biol.*, **36**, 239 (2012)
49. A.Garozzo, R.Timpanaro, A.Stivala, G.Bisignano, A.Castro. *Antiviral Res.*, **89**, 83 (2011)
50. A.Pliego Zamora, J.H.Edmonds, M.J.Reynolds, A.A.Khromykh, S.J.Ralph. *Virology*, **495**, 18 (2016)
51. Z.Yang, N.Wu, Y.Zu, Y.Fu. *Molecules*, **16**, 1044 (2011)
52. M.Lu, H.Zhiqiang, X.Yun, Y.Lei. *J. Microbiol. Biotechnol.*, **23**, 771 (2013)
53. K.Z.Bourne, N.Bourne, S.F.Reising, L.R.Stanberry. *Antiviral Res.*, **42**, 219 (1999)
54. Y.Li, Y.Lai, Y.Wang, N.Liu, F.Zhang, P.Xu. *Inflammation*, **39**, 1582 (2016)
55. M.Armaka, E.Papanikolaou, A.Sivropoulou, M.Arsenakis. *Antiviral Res.*, **43**, 79 (1999)
56. L.Civitelli, S.Panella, M.E.Marcocci, A.De Petris, S.Garzoli, F.Pepi, E.Vavala, R.Ragno, L.Nencioni, A.T.Palamara, L.Angiolella. *Phytomedicine*, **21**, 857 (2014)
57. H.Zhang, K.Rothwangl, A,D.Mesecar, A.Sabahi, L.Rong, H.H.S.Fong. *J. Nat. Prod.*, **72**, 2158 (2009)
58. M.E.Welsch, S.A.Snyder, B.R.Stockwell. *Curr. Opin. Chem. Biol.*, **14**, 347 (2010)
59. S.Bongarzone, M.L.Bolognesi. *Expert Opin. Drug Discov.*, **6**, 251 (2011)
60. O.O.Ajani, D.V.Aderohunmu, C.O.Ikpo, A.E.Adedapo, I.O.Olanrewaju. *Arch. Pharm. Chem. Life Sci.*, **349**, 475 (2016)
61. A.M.Jones. *Privileged Structures and Motifs (Synthetic and Natural Scaffolds) (Ser. Comprehensive Medicinal Chemistry III)*. (Eds S.Chackalamannil, D.Rotella, S.Ward). (Amsterdam: Elsevier, 2017)
62. C.Zhuang, W.Zhang, C.Sheng, W.Zhang, C.Xing, Z.Miao. *Chem. Rev.*, **117**, 7762 (2017)
63. K.Spilovska, F.Zemek, J.Korabecny, E.Nepovimova, O.Soukup, M.Windisch, K.Kuca. *Curr. Med. Chem.*, **23**, 3245 (2016)
64. L.Wanka, K.Iqbal, P.R.Schreiner. *Chem. Rev.*, **113**, 3516 (2013)
65. E.De Clercq. *Med. Res. Rev.*, **29**, 611 (2009)
66. G.V.Teplov, E.V.Suslov, V.V.Zarubaev, A.A.Shtro, L.A.Karpinskaya, A.D.Rogachev, D.V.Korchagina, K.P.Volcho, N.F.Salakhutdinov, O.I.Kiselev. *Lett. Drug Des. Discov.*, **10**, 477 (2013)
67. E.Suslov, V.V.Zarubaev, A.V.Slita, K.Ponomarev, D.Korchagina, D.M.Ayine-Tora, J.Reynisson, K.Volcho, N.Salakhutdinov. *Bioorg. Med. Chem. Lett.*, **27**, 4531 (2017)
68. Patent RU 2712135 (2020)
69. O.V.Ardashov, V.V.Zarubaev, A.A.Shtro, D.V.Korchagina, K.P.Volcho, N.F.Salakhutdinov, O.I.Kiselev. *Lett. Drug Des. Discov.*, **8**, 375 (2011)
70. O.S.Patrusheva, V.V.Zarubaev, A.A.Shtro, Y.R.Orshanskaya, S.A.Boldyrev, I.V.Ilyina, S.Yu.Kurbakova, D.V.Korchagina, K.P.Volcho, N.F.Salakhutdinov. *Bioorg. Med. Chem. Lett.*, **24**, 5158 (2016)
71. E.V.Nazimova, A.A.Shtro, V.B.Anikin, O.S.Patrusheva, I.V.Ilina, D.V.Korchagina, V.V.Zarubaev, K.P.Volcho, N.F.Salakhutdinov. *Chem. Nat. Compd.*, **53**, 260 (2017)
72. I.V.Ilyina, V.V.Zarubaev, I.N.Lavrentieva, A.A.Shtro, I.L.Esaulkova, D.V.Korchagina, S.S.Borisevich, K.P.Volcho, N.F.Salakhutdinov. *Bioorg. Med. Chem. Lett.*, **28**, 2061 (2018)
73. O.S.Patrusheva, K.P.Volcho, N.F.Salakhutdinov. *Russ. Chem. Rev.*, **87**, 771 (2018)
74. M.Z.Hassan, H.Osman, M.A.Ali, M.J.Ahsan. *Eur. J. Med. Chem.*, **123**, 236 (2016)
75. D.Yu, M.Suzuki, L.Xie, S.L.Morris-Natschke, K.H.Lee. *Med. Res. Rev.*, **23**, 322 (2003)
76. L.Huang, Y.Kashiwada, L.M.Cosentino, S.Fan, C.H.Chen, A.T.McPhai1, T.Fujioka, K.Mihashi, K.H.Lee. *J. Med. Chem.*, **37**, 3947 (1994)
77. L.Xie, Y.Takeuchi, L.M.Cosentino, K.H.Lee. *J. Med. Chem.*, **42**, 2662 (1999)
78. L.Xie, Y.Takeuchi, L.M.Cosentino, A.T.McPhail, K.H.Lee. *J. Med. Chem.*, **44**, 664 (2001)
79. T.T.Lee, Y.Kashiwada, L.Huang, J.Snider, M.Cosentino, K.H.Lee. *Bioorg. Med. Chem.*, **2**, 1051 (1994)
80. H.S.Liu, S.Q.Xu, M.Cheng, Y.Chen, P.Xia, K.Qian, Y.Xia, Z.Y.Yang, C.H.Chen, S.L.Morris-Natschke, K.H.Lee. *Bioorg. Med. Chem. Lett.*, **21**, 5831 (2011)
81. L.Xie, D.Yu, C.Wild, G.Allaway, J.Turpin, P.C.Smith, K.H.Lee. *J. Med. Chem.*, **47**, 756 (2004)
82. L.Xie, C.Zhao, T.Zhou, H.Chen, B.Fan, X.Chen, J.Ma, J.Li, Z.Bao, Z.Lo, D.Yue, K.H.Lee. *Bioorg. Med. Chem.*, **13**, 6435 (2005)
83. T.M.Khomenko, V.V.Zarubaev, I.R.Orshanskaya, R.A.Kadyrova, V.A.Sannikova, D.V.Korchagina, K.P.Volcho, N.F.Salakhutdinov. *Bioorg. Med. Chem. Lett.*, **27**, 2920 (2017)
84. W.Hu, S.Zeng, C.Li, Y.Jie, Z.Li, L.Chen. *J. Med. Chem.*, **53**, 3831 (2010)
85. X.Zhao, C.Li, S.Zeng, W.Hu. *Eur. J. Med. Chem.*, **46**, 52 (2011)
86. X.Zhao, Y.Jie, M.R.Rosenberg, J.Wan, S.Zeng, W.Cui, Y.Xiao, Z.Li, Z.C.Tu, M.G.Casarotto, W.H.Hu. *Antiviral Res.*, **96**, 91 (2012)
87. J.Dong, S.Chen, R.Li, W.Cui, H.Jiang, Y.Ling, Z.Yang, W.Hu. *Eur. J. Med. Chem.*, **108**, 605 (2016)
88. X.Zhao, R.Li, Y.Zhou, M.Xiao, C.Ma, Z.Yang, S.Zeng, Q.Du, C.Yang, H.Jiang, Y.Hu, K.Wang, C.K.P.Mok, P.Sun, J.Dong, W.Cui, J.Wang, Y.Tu, Z.Yang, W.Hu. *J. Med. Chem.*, **61**, 5187 (2018)
89. A.G.Martinez, E.T.War, A.G.Fraile, S.de la Moya Cerero, M.E.R.Herrero, P.M.Ruiz, L.R.Subramanian, A.G.Gancedo. *J. Med. Chem.*, **38**, 4474 (1995)
90. X.Zhao, Z.Zhang, W.Cui, S.Chen, Y.Zhou, J.Dong, Y.Jie, J.Wan, Y.Xu, W.Hu. *MedChemComm.*, **6**, 727 (2015)
91. A.S.Sokolova, .I.Yarovaya, À.V.Shernyukov, Yu.V.Gatilov, Yu.V.Razumova, V.V.Zarubaev, T.S.Tretiak, À.G.Pokrovsky, O.I.Kiselev, N.F.Salakhutdinov. *Eur. J. Med. Chem.*, **105**, 263 (2015)
92. V.V.Zarubaev, A.V.Garshinina, T.S.Tretiak, V.A.Fedorova, A.A.Shtro, A.S.Sokolova, O.I.Yarovaya, N.F.Salakhutdinov. *Antiviral Res.*, **120**, 126 (2015)
93. A.S.Sokolova, .I.Yarovaya, D.S.Baev, À.V.Shernyukov, A.A.Shtro, V.V.Zarubaev, N.F.Salakhutdinov. *Eur. J. Med. Chem.*, **127**, 661 (2017)
94. O.I.Artyushin, E.V.Sharova, N.M.Vinogradova, G.K.Genkina, A.A.Moiseeva, Z.S.Klemenkova, I.R.Orshanskaya, A.A.Shtro, R.A.Kadyrova, V.V.Zarubaev, O.I.Yarovaya, N.F.Salakhutdinov, V.K.Brel. *Bioorg. Med. Chem. Lett.*, **27**, 2181 (2017)
95. O.I.Artyushin, A.A.Moiseeva, V.V.Zarubaev, A.V.Slita, A.V.Galochkina, A.A.Muryleva, S.S.Borisevich, O.I.Yarovaya, N.F.Salakhutdinov, V.K.Brel. *Chem. Biodivers.*, **16**, e1900340 (2019)

96. O.I.Yarovaya, A.S.Sokolova, I.Y.Mainagashev, A.S.Volobueva, K.Lantsev, S.S.Borisevich, A.A.Shtro, V.V.Zarubaev, N.F.Salakhutdinov. *Bioorg. Med. Chem. Lett.*, **29**, 126745 (2019)
97. A.S.Sokolova, .I.Yarovaya, D.V.Korchagina, V.V.Zarubaev, T.S.Tretiak, P.M.Anfimov, O.I.Kiselev, N.F.Salakhutdinov. *Bioorg. Med. Chem.*, **22**, 2141 (2014)
98. A.S.Sokolova, .I.Yarovaya, A.V.Shernyukov, M.A.Pokrovsky, A.G.Pokrovsky, V.A.Lavrinenko, V.V.Zarubaev, T.S.Tretiak, P.M.Anfimov, O.I.Kiselev, A.B.Beklemishev, N.F.Salakhutdinov. *Bioorg. Med. Chem.*, **21**, 6690 (2013)
99. A.S.Sokolova, O.I.Yarovaya, N.I.Bormotov, L.N.Shishkina, N.F.Salakhutdinov. *MedChemComm.*, **9**, 1746 (2018)
100. K.S.Kovaleva, F.I.Zubkov, N.I.Bormotov, R.A.Novikov, P.V.Dorovatovskii, V.N.Khrustalev, Yu.V.Gatilov, V.V.Zarubaev, O.I.Yarovaya, L.N.Shishkin, N.F.Salakhutdinov. *MedChemComm.*, **9**, 2072 (2018)
101. A.S.Sokolova, D.V.Baranova, O.I.Yarovaya, D.S.Baev, O.A.Polezhaeva, A.V.Zybkina, D.N.Shcherbakov, T.G.Tolstikova, N.F.Salakhutdinov. *Russ. Chem. Bull., Int. Ed.*, **68**, 1041 (2019)
102. A.S.Sokolova, O.I.Yarovaya, M.D.Semenova, A.A.Shtro, I.R.Orshanskaya, V.V.Zarubaev, N.F.Salakhutdinov. *MedChemComm.*, **8**, 960 (2017)
103. A.Kononova, A.Sokolova, S.Cheresiz, O.Yarovara, R.Nikitina, A.Chepurnov, A.G.Pokrovsky, N.Salakhutdonov. *MedChemComm.*, **8**, 2233 (2017)
104. Patent RU 2649406 (2018)
105. Patent RU 2697716 (2019)
106. A.S.Sokolova, O.I.Yarovaya, N.I.Bormotov, L.N.Shishkina, N.F.Salakhutdinov. *Chem. Biodivers.*, **15**, e1800153 (2018)
107. M.S.Borisova, O.I.Yarovaya, M.D.Semenova, T.G.Tolstikova, N.F.Salakhutdinov. *Russ. Chem. Bull., Int. Ed.*, **67**, 558 (2018)
108. A.S.Sokolova, O.I.Yarovaya, A.A.Shtro, M.S.Borisova, E.A.Morozova, T.G.Tolstikova, V.V.Zarubaev, N.F.Salakhutdinov. *Chem. Heterocycl. Compd.*, **53**, 371 (2017)
109. Patent RU 2687254 (2019)
110. V.V.Chernyshov, O.I.Yarovaya, D.S.Fadeev, Yu.V.Gatilov, Ya.L.Esaulkova, A.S.Muryleva, K.O.Sinegubova, V.V.Zarubaev, N.F.Salakhutdinov. *Mol. Divers.*, **24**, 61 (2020)
111. V.V.Chernyshov, O.I.Yarovaya, R.Yu.Peshkov, N.F.Salakhutdinov. *Chem. Heterocycl. Compd.*, **56**, 763 (2020)
112. A.Astani, J.Reichling, P.Schnitzler. *Evid. Based Complement. Alternat. Med.*, Art. ID 253643 (2011)
113. G.Hu, C.Peng, X.Xie, S.Zhang, X.Cao1. *Evid. Based Complement. Alternat. Med.*, Art. ID 4850612 (2017)
114. H.Kiyohara, C.Ichino, Y,Kawamura, T,Nagai, N.Sato, H.Yamada. *J. Nat. Med.*, **66**, 55 (2012)
115. H.Wu, B.Li, X.Wang, M.Jin, G.Wang. *Molecules*, **16**, 6489 (2011)
116. Y.C.Li, S.Z.Peng, H.M.Chen, F.X.Zhang, P.P.Xu, J.H.Xie, J.J.He, J.N.Chen, X.P.Lai, Z.R.Su. *Int. Immunopharm.*, **12**, 294 (2012)
117. U.Sotanaphun, V.Lipipun, R.Suttisri, R.Bavovada. *Planta Med.*, **65**, 257 (1999)
118. F.Benencia1, M.C.Courreges. *Phytomedicine*, **6**, 119 (1999)
119. M.Paulpandi, S.Kannan, R.Thangam, K.Kaveri, P.Gunasekaran, C.Rejeeth. *Phytomedicine*, **19**, 231 (2012)
120. H.J.Zhang, V.H.Nguyen, M.C.Nguyen, D.D.Soejarto, J.M.Pezzuto, H.H.Fong, G.T.Tan. *Planta Med.*, **71**, 452 (2005)
121. H.J.Zhang, G.T.Tan, V.D.Hoang, N.V.Hung, N.M.Cuong, D.D.Soejarto, J.M.Pezzuto, H.H.Fong. *Tetrahedron*, **59**, 141 (2003)
122. J.P.Yong, H.A.Aisa. *Chem. Nat. Compd.*, **44**, 311 (2008)
123. J.Zhao, H.A.Aisa. *Bioorg. Med. Chem. Lett.*, **22**, 2321 (2012)
124. Y.W.He, C.Z.Dong, J.Y.Zhao, L.L.Mad, Y.H.Li, H.A.Aisa. *Eur. J. Med. Chem.*, **76**, 245 (2014)
125. L.L.Ma, H.Q.Wang, P.Wu, J.Hu, J.Q.Yin, S.Wu, M.Ge, W.F.Sun, J.Y.Zhao, H.A.Aisa, Y.H.Li, J.D.Jiang. *Free Radical Biol. Med.*, **96**, 347 (2016)
126. J.Zhao, C.Niu, G.Li, H.A.Aisa. *Chem. Nat. Compd.*, **53**, 276 (2017)
127. G.Li, J.Y.Zhao, C.Niu, L.F.Nie, C.Z.Dong, H.A.Aisa. *Bioorg. Med. Chem. Lett.*, **27**, 1484 (2017)
128. M.Obul, X.Wang, J.Zhao, G.Li, H.A.Aisa, G.Huang. *Mol. Divers.*, **23**, 1 (2019)
129. G.Li, M.Obul, J.Zhao, G.Liu, W.Lu, H.A.Aisa. *Bioorg. Med. Chem. Lett.*, **29**, 126605 (2019)
130. J.Zhao, C.Dong, H.A.Aisa. *Med. Chem. (Los Angeles)*, **6**, 322 (2016)
131. S.M.Adekenov. *Eurasian Chem. Technol. J.*, **15**, 163 (2013)
132. M.Chadwick, H.Trewin, F.Gawthrop, C.Wagstaff. *Int. J. Mol. Sci.*, **14**, 12780 (2013)
133. D.Chaturvedi. In *Opportunity, Challenge and Scope of Natural Products in Medicinal Chemistry*. (Trivandrum: Research Signpost, 2011). P. 313
134. M.J.A.Martínez, L.M.B.D.Olmo, L.A.Ticona, P.B.Benito. *Stud. Nat. Prod. Chem.*, **37**, 43 (2012)
135. Y.F.Dai, W.W.Zhou, J.Meng, X.L.Du, Y.P.Sui, L.Dai, P.Q.Wang, H.R.Huo, F.Sui. *Med. Chem. Res.*, **26**, 867 (2017)
136. Z.Wang, L.Yang, X.Yang, X.Zhang. *Synth. Commun.*, **44**, 1987 (2014)
137. S.Yeung, W.Pongtavornpinyo, I.M.Hastings, A.J.Mills, N.J.White. *Am. J. Trop. Med. Hyg.*, **71**, 179 (2004)
138. S.D Alessandro, D.Scaccabarozzi, L.Signorini, F.Perego, D.P.Ilboudo, P.Ferrante, S.Delbue. *Microorganisms*, **8**, 85 (2020)
139. T.Efferth, M.Marschall, X.Wang, S.M.Huong, I.Hauber, A.Olbrich, M.Kronschnabl, T.Stamminger, E.S.Huang. *J. Mol. Med.*, **80**, 233 (2002)
140. E.Oiknine-Djian, Y.Weisblum, A.Panet, H.N.Wong, R.K.Haynes, D.G.Wolf. Antimicrob. *Agents Chemother.*, **62**, e00288-18 (2018)
141. E.Oiknine-Djian, S.Bar-On, I.Laskov, D.Lantsberg, R.K.Haynes, A.Panet, D.G.Wolf. *Antiviral Res.*, **172**, 104639 (2019)
142. X.Wang, B.Zheng, U.Ashraf, H.Zhang, C.Cao, Q.Li, Z.Chen, M.Imran, H.Chen, S.Cao, J.Ye. *Antiviral Res.*, **179**, 104810 (2020)
143. S.Obeid, J.Alen, V.H.Nguyen, V.C.Pham, P.Meuleman, C.Pannecouque, T.N.Le, J.Neyts, W.Dehaen, J.Paeshuyse. *PLoS ONE*, **8**, e81783 (2013)
144. S.Jana, S.Iram, J.Thomas, M.Q.Hayat, C.Pannecouque, W.Dehaen. *Molecules*, **22**, 303 (2017)
145. C.Reiter, T.Fröhlich, L.Gruber, C.Hutterer, M.Marschall, C.Voigtlónder, O.Friedrich, B.Kappes, T.Efferth, S.B.Tsogoeva. *Bioorg. Med. Chem.*, **23**, 5452 (2015)
146. T.Fröhlich, C.Reiter, M.M.Ibrahim, J.Beutel, C.Hutterer, I.Zeitträger, H.Bahsi, M.Leidenberger, O.Friedrich, B.Kappes, T.Efferth, M.Marschall, S.B.Tsogoeva. *ACS Omega*, **2**, 2422 (2017)
147. A.Capci, M.M.Lorion, C.Mai, F.Hahn, J.Hodek, C.Wangen, J.Weber, M.Marschall, L.Ackermann, S.B.Tsogoeva. *Chem. – Eur. J.*, **26**, 12019 (2020)
148. C.Rezeng, D.Yuan, J.Long, D.Suonan, F.Yang, W.Li, L.Tong, P.Jiumei. *BioSci. Trends*, **9**, 420 (2015)
149. D.R.Hwang, Y.S.Wu, C.W.Chang, T.W.Lien, W.C.Chen, U.K.Tan, J.T.A.Hsu, H.P.Hsieh. *Bioorg. Med. Chem.*, **14**, 83 (2006)
150. E.Benassi-Zanqueta, C.F.Marques, S.R.Nocchi, B.P.Dias Filho, C.V.Nakamura, T.Ueda-Nakamura. *Intervirology*, **61**, 14 (2018)
151. B.Özçelik, I.Gürbüz, T.Karaoglu, E.Yeşilada. *Microbiol. Res.*, **164**, 545 (2009)

152. J.F.Liu, Y.F.Wang, Y.P.Bi, H.J.Li, L.Jia, Y.F.Bi, Y.B.Zhang. *Tetrahedron Lett.*, **54**, 4834 (2013)
153. A.Gliszczyńska, P.E.Brodelius. *Phytochem. Rev.*, **11**, 77 (2012)
154. C.L.Lee, L.C.Chiang, L.H.Cheng, C.C.Liaw, M.H.A.El-Razek, F.R.Chang, Y.C.Wu. *J. Nat. Prod.*, **72**, 1568 (2009)
155. I.Mazur, W.J.Wurzer, C.Ehrhardt, S.Pleschka, P.Puthavathana, T.Silberzahn, T.Wolff, O.Planz, S.Ludwig. *Cell Microbiol.*, **9**, 1683 (2007)
156. V.Olschläger, S.Pleschka, T.Fischer, H.J.Rziha, W.Wurzer, L.Stitz, U.R.Rapp, S.Ludwig, O.Planz. *Oncogene*, **23**, 6639 (2004)
157. A.Luttick, S.Hamilton, S.P.Tucker. *Methods Mol. Biol.*, **1030**, 383 (2013)
158. D.Daelemans, R.Pauwels, E.De Clercq, C.Pannecouque. *Nat. Protoc.*, **6**, 925 (2011)
159. Q.Li, Q.Liu, W.Huang, X.Li, Y.Wang. *Rev. Med. Virol.*, **28**, e1963 (2018)
160. C.Salata, A.Calistri, G.Alvisi, M.Celestino, C.Parolin, G.Palù. *Viruses*, **11**, 274 (2019)
161. B.Guan, X.Chen, H.Zhang. *Methods Mol. Biol.*, **998**, 79 (2013)
162. V.V.Zarubaev, E.A.Pushkina, S.S.Borisevich, A.V.Galochkina, A.V.Garshinina, A.A.Shtro, A.A.Egorova, A.S.Sokolova, S.L.Khursan, O.I.Yarovaya, N.F.Salakhutdinov. *Virology*, **524**, 69 (2018)
163. X.L.Wu, D.H.Ju, J.Chen, B.Yu, K.Li.Liu, J.X.He, C.Q.Dai, S.Wu, Z.Chang, Y.P.Wang, X.Y.Chen. *Curr. Microbiol.*, **67**, 431 (2013)