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Antiviral properties of diterpenes and their derivatives

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The review focuses on low-molecular-weight natural metabolites of the diterpene series and their semi-synthetic analogues, which exhibit antiviral activity. Data on the antiviral activity of both plant extracts and their components are provided. The structures of biologically active natural diterpenoids and their derivatives with a pronounced antiviral effect are presented. Mechanisms of therapeutic action of diterpenoids and their derivatives with a pronounced antiviral effect are considered for different viruses. The review summarizes the data over the last 12 years (2011 – 2022).
The bibliography includes 183 references.

Contents

1. Introduction

Virus is a noncellular infectious agent that reproduces only inside living cells. Viruses infect various types of organisms such as bacteria, plants, animals and humans. The officially assigned names of human viruses are associated with the type of pathological effect or the history of their discovery.

An important area of scientific research is the search for antiviral agents, motivated by the spread of a large number of viral infections and the emergence of new dangerous viral diseases caused by pathogenic strains such as the coronavirus SARS-CoV-2. Therefore, the design of new biologically active substances and the development of drugs based thereon for the prevention and treatment of viral infections is considered one of the most important tasks of modern organic, bioorganic and medicinal chemistry. Our previous study [1] published in 2021, outlines the effects that viruses have on infected cells, presents the main types of viruses that cause infections in humans, and provides a brief history of the discovery of potent antiviral drugs.

Natural compounds continue to play an outstanding role in the design of new drugs and the development of the global pharmaceutical industry.[2] Most low-molecular-weight natural compounds are classified as so-called secondary plant metabolites. Secondary metabolites have a diverse chemical structure: these are terpenoids, alkaloids, steroids, polyketides, phenolic metabolites, a number of carbohydrates, various lipids and peptides. According to the biological effect, antibiotics, hormones, toxins, pheromones, *etc*., are commonly distinguished among secondary metabolites. Terpene compounds can be attributed to natural compounds that are promising as a basis for designing new antiviral agents. Terpenes are classified by the number of isoprene units that form the carbon skeleton of the molecule. For example, diterpenes contain four isoprene units, while their derivatives with one or several oxygen atoms are referred to as diterpenoids. It should be noted that molecular mechanisms of antiviral activity of terpenoids have been scarcely studied, and the structure – antiviral activity relationships for such compounds were virtually not identified. The review [1] presented the literature data on the research of antiviral activity of mono- and sesqui-

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terpenoids. In the search for compounds with antiviral activity, Xiao *et al.*[3] focused on triterpene derivatives.

Diterpenes, as organic compounds of natural origin, are of great interest to researchers. Thus, the prospects of using diterpenes and their derivatives in the treatment of inflammatory diseases were noted.[4] Obviously, an increase in the number of carbon atoms leads to a variety of types of joining of isoprene units. Diterpenes are classified by the number of rings in the framework — from acyclic to tetracyclic one. No compounds with pronounced antiviral properties were found among acyclic diterpenes.

The search for scientific literature on the subject of this review was carried out using the international bibliographic databases Scopus (https://www.scopus.com/) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). A combination of the keywords diterpenes and antiviral activity was used to select publications. By October 2022, more than 6,000 articles have been found, with a noticeable increase in the number of publications starting in the 2000s and their number peaking in 2021. As for the geography of scientific papers, it was revealed that ~23% of the number of publications belong to authors from China, followed by researchers from the United States (~18%), followed by scientists from India (7.7%), Germany (7.1%) and Brazil (5.6%), while articles with the participation of Russian authors account for only 1%. The distribution of publications by branches of knowledge showed that most of the articles relate to biochemistry and molecular biology (24%), pharmacology (18%), chemistry (15.6%) and medicine (12.7%). (12.7%). Recently, reviews have appeared on the antiviral activity of diterpenes and their derivatives, but either they provide sporadic information,[5,6] or they are limited to the study of activity against a single viral species.[7,8] The present review gives an in-depth analysis of the literature data on the antiviral activity of diterpenoids and their derivatives. The information is given in accordance with the structural features of diterpene compounds. References to available original papers published between 2011 and 2022 are provided, as well as to some earlier publications that are of fundamental importance for the discussion of the material.

When studying antiviral activity of a drug, the key parameter is the selectivity index (SI), which is equal to the ratio of the concentration of the compound that causes the death of half of normal cells (CC_{50}) to the half-maximal inhibitory concentration (IC_{50}) of viral reproduction, expressed in μmol mL^{-1} (μM) or in μg mL^{-1}. A promising antiviral compound should have the highest CC_{50} (*i.e.*, be non-toxic) and the lowest IC_{50} value. The selectivity index indicates the compound safety and potency. It is believed that those compounds are active, for which this value exceeds 8. In this review, the antiviral activity rates of diterpenoids are presented as IC_{50} values, and the SI values indicated by the authors of the original publications are also given.

One of the major challenges in medicinal chemistry is identifying the mechanisms of action of antiviral agents. Testing compounds involving an infectious virus does not provide insight into their mechanism of action, and more research is needed. Noteworthy that this rather laborious work requires the use of a large arsenal of methods of virology and molecular biology. Not always specialists have the opportunity to perform such studies, therefore, publications most often contain only primary screening data. In cases where the authors suggested a mechanism, we included it in the discussion of the presented work. Another extremely important problem is the study of the relationship between the structure of new substances and their biological activity. Such an analysis is extremely useful for understanding the choice of directions of chemical modification affording novel potent drugs, including antiviral agents. However, the structure–activity relationship can only be analysed within libraries of structurally related compounds. When sufficiently large libraries were described by the authors of the original publications, we included the corresponding analysis of such compounds in the review.

2. Abietane and pimarane type diterpenoids

Resin acids of conifers are the most available class of diterpenes. These acids *per se* and their derivatives are widely used in production of varnishes, paints, synthetic rubbers, rubber products, *etc*. Moreover, the possibility of obtaining resin acids in the form of individual compounds has become an attractive direction for researchers working in the field of organic and medicinal chemistry. A monograph,[9] published in 2011 and devoted to the chemical transformations of resin acids isolated from conifers in Russia, contains detailed information on the chemical transformations and biological activities of both acids themselves and the compounds derived therefrom. In this review, key compounds of this series exhibiting antiviral activity are discussed.

Most ubiquitous representatives of abietane resin acids are abietic (**1**), dehydroabietic (**2**) and levopimaric (**3**) acids (Fig. 1). The term abietane comes from the Latin name for fir (*Abies*), from which compounds of this type were first isolated. Synthetic transformations of aromatic diterpene abietane acids and their biological activities, mainly, antitumour, are covered in a review.[10]

A number of compounds containing benzimidazole, indole and quinoxalidine moieties were prepared from methyl dehydroabietate (**4**).[11] These heterocyclic derivatives were evaluated for their inhibitory activity against a variety of viruses. It was revealed that compounds **5**–**8** (Fig. 2) can inhibit varicella-zoster virus (VZV) and cytomegalovirus (CMV) replication in human embryonic lung cells at concentrations significantly less than cytotoxic ones (SI = 10–25). Activity of the tested compounds was com-

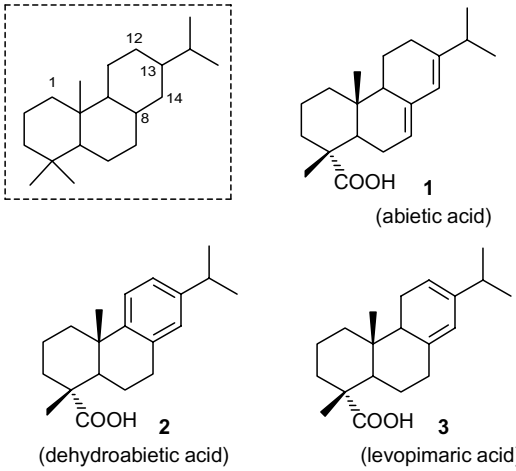
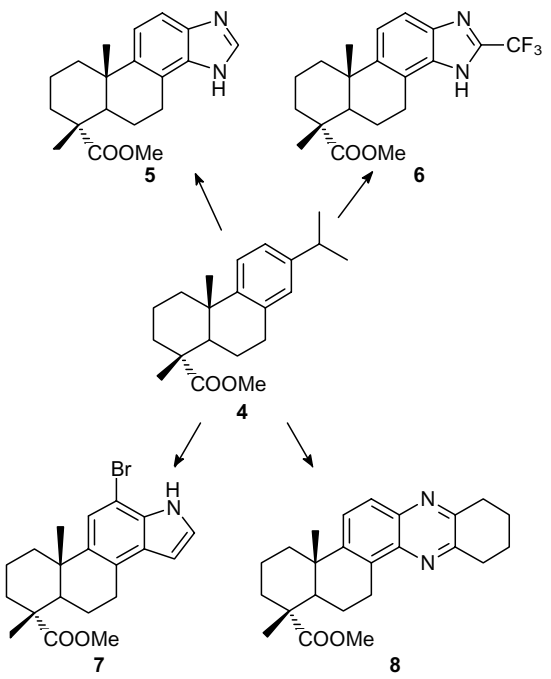


Figure 1. Abietane-type carbon skeleton (in the frame) and structures of abietic (**1**), dehydroabietic (**2**), and levopimaric (**3**) acids.



Compound	IC_{50}, μg mL^{-1}		CC_{50}, μg mL^{-1}
	CMV	VZV	
5	> 0.2	0.2 – 0.5	5.1
6	1.0 – 1.2	0.8 – 1.5	10.8
7	1.5 – 1.6	0.7 – 2	12.5
8	0.9 – 1.1	0.3 – 0.9	13
Acyclovir	–	0.3 – 3.0	> 200
Gancyclovir	0.9 – 1.5	–	200

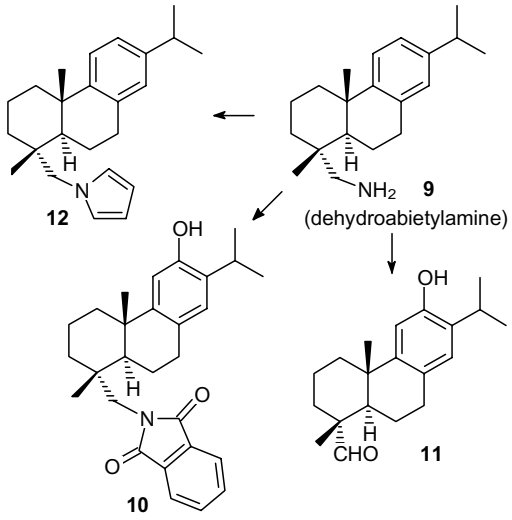
Figure 2. Structures of methyl dehydroabietate derivatives (**4**) — compounds **5**–**8** — and their antiviral activity in comparison with known drugs. Here and below, a dash means no data.[11]

parable to that of the known antiviral agents, acyclovir and gancyclovir. However, compounds **5**–**8** had no specific activity against cowpox, herpes types 1 and 2, vesicular stomatitis, human immunodeficiency type 1 (HIV-1) and type 2 (HIV-2), parainfluenza and Coxsackie B4 viruses. The authors argued that the modification of diterpene compounds by incorporating fused N-heterocycles into their molecules is a promising trend in the design of potential antiviral agents. At the same time, it should be noted that such diterpenoids proved to be rather cytotoxic against the tested cell lines.

Dehydroabietylamine (**9**) is a commercially available compound with an abietane scaffold, which can be easily prepared from dehydroabietic acid (Fig. 3). This compound is also found in the literature under the name leelamine. Recently, it has attracted increased attention of specialists due to the high cytotoxicity of its hydrochloride, which was demonstrated on a number of cancer cells. It was found that dehydroabietylamine has high inhibitory activity and can selectively kill the melanoma cells through lowering cell proliferation and increasing apoptosis.[12] The antiviral activity of various dehydroabiethylamine salts against H1N1 influenza virus was studied and it was shown that dehydroabiethylamine glycerate is active in the micromolar concentration range (IC_{50} = 9.8 μM, SI = 35), while amine **9** itself and its hydrochloride are highly toxic.[13]

A library of dehydroabietylamine-based compounds was synthesized bearing the hydroxy group in the aromatic ring.[14] The resultant derivatives were evaluated for their inhibitory activity against human herpes viruses types 1 and 2, as well as Dengue virus type 2. Agents **10** (SI = 58) and **11** (SI = 10) showed the highest activity against Dengue virus (DENV-2); the same compounds could inhibit herpes virus type 2 (HSV-2) replication with moderate selectivity indices (see Fig. 3). Compound **10** was *ca.* 10 times more potent against Dengue virus type 2 than the control ribavirin. According to the authors,[15] 12-hydroxyabieta-8,11,13-triene scaffold is a promising basis for the design of new antiviral drugs. Among compounds derived from dehydroabietylamine, aldehyde **11** also showed significant activity againt Zika virus (ZIKV), it also had the highest selectivity index (SI = 13.5).[15] Dehydroabietylamine derivatives obtained *via* the modification of the primary amino group, were evaluated for their activity against influenza A virus (H1N1).[16] Compound **12** showed moderate activity and the highest selectivity index among the tested compounds (⩾13).

The presence of 1,3-homodiene unit in the framework contributes to the high reactivity of levopimaric acid in [4 + 2]-cycloaddition reactions. The method for isolating of an adduct of this acid with maleic anhydride from the pine resin was known as early as the 30s of the XXth century. The wide availability of maleopimaric (**13**) and quinopimaric (**14**) acids enables their synthetic transformations affecting various fragments of the natural skeleton (Fig. 4). More than 30 derivatives were synthesized, and their antiviral activity was evaluated.[17] Both starting and resultant compounds showed no specific activity against influenza A (H1N1, H3N2, H5N1), influenza B, SARS viruses, rhinovirus and adenovirus, and also hepatitis B and C strains.



Compound	IC_{50}, μM (SI)			
	DENV-2	HSV-2	ZIKV	H1N1
10	1.4 (58)	19.2 (10)	–	–
11	5.0 (10)	16.6 (5.9)	2.6 (13.5)	
12	–	–	–	71 (13)
Ribavirin	13.5	–	98 (26)	–

Figure 3. Structures of dehydroabietylamine (**9**) and its derivatives **10**–**12**, and their antiviral activity.[12–16]

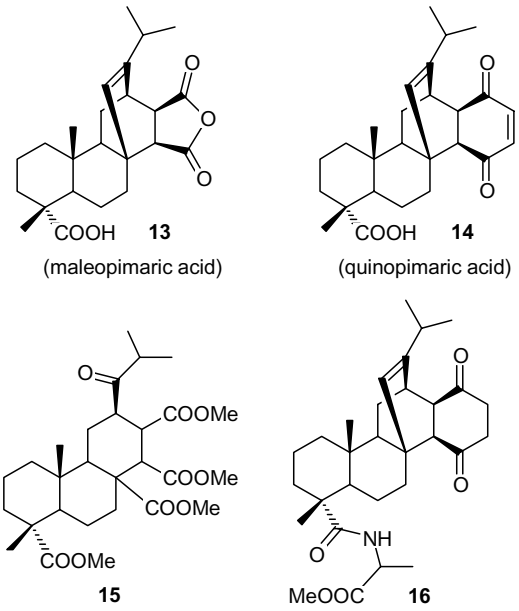
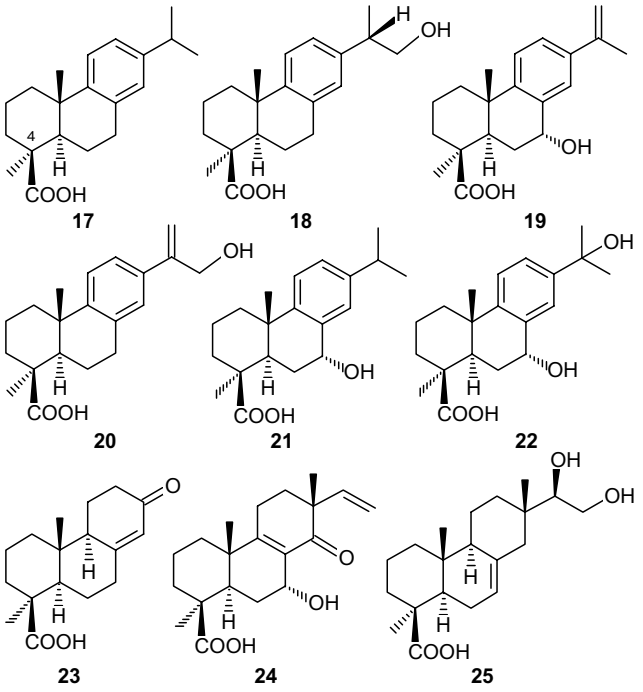


Figure 4. Structures of maleopimaric (**13**) quinopimaric (**14**) acids and their derivatives **15**, **16**.[17]



Compound	IC$_{50}$, μM (SI)		
	CVB2	CVB3	CVB6
17	–	3.3 (6.7)	–
18	–	17.4 (8)	–
19	6.3 (27)	4.9 (30)	2.6 (56)
20	4.7 (53)	13.3 (15)	5.0 (50)
21	2.7 (90)	18.1 (14)	3.6 (69)

Compound	CVB3	
	IC$_{50}$, μM	SI
22	22	46
23	14	41
24	12	49
25	7	37

Figure 5. Structures and antiviral activity of 4-*epi*-dehydroabietic acid **17**, its derivatives **18**–**22** and diterpenoids **23**–**25** isolated from plants of the genus *Illicium*.[18–20]

However, a noticeable activity against human papilloma virus was revealed for compounds **15** [the product of ozonolysis of maleopimaric acid (SI = 30)] and **16** [dihydroquinopimaric acid amide (SI = 20)] (see Fig. 4, the IC$_{50}$ values were not given in the original publication). Amide **16** also displayed a pronounced inhibition (61%) of hepatitis C virus replication at a dose of 10 μM with low toxicity. The authors concluded that the modification of diene adducts of levopimaric acid does not lead to compounds active against viral respiratory infections. Only dihydroquinopimaric acid and 5′-caprolactame (a product of the Beckmann rearrangement of monooxome of reduction product of dihydroquinopimaric acid) showed minimal activity against influenza B virus and atypical pneumonia caused by the SARS virus, respectively. At the same time, functionalization of the carboxy group at the C(20) atom of dihydroquinopimaric acid with the introduction of the L-alanine moiety into the diterpenoid structure contributes to the emergence of activity against papilloma and hepatitis C viruses.

Diterpenoids, both previously known and novel, were isolated from the roots of *Illicium majus*.[18] Abietanes — 4-*epi*-dehydroabietic acid (**17**) and its hydroxy derivative **18** (Fig. 5) were the most active against Coxsackie B3 virus (CVB3). A number of resin acids were isolated from the roots of the anise tree *Illicium jiadifengpi*, and these diterpenoids were tested for their inhibitory activity against Coxsackie B virus on four strains.[19] Hydroxy-substituted 4-*epi*-dehydroabietane analogues **19**–**21** proved to be the most active; the values of their selectivity indices ranged from 27 to 90 against Coxsackie B2 strain (CVB2), from 14 to 30 against B3 strain and from 56 to 69 against B6 strain (CVB6), respectively. The same authors[20] isolated resin acids from the stems of *Illicium jiadifengpi*; among those diterpenoids, compounds **22**–**25** (SI = 37–49) were the most potent against Coxsackie B3 virus.

Mention should be made of much less availability of diterpene acids **17**–**25** as compared to diterpene compounds, which can be isolated from conifers. To gain access to agents possessing pronouced antiviral activity, a crude extract was isolated from the Moroccan sandarac resin, comprising 4-*epi*-dehydroabietic (**17**), sandaracopimaric (**26**) and isopimaric (**27**) acids.[21] The acid mixture was converted to methyl 4-*epi*-dehydroabietic acid (**28**). Further modification of the skeleton of ester **28** gave jiadifenoic acid C (**20**) (Fig. 6).

Representatives of diterpenoids such as carnosic acid (**29**) and carnosol (**30**) (Fig. 7) show a broad spectrum of biological activities including antiinflammatory, anticancer and antioxidant properties.[22,23] Antiviral activity of carnosic acid, isolated from the aerial part of *Rosmarinus officinalis* L, was studied. This compound demonstrated a direct unhibitory effect against human respiratory syncytial virus (HRSV), which can cause lower respiratory infections.[24] Carnosic acid effectively suppress the replication of A and B types of HRSV, but does not effect influenza A virus. The authors demonstrated that this natural compound is active at the early stages of the viral replication and possibly interacts with the F or G viral surface proteins.

Previously, carnosic acid, products of its oxidation with air oxygen in methanol and ethanol, as well as carnosol and its semisynthetic derivative **31** have been studied[25] as HIV-1 protease inhibitors. The carnosic acid showed the most pronounced inhibitory effect (IC$_{90}$ = 0.08 μg mL^{-1}). At

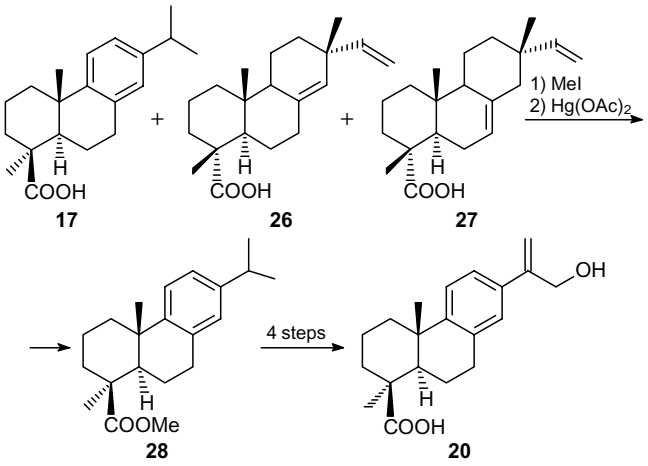


Figure 6. The scheme of transformation of a mixture of 4-*epi*-dehydroabietic (**17**), sandaracopimaric (**26**) and isopimaric (**27**) acids to compounds **28** and **20**.[21]

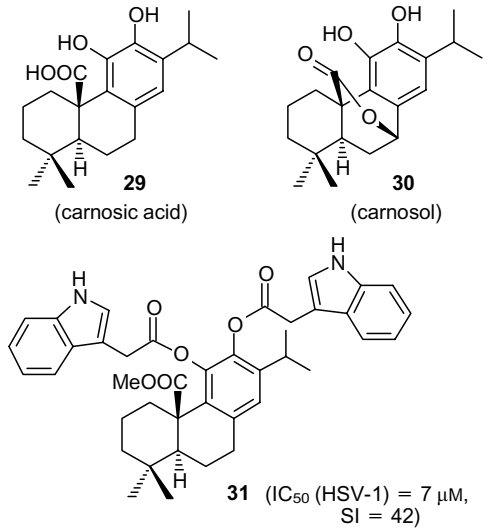


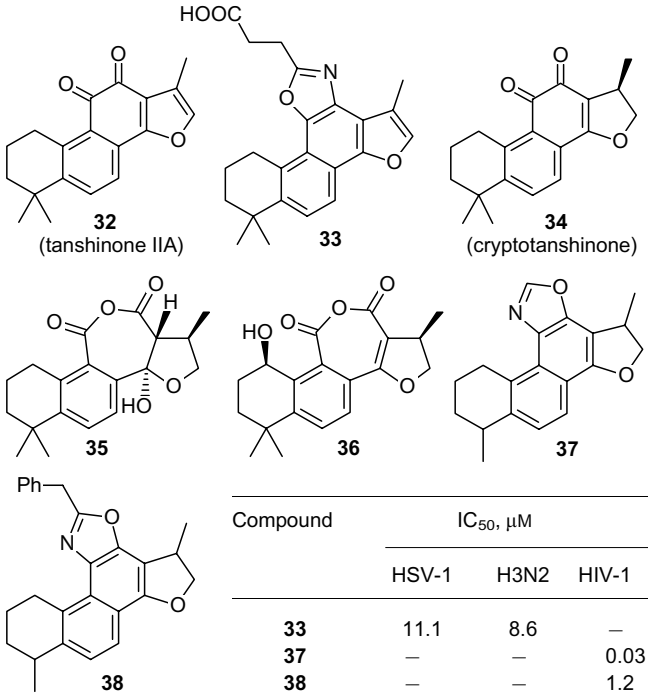
Figure 7. Structures of carnosic acid (**29**), carnosol (**30**) and compound **31**.[25,26]

the same time, among various carnosic acid esters, compound **31** was the only one that showed activity in Vero cells against herpes virus type 1 and exhibited immunomodulatory effect due to the modulation of the production of cytokines and signaling pathways in macrophages infected with herpes virus.[26]

A well-known abietane type diterpenoid, quinone tanshinone IIA (**32**) (Fig. 8), is a main biologically active substance of the roots of the Chinese medicinal plant *Salvia miltiorrhiza*. Diterpene **32** is used in the treatment of cardiovascular diseases, diabetes, arthritis, sepsis, and also as a a chemotherapeutic drug.[27] Antiviral activity of two promising agents from the studied natural compounds, tanshinone IIA and carnosic acid, against SARS-CoV-2 virus was studied. For diterpene compound **32**, the values of IC_{50} = 4 ng mL^{-1} and SI = 14 were found in the assay using hCoV-19/Egypt/NRC-03/2020 strain on Vero cells. The authors carried out a preliminary study of the mechanism of action using virology and molecular modeling methods and suggested that tanshinon IIA has the most pronounced inhibitory effect on virus adsorption, rather than on its replication. Further advanced clinical studies were recommended for tanshinone IIA to be applied for the treatment of COVID-19 either alone or in combination with carnosic acid or a polyphenol (rosmarinic acid).[28] Derivative of tanshinone IIA **33**, isolated from the rhizomes of *Salvia miltiorrhiza*, showed moderate inhibitory activity against herpes simplex virus type 1 (HSV-1) and influenza A virus H3N2.[29]

Another major ingredient of the diterpene structure, cryptotanshinone (**34**), was also isolated from *Salvia miltiorrhiza* (see Fig. 8). Its spectrum of biological activities is close to that of tanshinone IIA, particularly when used in the treatment of cardiovascular and inflammatory diseases.[30] Biotransformations of cryptotanshinone by the fungus *Mucor rouxii* produced 7 metabolites, which were evaluated for their anti-influenza A virus activity.[31] Compounds **35**, **36** and cryptotanshinone (**34**) showed noticeable activity: at a concentration of 10 μM, the inhibition of the influenza virus was 98, 96, and 97%, respectively, with reduced cytotoxicity of the derivatives compared to the starting quinone (CC_{50} values were >40, 40 and 7.6 μM). Analogues of cryptotanshinone were also isolated from the cell cultures of *Salvia miltiorrhiza*.[32] Compounds **37** and **38** demonstrated considerable activity against HIV-1 with IC_{50} values of 0.03 and 1.2 μM, respectively. It was found that compound **37** inhibits the HIV-1 replication by blocking the virus transcription.

Sugiol (**39**) is an abietane diterpenoid isolated from *Metasequoia glyptostroboides* (Fig. 9). Publication[33] indicates that sugiol is considered a promising anti-influenza agent, as confirmed by its high antiviral activity (IC_{50} = 1.6 μM) against the H1N1 influenza virus. Among previously known and first discovered diterpenoids isolated from *Isodon lophanthoides*, compound **40** is the most active



Compound	IC_{50}, μM		
	HSV-1	H3N2	HIV-1
33	11.1	8.6	–
37	–	–	0.03
38	–	–	1.2

Figure 8. Structures of tanshinone IIA (**32**), cryptotanshinone (**34**) and their derivatives **33**, **35**–**38**, and antiviral activity of compounds **33**, **37** and **38**.[29,31,32]

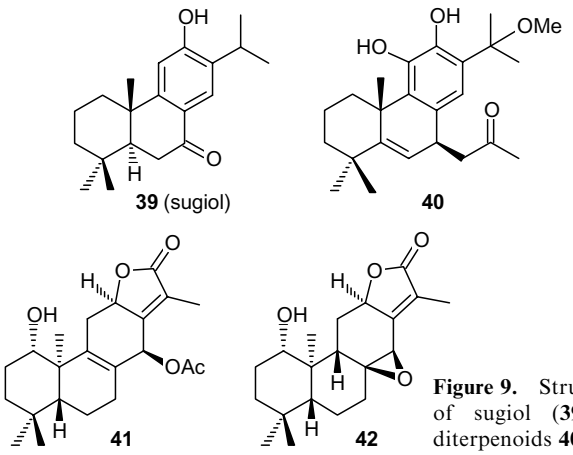


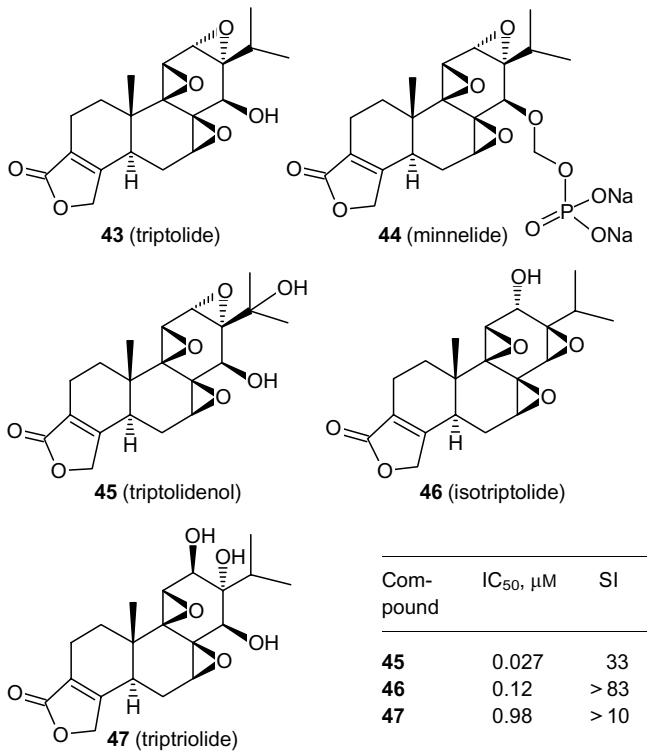
Figure 9. Structures of sugiol (**39**) and diterpenoids **40**–**42**.[33]

against hepatitis B surface antigen B HBsAg ($IC_{50} < 0.02$ μM, SI > 3) in hepatoblastoma cells Hep G 2.2.15.[34] Among 18 novel diterpenoids of *Euphorbia neriifolia*, compounds **41** and **42** showed significant antiviral effect on HIV-1 in the MT4 cell lines with IC_{50} values of 3.6 (SI = 8.6) and 7.4 μM (SI = 10.3), respectively.[35]

Special attention should be given to a diterpene compoud such as triptolide (**43**) (Fig. 10), which is 18(4→3)-*abeo*-abietane isolated from the perennial vine of Celastraceae family (*Tripterygium wilfordii*).[36, 37] This plant is referred to as Thunder God Vine, probably because it is quite poisonous.[38] Back in the 1930s, it was used as an insecticide, and since the 1960s it was considered as a promising medicinal herb employed, *e.g.*, in the traditional Chinese medicine to improve immunity and also against rheumatoid arthritis and cancer. Isharwal *et al.*[39] prepared its water-soluble analogue, minnelide (**44**), which is currently at the stage of clinical trials. In addition to high cytotoxicity, triptolide displays significant activity against HIV-1 and Dengue virus,[40] and also potential therapeutic targets for this compounds were identified.[41] Thus, triptolide acts as an inhibitor of transcription and replication of the HIV-1 genome by prompting the proteasomal degradation of the viral protein. Ni *et al.*[42] isolated 18(4→3)-*abeo*-abietanes, both novel and previously reported, from the leaves of *Tripterygium wilfordii*. Triptolidenol (**45**), isotriptolide (**46**) and triptriolide (**47**) exhibited inhibitory effects on HIV-1 replication with IC_{50} values in the range of 0.027–0.98 μM. For the first two compounds, a significant inhibition of the NO production was also found (see Fig 10).

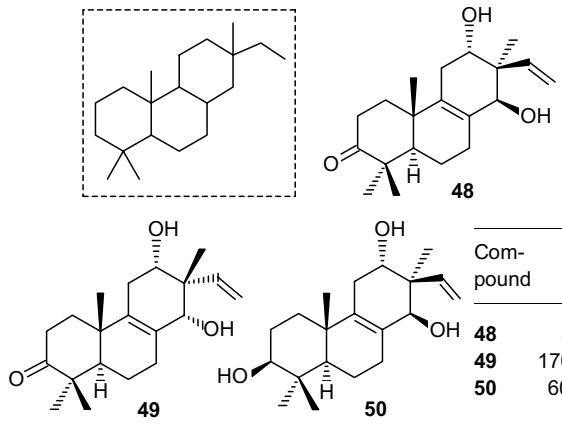
When searching for antiviral agents, special attention is paid to diterpenes isolated from plants of the genus *Euphorbia* of the Euphorbiaceae family. Euphorbia was known in ancient Egypt, Greece and Rome, where the healing properties of the milky juice of this plant were widely used. A review[43] should be mentioned on diterpene compounds occurring in plants of the Euphorbiaceae family, which contains a description of the structures of *Euphorbia* diterpenoids of plants and detailed information on their various biological activities, primarily antitumour. The review[44] considers diterpenes isolated from *Jatropha* plants of the Euphorbiaceae family. Specialists in the field of medicinal chemistry pay close attention to the strategy of searching for cytotoxic agents among plants and their components.[45] Also, of great interest to virologists are compounds that show activity against cancer cells and inhibit the virus.

In the present review, representatives of *Euphorbia* diterpenoids having a pronounced antiviral activity are only considered. Thus, diterpene alcohols with pimarane skeleton were isolated from the *Excoecaria acerifolia* plant belonging to the Euphorbiaceae family, which is quite widespread in the hot dry valleys of China's provinces.[46] These compounds were evaluated for their anti-HIV-1 bioactivity, and it was found that agent **48** is active against this virus with the selectivity index of 113 (Fig. 11).[47] For the compound to be active, the spatial arrangement of substituents in the pimaran skeleton and the presence of a keto group in the ring A are essential. Isomeric compound



Compound	IC_{50}, μM	SI
45	0.027	33
46	0.12	> 83
47	0.98	> 10

Figure 10. Structures of triptolide (**43**), minnelide (**44**), triptolidenol (**45**), isotriptolide (**46**) and triptriolide (**47**), and anti-HIV-1 activity of compounds **45**–**47**.[42]



Compound	IC_{50}, μM (SI)
48	5.6 (113)
49	170 (3.7)
50	60.1 (2.7)

Figure 11. Pimarane-type carbon skeleton (in the frame), structures and anti-HIV-1 activity of diterpene alcohols **48**–**50** with pimarane skeleton.[47]

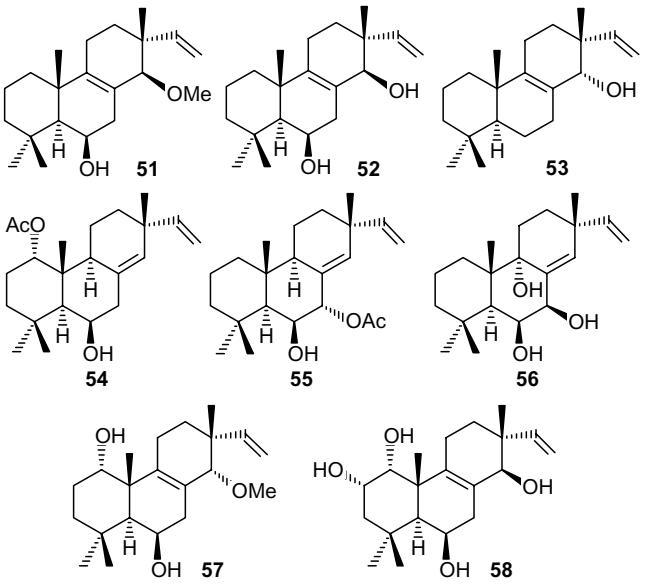


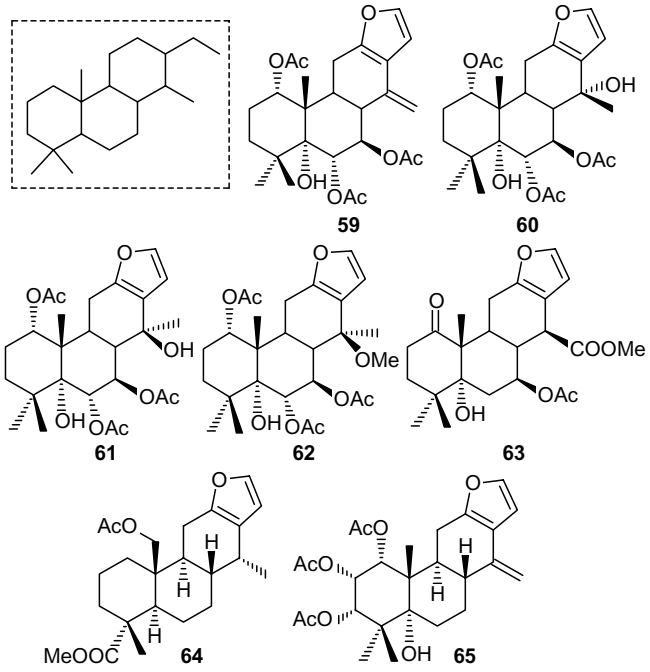
Figure 12. Structures of isopimarane diterpenoids **51**–**58** isolated from *Kaempferia pulchra*.[49]

49 with the same toxicity (~630 μM) is almost inactive, while for triol **50**, the latter noticeably decreases with increasing toxicity. The authors did not study the mechanism of antiviral action.

The medicinal plant *Kaempferia pulchra*, native to Myanmar, is of interest as part of adjuvant therapy in the treatment of AIDS.[48] It was found that chloroform-soluble extract of the rhizomes of this plant has an inhibitory effect on the activity of the viral protein R (Vpr) gene, which is an auxiliary gene of HIV-1, determines the synthesis of the Vpr and plays an important role in viral pathogenesis. From this extract, 30 isopimarane diterpenoids were isolated, of which compounds **51**–**56** (Fig. 12) significantly inhibited the activity of this gene in Vpr-induced cells in the concentration range from 1.56 to 6.25 μM.[49] Based on this findings, it was suggested that the presence of the C(14)-hydroxy group in the isopimara-8(9),15-diene skeleton and an acetoxy group at C(1) or C(7) in the isopimara-8(14),15 skeleton favours inhibition. In a follow-up study,[50] six novel isopimarane diterpenoids were isolated from ethyl acetate-soluble extract of the rhizomes of *Kaempferia pulchra*, and their Vpr inhibitory activities were evaluated. Compounds **57** and **58** were the most potent inhibitors. It can be assued that the presence of hydroxy groups at positions 4 and 10 of the natural backbone is essential for the manifestation of the said activity.

3. Cassane and rosane type diterpenoids and podocarpane derivatives

Cassane diterpenoids are generally rather toxic and in non-toxic doses show various physiological activities; some of these compounds are of interest as anti-inflammatory and cardiovascular drugs.[51] A number of cassane furanoditerpenes have previously been isolated from *Caesalpinia minax*.[52] It was shown that diterpenes **59**–**62** are highly potent against parainfluenza virus type 3 (PIV3), capable of causing acute respiratory viral infection (Fig. 13). Selectivity indices for these compounds ranges from 16 to 24 and are comparable with that for ribavirin (SI = 24).



Compound	PIV3		Compound	IC_{50}, μM (SI)	
	IC_{50}, μM	SI		PIV3	H5N1
59	8.2	24	**62**	7.8 (18)	–
60	9.6	19	**63**	–	29
61	10.3	16	**64**	–	24

Figure 13. Cassane-type skeleton, structures and antiviral activity of furane diterpenoids **59**–**65** isolated from plants of the genus *Caesalpinia*.[52–54]

Seven novel cassane furanoditerpenes were isolated from the seeds of *Caesalpinia minax*.[53] These compounds showed antiviral effect *in vitro* due to the moderate inhibition of activity of influenza A H5N1 virus neuraminidase, which is an important surface viral protein, with compound **63** being the most active (IC_{50} = 29 μM). Among compounds isolated from the roots of *Caesalpinia decapetala*, cassane type diterpene **64** (IC_{50} = 24 μM) exhibited the highest neuraminidase inhibitory activity.[54] Another 13 cassan type diterpenes were isolated from the seeds of *Caesalpinia decapetala*.[55] The highest antiviral activity against tobacco mosaic virus that infects plants of the Solanacea family was revealed in compound **65** (at 500 μg mL^{-1} it showed 30.2% inactivation and 37.6% protection effect), which is comparable to the effect of ribavirin (39.4 and 38.1%, respectively).

From the acetone extract of the dried aerial part of *Euphorbia milii*, 13 *ent*-rosane diterpenoids were isolated and their effects on the Epstein–Barr virus DNA replication were evaluated.[56] Compounds **66** and **67** (Fig. 14) proved to be the most potent inhibitors with IC_{50} values of 5.4 and 29.1 μM, and SI values exceeding 9.3 and 6.9, respectively.

When searching for anti-influenza A agents, several diterpenoids were selected including (+)-podocarpic acid (**68**) belonging to the group of tri-*nor*-abietane metabolites (Fig. 15).[57] A series of podocarpic acid derivatives were synthesized and their activity against an H1N1 influenza A

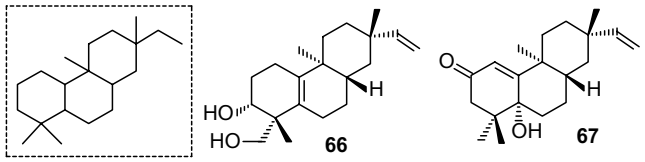
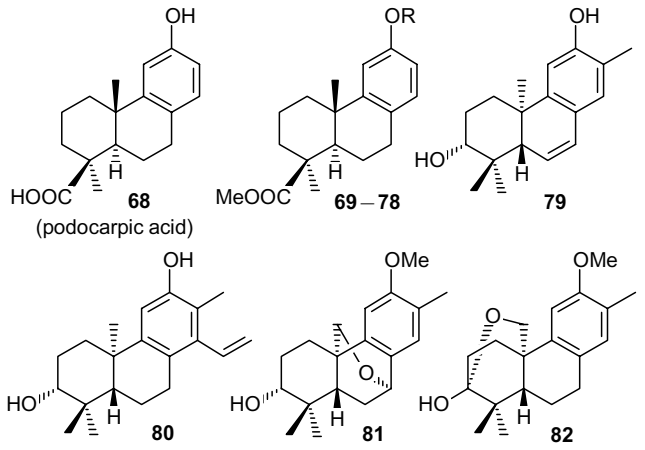


Figure 14. Rosane-type skeleton (in the frame) and structures of *ent*-rosane diterpenoids **66** and **67** isolated from *Euphorbia milii*.[56]



Compound	R	IC_{50} (H1N1), μM	CC_{50}, μM
68		18.2	91.2
69	H	0.16	> 40
70	$COCH{=}CH_2$	0.64	> 40
71	$CO(CH_2)_2CO_2H$	0.18	> 40
72	$CO(CH_2)_3CO_2H$	0.37	> 40
73	$CO(CH_2)_2Br$	0.21	> 40
74	$CO(CH_2)_3Br$	0.57	> 40
75	$CO(CH_2)_4Br$	0.42	> 40
76	$COPr^i$	0.32	> 40
77	$COCHMeCH_2F$	0.15	> 40
78	Ac	0.14	> 40
Oseltamivir		> 20	

Compound	IC_{50} (HCV), μM	SI	Compound	IC_{50} (HCV), μM	SI
79	5.6	9.8	**81**	7.5	55.9
80	5.0	10.5	**82**	6.6	45.0

Figure 15. Structures and antiviral activity of podocarpic acid (**68**), its derivatives **69**–**78** and norditerpenes **79**–**82** isolated from *Flueggea virosa*.[57, 58]

virus resistant to antiviral drugs, oseltamivir and amantadine was evaluated. According to the authors, methyl podocarpate (**69**) and its derivatives **70**–**78** can be considered as potential drugs for the treatment of some strains of the influenza A virus that are resistant to therapeutics; benzyl ester and its derivatives showed much less activity against this virus. Methyl podocarpate (**69**) and its *O*-acetyl derivative **78** exhibited the highest activity against oseltamivir-resistant H1N1 influenza A virus. Based on the study of the mechanism of action of the resultant antiviral agents, it was assumed that podocarpic acid derivatives are inhibitors of hemagglutinin (HA), the influenza virus surface glycoprotein crucial for the viral entry.

Norditerpenoids, both novel and previously known, were isolated from the roots of *Flueggea virosa* of the Phyllanthaceae family, some of which showed significant activity against hepatitis C virus (HCV).[58] Thus, 13-methyl-*ent*-podocarpanes **79**–**82** can be considered promising drugs for the treatment of hepatitis.

4. Atisane and kaurane type diterpenoids

Atisane and kaurane type diterpene compounds have a tetracyclic scaffold. Five previously unknown atisane diterpenes (in addition to 9 already reported) were isolated from the ethanolic extract of the whole plant *Spiraea japonica*.[59] Among these compounds, diterpenoids **83** showed significant anti-tobacco mosaic virus activity (at 100 μg mL^{-1}, 93% protection and 41% therapeutic inhibitory effects were observed), **84** (87 and 21%) and **85** (85 and 48%), not inferior to the effect of a conventional antiviral agent, ningnanmycin (48 and 51%, respectively) (Fig. 16).

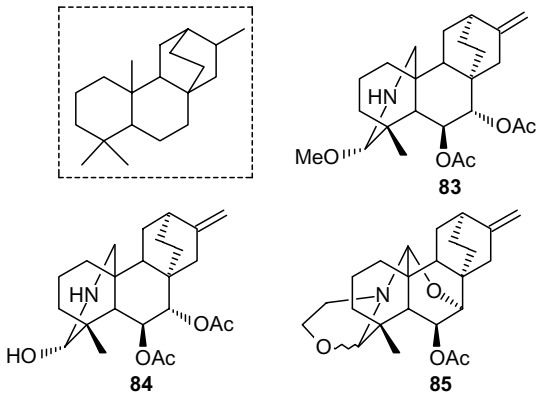
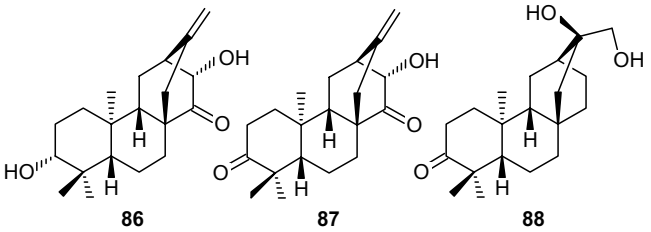
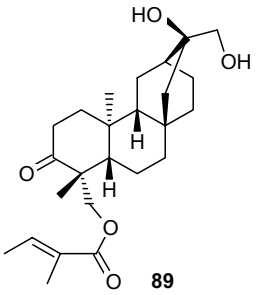


Figure 16. Atisane-type skeleton (in the frame) and structures of diterpenoids **83**–**85** isolated from *Spiraea japonica*.

Diterpenoids of the *ent*-atisane type were isolated from the roots of *Euphorbia ebracteolata*.[60] Compounds **86** and **87** (Fig. 17) displayed moderate antiviral activity against human rhinovirus 3 (HRV3), and against epidemic-prone pathogenic enterovirus 71 at a concentration of 100 μM. Diterpenoids of the *ent*-atisane type were also isolated from *Euphorbia neriifolia*.[61] Compounds **88** and **89** showed significant anti-HIV-1 activity. It should be noted that these agents were isolated in microgram amounts from more than 20 kg of plant material.

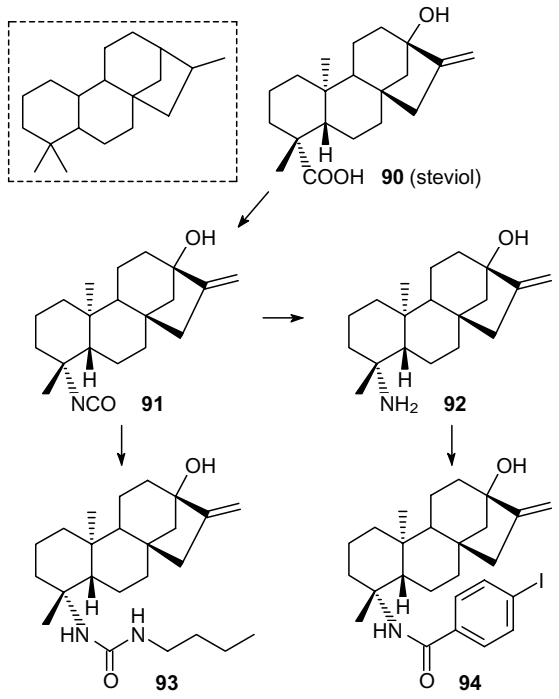
Of particular interest are studies of chemical modification of steviol (**90**), a tetracyclic kaurane diterpenoid (Fig. 18). This diterpenoid can be easily obtained from the known glycoside stevioside used as a sweetener. The reactivity of steviol, due to the presence of functional substituents and a double bond, draws attention to both this compound and its analogues. Modification of a carboxy group of steviol *via* the formation of isocyanate **91** and amine **92** gave a number of ureas and amides.[62] n-Butyl-substituted compound **93** displayed a significant inhibitory effect on the replication of hepatitis B virus (HBV), showing the highest selectivity index (SI = 58). Activity displayed by steviol (SI = 24) and amide **94** (SI = 19) bearing *p*-iodoben-





Compound	IC_{50}	
	HRV3, μM	HIV-1 μg mL^{-1}
86	49	–
87	25	–
88	–	6.6
89	–	6.4

Figure 17. Structures and antiviral activity of *ent*-atisane diterpenoids **86**–**89** isolated from plants of the genus *Euphorbia*.[60,61]



Compound	IC_{50}, μM	SI	Compound	IC_{50}, μM	SI
90	19.9	24	**93**	16.9	58
91	30.0	11	**94**	21.9	19
92	35.8	4.7			

Figure 18. Kaurane-type skeleton (in the frame), and also structures and anti-hepatitis B activity of steviol (**90**) and derivaties **91**–**94**.[62]

zylamide moiety was comparably to that of the lamivudine positive control (SI = 22). Based on these data, it was assumed for the lead compound of the synthesized library, that the inhibition mechanism may occur by a signaling pathway, the central component of which is the transcription factor NF-κB. The results of biological assays indicate

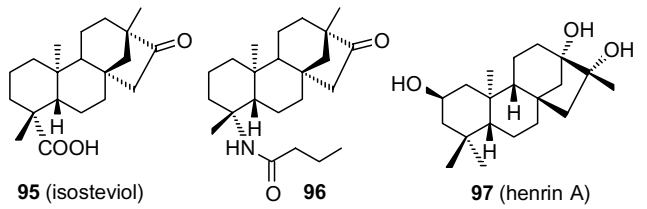


Figure 19. Structures of isosteviol (**95**), derivative **96** and henrin A (**97**).

that agent **93** can reduce the overall expression of NF-κB-related proteins, phosphorylation and subsequent activation. Moreover, compound **93** downregulates expression of the MAPK signaling pathway and proteins associated with this signaling pathway, inhibiting their phosphorylation. In general, it should be noted that the synthetic strategy for diterpene derivatives using the corresponding isocyanates and amines is a promising trend in the search for novel antiviral agents.

Acid hydrolysis of stevioside affords another diterpenoid, isosteviol (**95**) (Fig. 19), the similar modification of a carboxy group in which gave rise to a number of amines.[63] Compound **96** exhibited significant inhibitory activity against secretion of HBsAg (SI = 6.3) and hepatitis B virus replication with the highest selectivity index (SI = 11.4). For amide **96** it was established that the transcription factor NF-κB also plays a central role in the hepatitis B virus inhibition. At the same time, a comparison of the biological activity of isosteviol derivatives with similar steviol-based compounds shows that the use of diterpene alcohol, steviol (**90**), as the starting molecule is more effective.

Henrin A (**97**), a tetracyclic *ent*-kaurane diterpenoid, was isolated from the methanolic extract of the fern leaves of *Pteris henryi* (see Fig. 19).[64] It was found that this triol has low cytotoxicity and shows activity (IC_{50} = 9.1 μM) against the pseudoviral system responsible for the late stages of the HIV replication with selectivity index of 12.2. The authors did not study the mechanism of action in more detail.

Several *ent*-kaurane diterpenoids were isolated from the aerial parts of *Rabdosia japonica*.[65] Some of them displayed anti-hepatitis B activity; compound **98** (Fig. 20) showed a significant inhibitory effect (59%) on HBsAg secretion at a concentration of 20 μg mL^{-1}. Based on experimental data, oridonin (**99**) was distinguished as a promising substrate for the development of antiviral drugs inhibiting the function of Nsp9-replicase during coronavirus SARS-CoV-2 replication.[66]

Eight known *ent*-kaurane diterpenoids were isolated from the aerial parts of *Sideritis lycia*.[67] The whole acetone extract and several compounds showed inhibitory activity

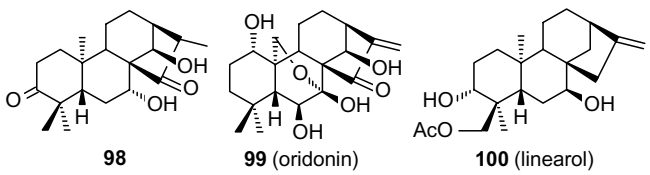
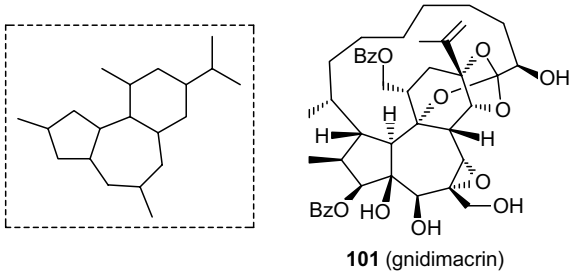


Figure 20. Structures of *ent*-kaurane diterpenoids **98**–**100**.

against human parainfluenza virus type 2 but with low selectivity index, which was 2.3 for linearol (**100**).

5. Daphnane type diterpenoids

Tigliane and daphnane diterpenoids have similar carbon skeletons. Particularly noteworthy is gnidimacrin (**101**), the natural daphnane type diterpenoid with more complex structure, isolated from the roots of *Stellera chamaejasme* of the Thymelaeaceae family, which exhibit very high anti-HIV-1 activity (Fig. 21).[68] The data of the study [69] indicate that gnidimacrin can activate HIV-1 in the latent stage of the disease, specifically kill cells infected with this virus, and inhibit HIV in picomolar concentrations (1 – 50 pM). It was suggested that this diterpenoid could lead to eradication of the virus and a cure for HIV infection. The use of the combination of gnidimacrin, which is a protein kinase C agonist, and histone deacetylase inhibitor not only reduces the required concentration of gnidimacrin, but also mitigate its side effects.[70]

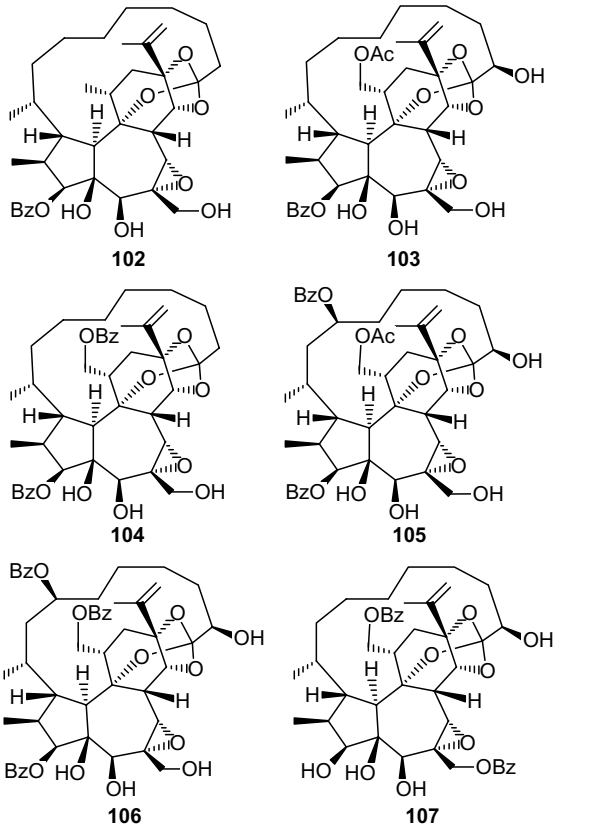


101 (gnidimacrin)

Figure 21. Daphnane-type skeleton (in the frame) and structure of gnidimacrin (**101**).

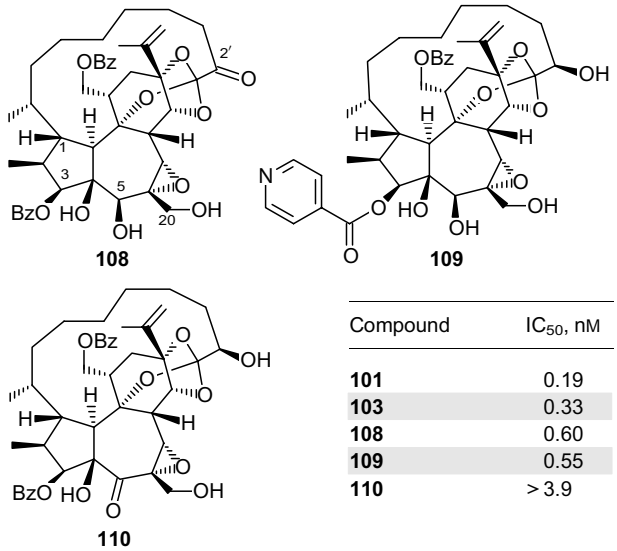
Gnidimacrin and several analogues thereof were isolated from the methanolic extract of the roots of *Stellera chamaejasme*.[71] Gnidimacrin, the previously known compound **102** and two novel diterpenoids **103** and **104** (Fig. 22) showed extremely high potency against HIV-1 with IC_{90} values of 0.4, 1.4, 0.4 and 1.6 nM, respectively, and relatively low cytotoxicity ($CC_{50} \geqslant 2.8$ μM). Gnidimacrin analogues **105** – **107** isolated from petroleum ether extract of the roots of *Stellera chamaejasme* showed similar unique activity against human immunodeficiency virus.[72] Compounds **105** – **107** and agent **102** displayed anti-HIV-1 potency in a nanomolar concentration (~1 nM) with the SI values in a range of 12 900 – 15 300; for gnidimacrin, selectivity index was equal to 21 500, while for the positive control it was as low as 116.

To search for agents that reverse the viral latency period and are capable of reactivating latent HIV, in addition to the inhibitory concentration of HIV replication, the concentrations at which 50% activation of the latent virus is achieved were also calculated. Comparison of these values for 20 diterpenoids isolated from *Stellera chamaejasme* and *Wikstroemia retusa*, and their 8 derivatives demonstrated the highest activity of gnidimacrin (IC_{50} = 0.19 nM) and diterpenoid **103** (IC_{50} = 0.33 nM).[73] It was noted that the potency of such compounds depend on the nature of substituents in the five-membered ring and decreases when it is devoid of a hydroxy group at the 2′-position. Various derivatives of gnidimacrin were prepared *via* esterification and modification of hydroxy groups, and IC_{50} values were



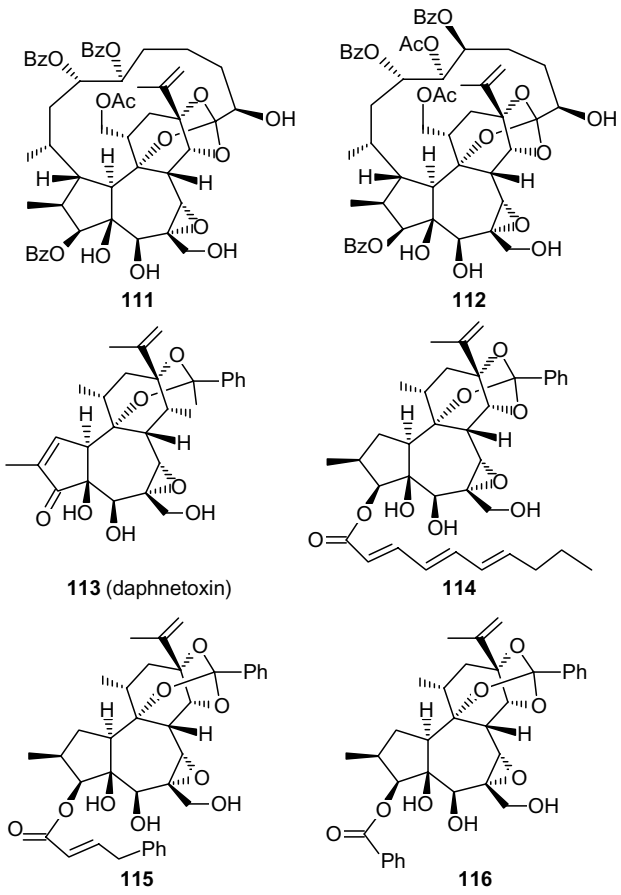
Compound	IC_{50}, nM	SI	Compound	IC_{50}, nM	SI
101	0.06	21 500	**106**	0.73	15 300
102	1.1	14 300	**107**	0.98	13 200
105	0.93	12 900			

Figure 22. Structures and anti-HIV-1 activity of gnidimacrin analogues **102** – **107** isolated from *Stellera chamaejasme*.[71, 72]



Compound	IC_{50}, nM
101	0.19
103	0.33
108	0.60
109	0.55
110	> 3.9

Figure 23. Structures of gnidimacrin derivatives **108** – **110** and anti-HIV-1 activity of compounds **101**, **103**, **108** – **110**.[74]



Compound	IC_{50}, nM	SI	Compound	IC_{50}, nM	SI
111	0.16	156	**115**	1.46	86 000
112	0.25	100	**116**	0.17	187 000
114	0.82	111 000			

Figure 24. Structures and anti-HIV-1 activity of daphnane-type diterpenoids **111**–**116** isolated from the plants of the genus *Daphne*.[75–77]

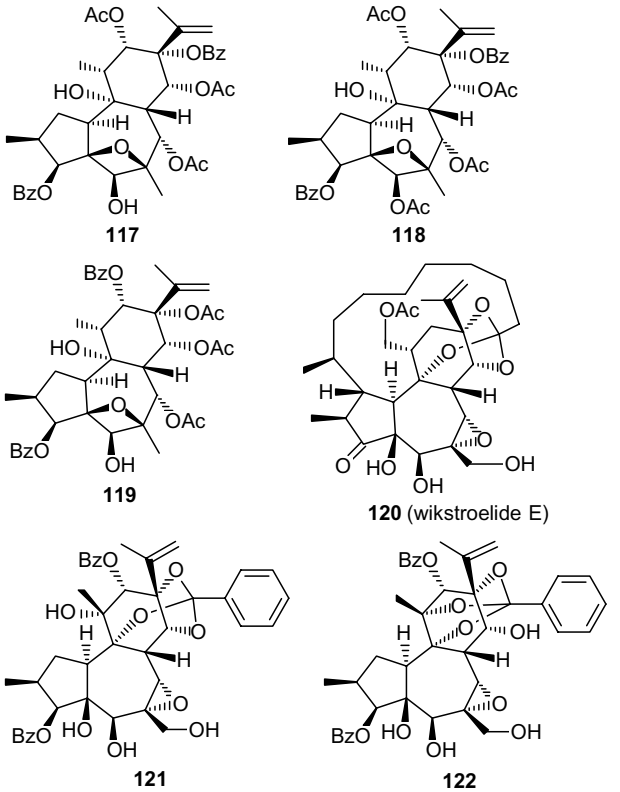
measured for compounds **108**–**110** (Fig. 23).[74] Based on this findings and activity values against HIV-1 replication, the importance of the 5- and 20-positioned free hydroxy group for the antiviral effect to occur was stressed.

In addition to gnidimacrin, three novel macrocyclic daphnane diterpenoids were isolated from *Daphne odora* of Thymelaeaceae family, and their anti-HIV-1 activity was evaluated in the MT4 cell line.[75] Like gnidimacrin (**101**), compounds **111**, **112** (Fig. 24) considerably inhibited HIV-1 replication with IC_{50} values of 0.16, 0.25 and 0.06 nM, respectively. The presence of benzoyloxy moiety at the 20-position instead of 3-position reduces the antiviral activity of this derivative. Daphnetoxin (**113**) isolated from the extract of the aerial part of *Daphne gnidium*, showed sifnificant inhibitory potency against multiresistant HIV strains ($IC_{50} \approx 20$ nM).[76] Based on the studies of the mechanism of action of this compound, its direct interference with the expression of two main HIV co-receptors was suggested. Several daphnane diterpenoids were derived from the ethyl acetate extract of *Daphne acutiloba*.[77] Significant inhibition of the cytopathic effect (direct pathogenic effect) of HIV-1 ($IC_{50} < 1.5$ nM) was observed in 9 compounds, and diterpenoids **114**–**116** were active at subnanomolar concentrations and their selectivity indices were $> 86\,000$.

Three novel and several previouly known daphnane diterpenoids were isolated from the stems and leaves of *Wikstroemia chuii* of Thymelaeaceae family.[78] All compounds both had antiiflammatory activity and showed significant effect ahainst HIV-1 reverse transcriptase, that is essential for the retrovirus life cycle. Previously unknown diterpenoids **117**–**119** displayed significant anti-HIV-1 potency ($IC_{50} \leqslant 0.21$ μM) with SI > 930 (Fig. 25). Wikstroelide E (**120**) derived from the buds of *Wikstroemia chamaedaphne*, proved to be very promising HIV-latency reversing agent. It was 2500-fold more potent than the used tigliane diterpenoid prostratine.[79] It was found that the NF-κB and JAK-STAT signaling pathways are involved in the reactivation of latent HIV in cells treated with compound **120**.

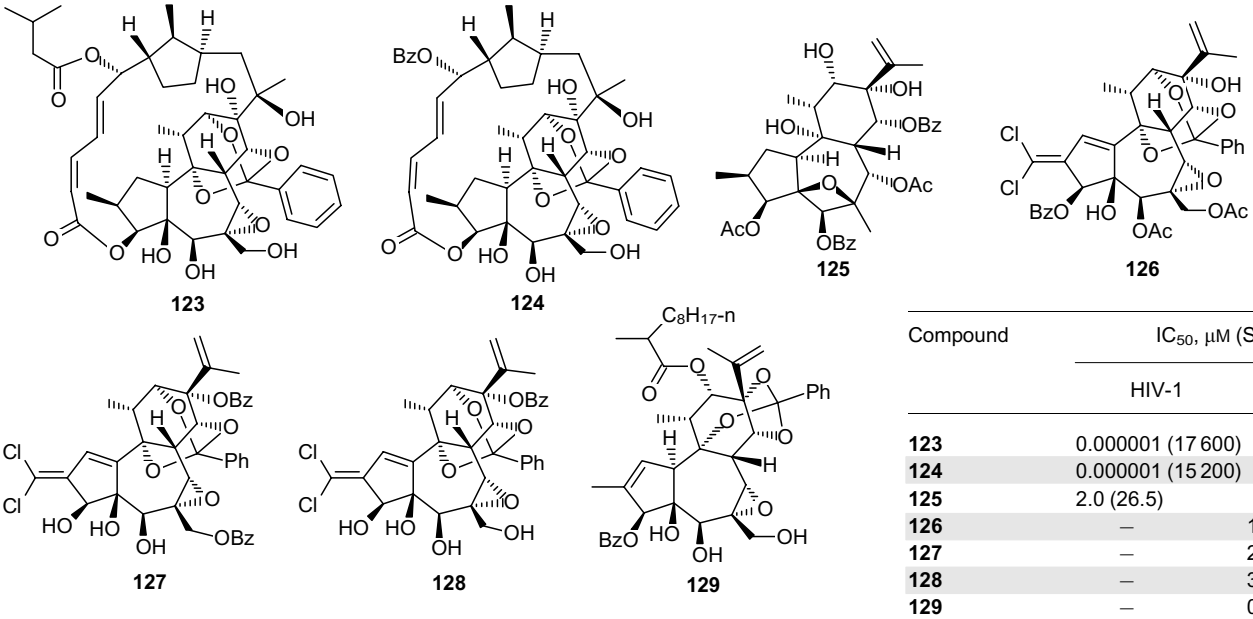
Two novel daphnane diterpenoids were isolated from the bark extract of *Codiaeum peltatum*.[80] Compounds **121** and **122** showed activity against Chikungunya virus, comparable to that of the well-known drug chloroquine.

A large number (31 compounds) of daphnane diterpenoids were derived from the methanolic extract of the leaves and twigs of *Trigonostemon thyrsoideum* of the Euphorbia-



Compound	HIV-1		Compound	CHIKV	
	IC_{50}, μM	SI		IC_{50}, μM	SI
117	0.095	2100	**121**	10.0	5
118	0.18	1090	**122**	4.4	11
119	0.21	930	Chloroquine	11	8

Figure 25. Structures and antiviral activity of daphnane-type diterpenoids **117**–**122** isolated from the plants of the genus *Wikstroemia* and from *Codiaeum peltatum*.[78, 80]



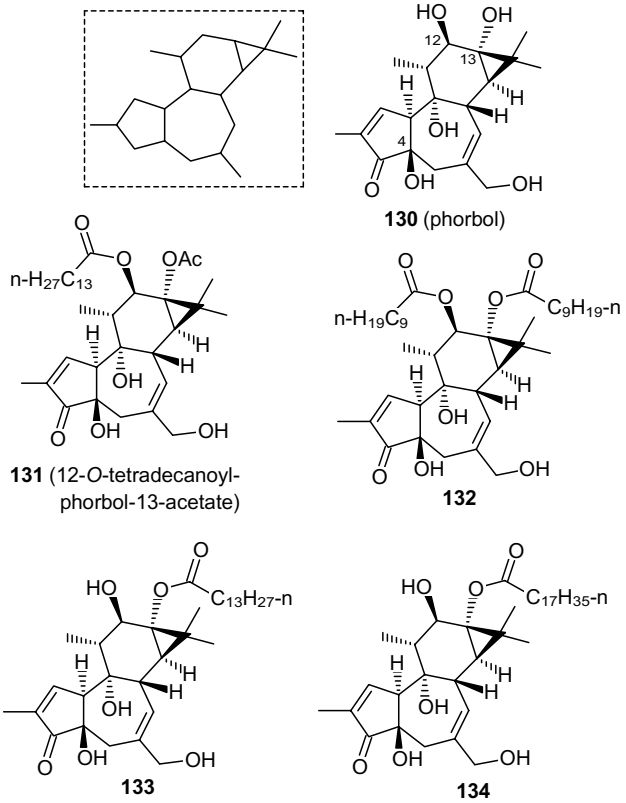
Compound	IC_{50}, μM (SI)	
	HIV-1	CHIKV
123	0.000001 (17 600)	–
124	0.000001 (15 200)	–
125	2.0 (26.5)	–
126	–	1.5 (24)
127	–	2.6 (35)
128	–	3.0 (7.7)
129	–	0.6 (72)

Figure 26. Structures and antiviral activity of daphnane-type diterpenoids **123**–**129** isolated from the plants of the genus *Trigonostemon*.[81–85]

ceae family.[81] These diterpenoids were evaluated for their anti-HIV-1 activity *in vitro*. Five compounds showed extremely high antiviral activity ($IC_{50} \leqslant 0.015$ nM, SI > 1600), maximum values were observed in derivatives **123** and **124** (IC_{50} = 0.001 nM, SI > 15 200) (Fig. 26). The anti-HIV-1 activity of daphnane diterpenoids isolated from the stems of *Trigonostemon lii* was evaluated.[82] These compounds demonstrated moderate activity with compound **125** (IC_{50} = 2 μM, SI = 26.5) being the most potent. Chlorinated daphnane type orthoesters were isolated from the bark and the wood of *Trigonostemon cherrieri*, an endemic plant of New Caledonia.[83] Compounds **126**–**128** displayed activity against Sindbis virus and proved to be effective and selective inhibitors of Chikungunya virus replication ($IC_{50} \leqslant 3$ μM, SI $\geqslant$ 7.7). Compounds **126** (SI = 24) was 3 times more potent than the reference compound chloroquine (SI = 8).[84] Also, the leaves of *Trigonostemon cherrieri* afforded, in addition to chlorinated diterpenoids, orthoester **129**, which proved to be very potent and selective inhibitor of Chikungunya virus replication.[85]

6. Tigliane type diterpenoids

Daphnane, ingenane or tigliane diterpenoids, derived from various plants of the Euphorbiaceae family, attract special attention of researchers after the discovery of high activity of these compounds on tumour cells. A review paper[86] is decicated to isolation, elucidation of the structure and description of the pharmaceutical potential of tigliane diterpenoids — phorbol esters. Phorbol (**130**) is a plant-derived compound that was first isolated in 1934 as a hydrolysis product of croton oil obtained from the seeds of *Croton tiglium* (Fig. 27). The most common phorbol ester is 12-*O*-tetradecanoylphorbol-13-acetate, or phorbol-12-myristate-13-acetate (**131**), used in biomedical research in models of carcinogenesis. This diterpenoid is a known natural irritant.



Compound	IC_{50}, nM (SI)	
	HIV-1	CHIKV
131	0.9 (20 200)	2.9 (1965)
132	1.2 (13 750)	6.0 (686)

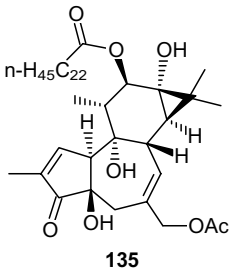
Compound	IC_{50}, nM (HIV-1)
133	60
134	30

Figure 27. Tigliane-type skeleton (in the frame), structures of phorbol (**130**) and its esters **131**–**134**, and their antiviral activity.[87,88]

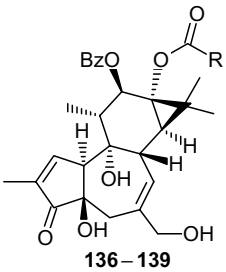
It was found that phorbol *per se* has no antiviral effect, however, its esterified derivatives **131** and **132** showed significant activity ($IC_{50} \leqslant 6$ nM) against Chikungunya virus with selectivity indices of 1965 and 686, respectively (see Fig. 27).[87] Also, these compounds were very potent inhibitors of HIV-1 and HIV-2 replication *in vitro* at nanomolar concentrations with high selectivity (SI > 13 700). It was found that the spatial location of a hydroxy group at the 4-position (4β-derivatives are far more potent than 4α-epimers) and the carbon chain length at the 12-positioned oxygen atom (particularly, the presence of a substituent comprising at least 10 carbon atoms) significantly affect the antiviral activity. A library of phorbols esterified on the 13-hydroxy group is described and it was found that the elongation of the substituent chain improves the anti-HIV-1 activity of the derivatives. Thus, the most potent were phorbol myristate (**133**) and stearate (**134**) with IC_{50} values of 0.06 and 0.03 μM, respectively.[88] The authors indicate that phorbol 13-monoesters bearing medium or long aliphatic residues of fatty acids are potent antagonists of HIV-1 latency acting *via* protein kinase-dependent NF-κB activation.

Twigs and leaves of *Ostodes katharinae* of the Euphorbiaceae family afforded previously unknown phorbol ester **135** (Fig. 28).[89] This compound suppresses replication of HIV-1 and HIV-2 strains, including resistent ones, with IC_{50} values ranging from 0.1 to 8.0 μM with low cytotoxicity. For ester **135**, a new mechanism for the inhibition of HIV replication in cells was established, involving stimulation of APOBEC3G exression, which reduces the infectivity of the progeny virus. Phorbol esters were also isolated from the roots of *Stellera chamaejasme* of the Thymelaeaceae family.[90] Stellerarin (**136**) and esters **137**–**139** showed significant anti-HIV-1 activity (IC_{90} = 0.50–6.8 nM) in MT4 cell line with low cytotoxicity ($CC_{50} \geqslant 4.4$μM).

12-Deoxyphorbol-13-acetate (**140**), more commonly known as prostratin, is an effective of protein kinase C inhibitor (Fig. 29). This ester was derived from the bark of *Homalanthus nutans*, the extract of which has long been used by healers in Samoa to fight against viral hepatitis.[91] Studies of prostratin isolated from the bark of this plant showed that under laboratory conditions it both markedly suppresses the activity of HIV-1 and kills viruses in a latent



135

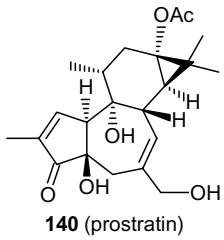


136–**139**

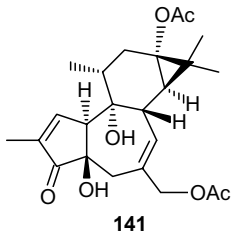
R = C_9H_{19}-n (**136**, stellerarin), C_7H_{15}-n (**137**), $(CH_2)_2(CH{=}^{Z}CH)(CH_2)_4Me$ (**138**), $(CH_2)_2(CH{=}^{Z}CH)CH_2(CH{=}^{Z}CH)Et$ (**139**)

Compound	IC_{90}, nM
136	0.50
137	0.56
138	0.66
139	6.8

Figure 28. Structures and anti-HIV-1 activity of phorbol esters **135**–**139**.[90]



140 (prostratin)

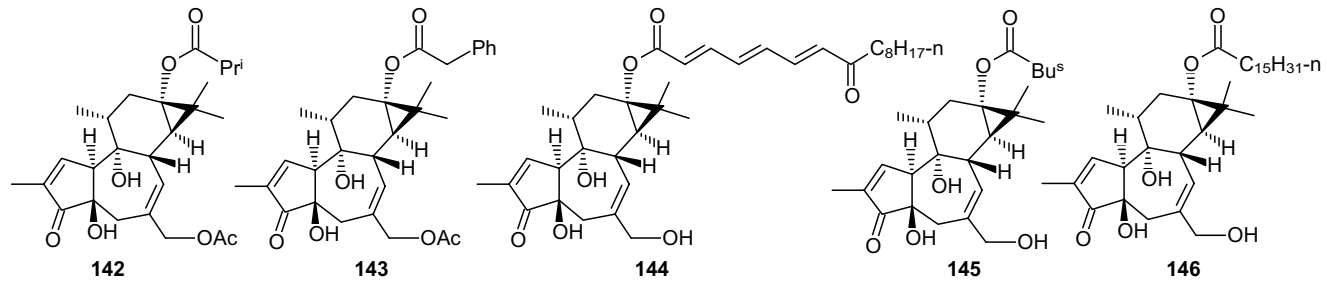


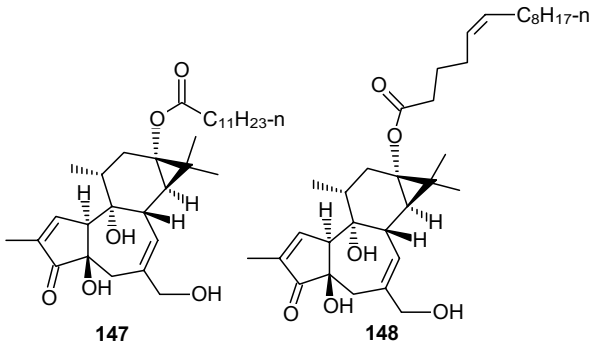
141

Figure 29. Structures of prostratin (**140**) and 12-deoxyphorbol-13,20-diacetate (**141**).

state that are not clinically detectable.[92] Since these viruses reside in so-called cellular reservoirs — the central nervous system, peripheral blood cells, lymph nodes, liver, spleen, they are not even affected by effective drugs used to combat AIDS. Due to this effect, unique properties of prostratine have attracted the attention of clinicians as well.[93] Among tigliane diterpenoids, including 20-*O*-glycosides and those derived from *Euphorbia fischeriana*, it was prostratin which showed the maximum inhibition of the cytopathic effect of HIV-1 (SI = 8500); 12-deoxyphorbol-13,20-diacetate (**141**) also exhibited high activity (SI = 366).[94] However, the presence of the 20-positioned substituent in prostratin can dramatically reduce its antiviral activity. Prostratin proved to be inactive against Sindbis virus but noticeable inhibited Chikungunya virus replication with the values of IC_{50} = 2.6 μM and SI ≈30. At the same time, 12-*O*-tetradeconoylphorbol-13-acetate (**131**) was much more potent against Chikungunya virus (IC_{50} ≈3 nM and SI ≈2000).[95] Despite the significant antiviral potential of prostratin, a very small number of works have been found in the literature on the chemical modifications of this compound while retaining its backbone, which, apparently, is associated with the high cost of this diterpenoid. The preparation of prostratin from more available phorbol[96] and a multistep synthesis of (±)-prostratin from monocyclic compounds is described.[97]

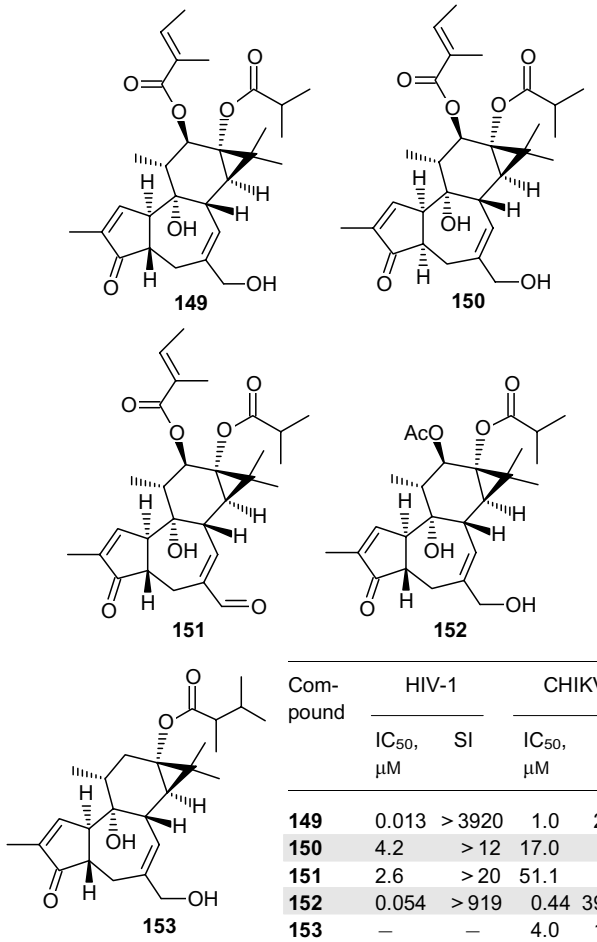
The activity of 12-deoxyphorbol esters was studied and these compouds were shown to display a pronounced antiviral effect. Thus, in the MT4 cell line, ester **142** significantly inhibits replication of HIV-1 (SI = 221) and HIV-2 (SI = 958), and ester **143** is even more potent (SI = 737 and 7818, respectively) (Fig. 30).[87] In this study, both esters were more active as compared to prostratine. Previously unknown ester **144**, isolated from the leaves of *Stillingia lineata* of the Euphorbiaceae family, shows activity against HIV-1 (SI = 299) and HIV-2 (SI = 1431), and also slight inhibitory activity against Chikungunya virus replication (SI = 5.9).[98] Ester **145** derived from the same plant exhibits activity both against HIV-1 (SI = 899) and HIV-2 (SI = 2056), and inhibits Chikungunya virus replication with a high selectivity index (> 240). 12-Deoxyphorbol derivatives were isolated from the twigs and leaves of *Reutealis trisperma* of the Euphorbiaceae family, and their anti-HIV-1 activity was evaluated in the MT4 cell line.[99] Several similar compounds displayed considerable activity, particularly, esters **146** (SI > 714) and **147** (SI > 83). This findings suggest that the presence of a carbonyl moiety at the 20-position or oxygen-containing substituents at 6- and 7-positions of diterpene decreases its anti-HIV activity. Various di- and triterpenoids were isolated from the roots of *Stillingia loranthacea*.[100] Several compounds displayed noticeable activity against Zika virus replication in Vero





Compound	HIV-1		HIV-2		CHIKV	
	IC_{50}, μM	SI	IC_{50}, μM	SI	IC_{50}, μM	SI
140	1.9	> 171	0.9	> 370	2.7	23
142	0.6	221	0.20	958	0.7	5.0
143	0.3	> 737	0.031	> 7818	51	1.9
144	0.043	299	0.018	1431	2.2	5.9
145	0.129	899	0.056	2056	1.2	> 240
146	0.0023	> 714	–	–	–	–
147	0.022	> 83	–	–	–	–

Figure 30. Structures and antiviral activity of 12-deoxyphorbol esters **142** – **148**.[87,98–100]



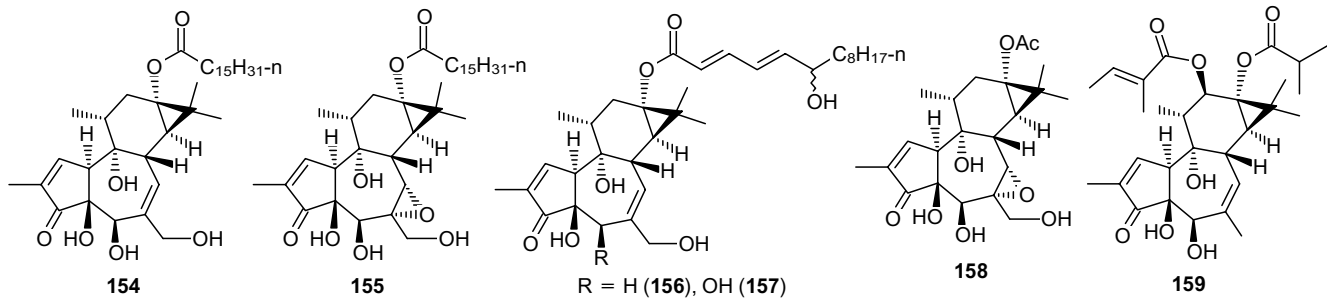
Compound	HIV-1		CHIKV	
	IC_{50}, μM	SI	IC_{50}, μM	SI
149	0.013	> 3920	1.0	25
150	4.2	> 12	17.0	7
151	2.6	> 20	51.1	3
152	0.054	> 919	0.44	390
153	–	–	4.0	10.6

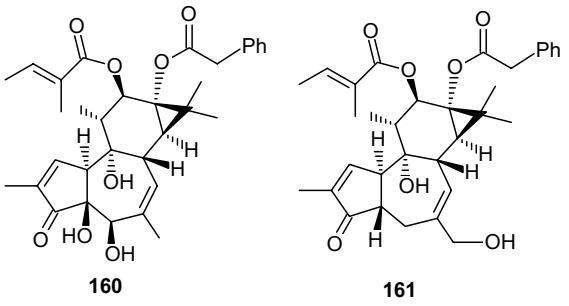
Figure 31. Structures and antiviral activity of 4-deoxyphorbol esters **149** – **153**.[101]

cells, among them, ester **148** showed the highest effect and is considered as a good candidate for the *in vivo* studies.

Using supercritical fluid chromatography, a number of terpenoids was isolated from the extract of *Euphorbia semiperfoliata*, among which four 4-deoxyphorbol derivatives **149** – **152** were identified showing antiviral activity (Fig. 31).[101] It was revealed that ester **149** is a potent and selective inhibitor of HIV-1 replication and display antiviral activity against Chikungunya virus (CHIKV). At the same time, ester **152** shows significant activity both against Chikungunya virus and HIV-1. β-Orientation of the hydrogen atom on the 4-positioned carbon is a key factor for the antiviral activity to be displayed, since compound **150** proved to be far less active. Antiviral activity also decreases considerably when a 20-positioned carbonyl moiety is present in the molecule. It was found that ester **149**, in addition to virus inhibition, can reactivate latent HIV through activating PKCθ/MEK and NF-κB, and also decreasing the size of viral reservoirs.[102] When combined with an histon deacetylase inhibitor vorinostat, compound **149** shows a consistent synergistic effect, improving the efficacy of the drug and lowering the required effective concentration of the drug. In general, this compound can be considered as an agent capable of eradicating HIV reservoirs. Esposito *et al.*[103] isolated several diterpenoids from the extract of the aerial part of *Euphorbia pithyusa* of the Euphorbiaceae family, and evaluated for their antiviral effect on Chikungunya virus. 4β-4,12-Dideoxyphorbol ester **153** was the most potent.

Among 12-deoxyphorbol derivatives, compounds **146**, **154** and **155** showed the extreme activity against Chikungunya virus with IC_{50} values in the range of 0.02 – 0.13 μM and selectivity indices in the range of 54 – 1500 (Fig. 32).[104] These compounds also proved to be very potent against HIV-1 and HIV-2: IC_{50} values were below 4 nM, and selectivity indices ranged from 4225 to 24 000.





Compound	HIV-1		HIV-2		CHIKV	
	IC_{50}, μM	SI	IC_{50}, μM	SI	IC_{50}, μM	SI
146	0.0009	16 000	0.0006	24 000	0.02	1500
154	0.002	8450	0.001	16 900	0.13	98
155	0.004	4225	0.003	5633	0.09	54
156	0.046	299	–	–	–	–
157	0.036	441	–	–	–	–
158	0.258	> 1837	–	–	–	–

Figure 32. Structures of tigliane-type diterpenoids **154**–**161** and antiviral activity of compounds **146**, **154**–**158**.[104–106]

Several tigliane and daphnane type diterpenoids were isolated from plant stem extracts of *Excoecaria acerifolia* of the Euphorbiaceae family.[105] Compounds **156**–**158** demonstrated marked anti-HIV-1 activity, with their IC_{50} values ranging from 0.036 to 0.258 μM, and selectivity indices from 299 to 1837. Also, the plausible route was also proposed for the conversion of 12-deoxyphorbol derivatives into daphnan type diterpenoids. In a study,[106] previously known compounds **159**–**161** were isolated from the sap of *Euphorbia umbellata* using a fractionated process and their ability towards HIV-1 latency reactivation *in vitro* was observed. Using ingenol B at a concentration of 2.24 μM, it was found that all compounds show significant activity (reactivation 70–75%) in the concentration ranges of 9.7–0.097, 8.8–0.088 and 9.1–0.091 μM for compounds **159**, **160** and **161**, respectively. Diterpen **161** was particularly potent. Thus, at extremely low concentration of this compound (0.091 nM), 62% reactivation of cells was achieved. Therefore, 4-deoxy-4β-phorbol-12-tiglate-13-phenyl acetate (**161**) can be considered a very promising compound for the search for novel strategies for fighting HIV infection and, according to the authors,[106] it should be studied in the *in vivo* trials.

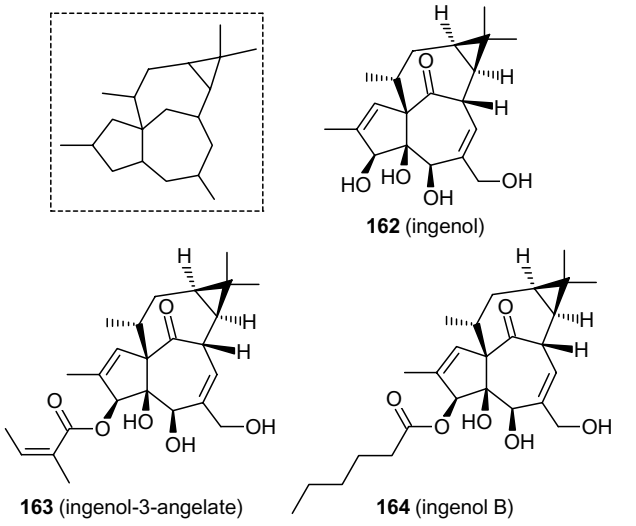
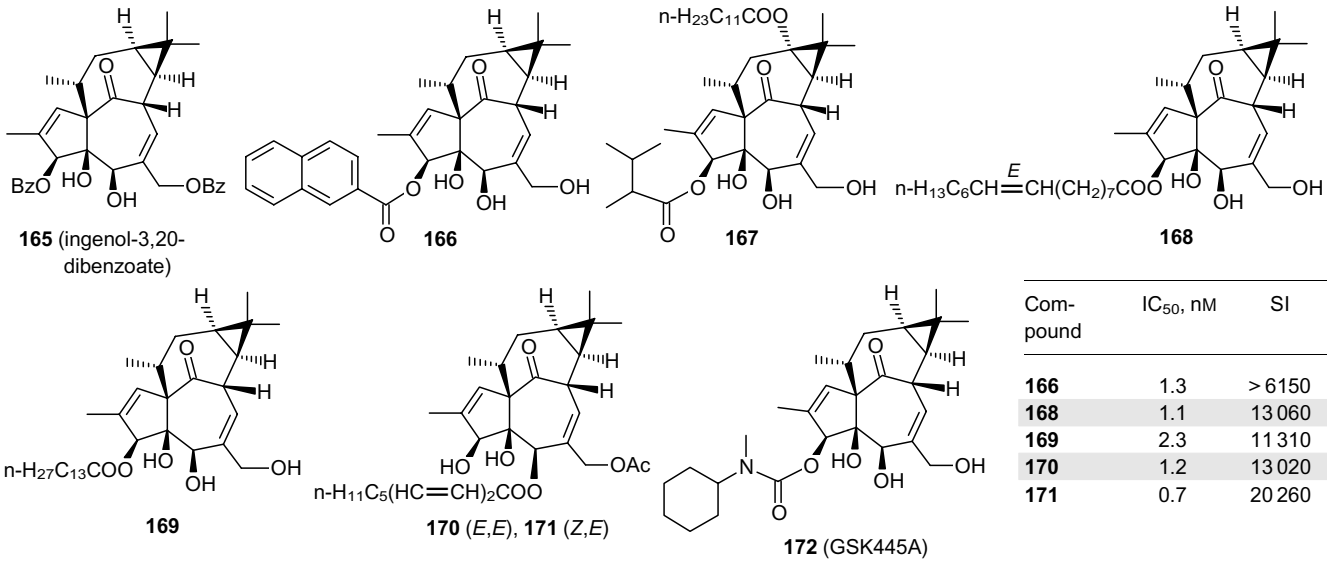


Figure 33. Ingenane-type skeleton (in the frame) and structures of (**162**) and its esters **163**, **164**.

7. Ingenane type diterpenoids

Ingenol (**162**), which is a protein kinase C agonist, and its ester of angelic acid — 3-angelate or mebutate (**163**), were isolated from plants of the genus *Euphorbia* (Fig. 33). Ingenol-3-angelate was approved by the U.S. Food and Drug administration (FDA), the Health Canada and the European Medicines Agency as a drug for the treatment of senile actinic keratoses (a common type of skin lesion — a precursor to non-melanoma skin cancer).[107] When applied topically, this ester very rapidly kills pre-cancerous cells without damaging normal cells.[108] There are reasons to believe that ingenol can also be used to treat other types of oncological diseases with appropriate delivery of the drug to the tumour.

In addition to high antitumor effect, natural ingenol-3-angelate was found to be able to reactivate latent HIV through activation of the NF-κB signaling pathway in an *in vitro* model.[109] A combination of agonist P-TEFb and ester **163** reactives HIV from latency 7.5-fold higher than ingenol-3-angelate *per se*. Among several candidates including prostratin and bryostatin-1, ingenol-3-angelate showed higher potency and lower cytotoxicity and seems a better drug for the reactivation latent HIV and also to create potential HIV treatment strategies.[110] In order to search for low-toxicity agents capable of reactivating latent HIV, several ingenol esters were prepared, among which an n-caproic acid ester, ingenol B (**164**), showed the highest ability to activate the latent HIV-1 reservoirs.[111] It was found that ingenol B can reactivate HIV expression by both activating protein kinase C and directly inducing NF-κB



Compound	IC_{50}, nM	SI
166	1.3	> 6150
168	1.1	13 060
169	2.3	11 310
170	1.2	13 020
171	0.7	20 260

Figure 34. Structures of ingenol esters **165**–**172** and anti-HIV-1 activity of compounds **166** and **168**–**171**.[114,117–119]

expression.[112] The toxicity of this compounds was evaluated *in vivo* upon oral administration not only in rats and dogs but also in rhesus monkeys.[113] Ingenol B showed low toxicity and had almost no side effects at a daily dose of 4 mg kg^{-1}. This fact allows this compound to be considered as a candidate for clinical trials.

One strategy to dampen cytokine release syndrome associated with protein kinase C activation by ingenol esters can be the addition of agents to reduce pro-inflammatory response. It was revealed that co-administration of ruxolitinib, a well-known Janus kinase inhibitor, and ingenol-3,20-dibenzoate (**165**) (Fig. 34) significantly reduces the release of cytokines without impairing the ability of the latter to reactivate latent HIV.[114] A crude extract of traditional Chinese medicine *Euphorbia kansui*, containing ingenol and its esters, reactivates latent HIV.[115] The methanolic extract of the roots of *Euphorbia kansui* displayed significant anti-HIV-1 activity (EC_{50} = 150 ng mL^{-1}).[116] Chemical modification of ingenol found in the extract afforded ester **166**, which showed the greatest inhibition of HIV-1 activity (IC_{50} = 1.3 nM, SI > 6150) and was able to reactivate latent HIV-1 at low concentration (EC_{50} = 2.4 nM) and with low cytotoxicity (CC_{50} > 2 μM). Along with other esters, compound **167** was isolated from the roots of *Euphorbia kansui*, being 200 times more potent in reactivating HIV-1 than prostratin.[117] A number of novel and known ingenol esters were identified in the roots of *Euphorbia ebracteolata*.[118] Unlike ingenol, its esters demonstrated significant anti-HIV-1 activity showing IC_{50} values from 0.7 to 9.7 nM and SI > 96. Compounds **168**–**171** were the most potent; selectivity indices of these compounds ranged from 11 310 to 20 260. Ingenol derivative **172** (GSK445A), which is a potent protein kinase C inhibitor, also has good prospects for the reactivation of latent HIV.[119] This compound was evaluated in experiments with simian immunodeficiency virus-infected rhesus macaque and showed efficacy and no side effects at a dose of 15 μg kg^{-1}, and therefore requires further research. Due to the high importance of phorbol and ingenol derivatives, studies [120,121] have been focused on chromatographic methods of isolation of these compounds from natural sources and their detailed characteristics.

8. Jatrophane and lathyrane type diterpenoids

One more class of compounds derived from the plants of the Euphorbiaceae family should be noted, namely, jatrophane diterpenoids, which are bicyclic esters possessing a broad spectrum of biological activities.[122] It has previously been found that compound **173**, secondary plant metabolite of *Euphorbia hyberna*, is a protein kinase C activator and exhibits high activity against HIV-1 due to the suppression of HIV receptors CD4, CXCR4 and CCR5 (Fig. 35).[123] In the reactivation model of latent HIV-1, this terpene (IC_{50} = 0.25 μM) was 10-fold more potent than prostratin. Among diterpenoids isolated from the plant *Euphorbia amygdaloides*, ester **174** proved to be the most potent and selective inhibitor of HIV-1 (IC_{50} = 0.34 μM, SI > 96), HIV-2 (IC_{50} = 0.043 μM, SI > 751) and Chikungunya virus (IC_{50} = 0.76 μM, SI = 208) replication.[124] The authors suggested that the antiviral activity against Chikungunya virus may be due to the activation of protein kinase C. Also, a number of jatrophane type esters were derived from the latex of *Euphorbia dendroides*, among which only compound **175** showed noticeable activity against Chikungunya virus with IC_{50} = 5.5 μM and SI = 3.2 values.[125] Several diterpenoids were isolated from the whole plants of *Euphorbia helioscopia*.[126] Compound **176**, representing 7,8-*seco*-jatrophane, showed modest activity against herpes simplex virus 1 (IC_{50} = 6.4 μM).

Both novel and previously reported diterpenoids were isolated from the roots of *Euphorbia jolkinii*.[127] Lathyrane type diterpenoid jolkinol A (**177**) displayed high potency against respiratory syncytial virus (IC_{50} = 10 μM, SI = 8), comparable with that of ribavirin (IC_{50} = 7 μM) (Fig. 36). Among lathyrane type diterpenoids isolated from an ethanolic extract of the roots of *Euphorbia micractina*, only compound **178** were moderately active against HIV-1 replication *in vitro* (IC_{50} = 8.2 μM).[128] Similar activity (IC_{50} = 1.4 μM) was also observed for compound **179**, a terpenoid isolated from an acetone extract of the stems of

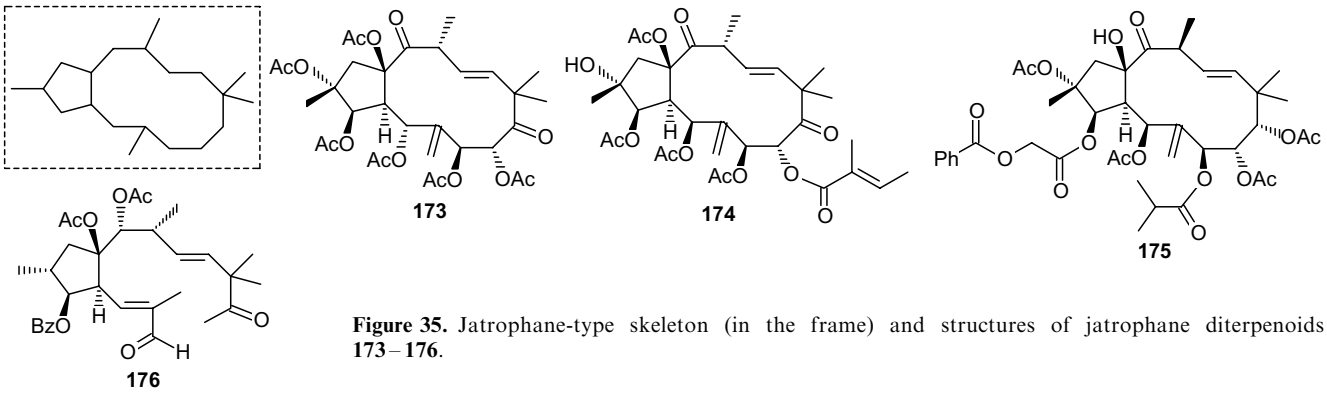


Figure 35. Jatrophane-type skeleton (in the frame) and structures of jatrophane diterpenoids **173**–**176**.

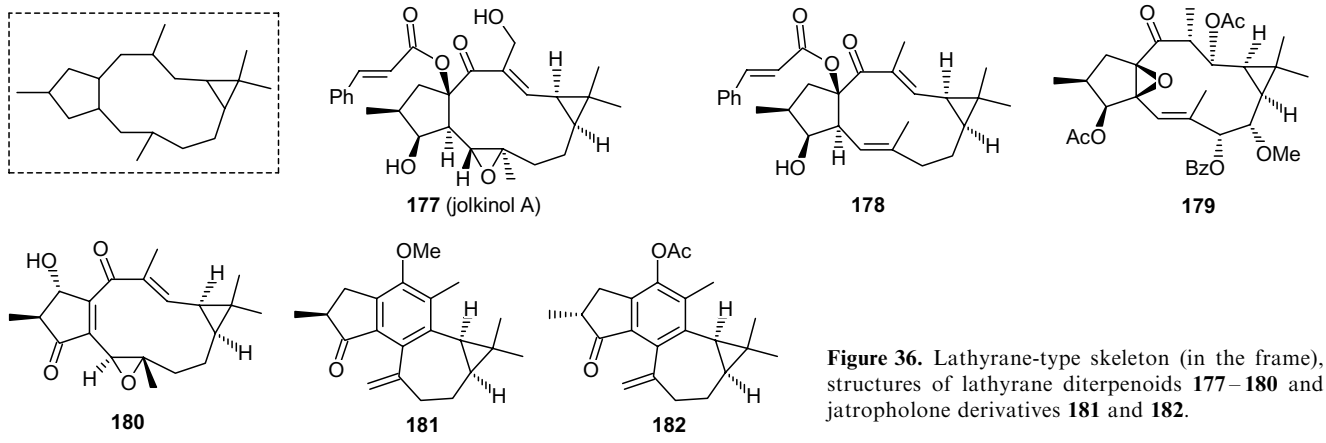


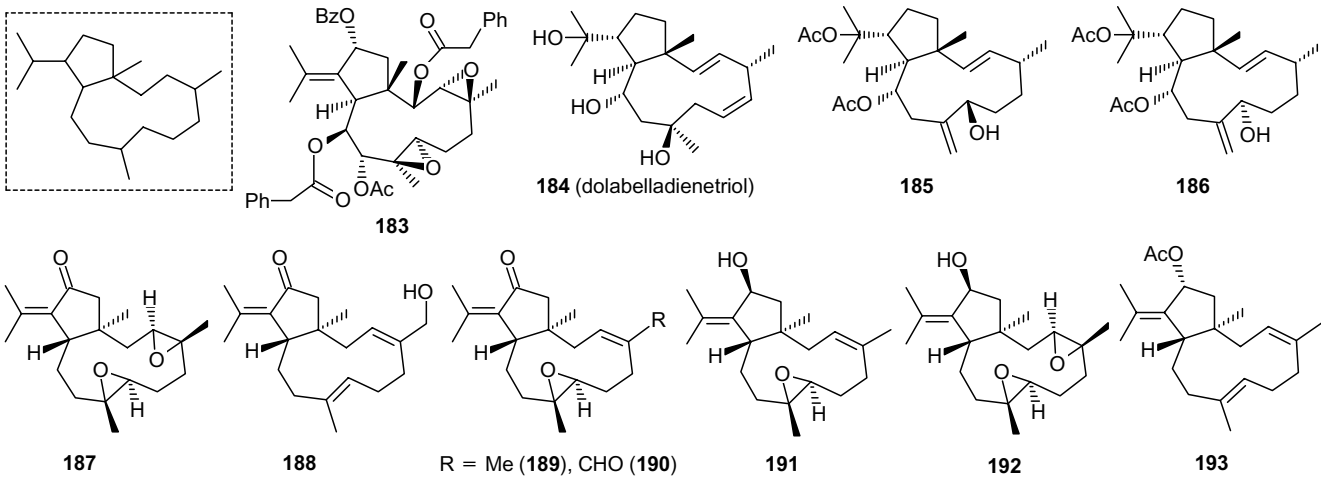
Figure 36. Lathyrane-type skeleton (in the frame), structures of lathyrane diterpenoids **177**–**180** and jatropholone derivatives **181** and **182**.

Euphorbia antiquorum.[129] An extract of the trunk bark of *Sandwithia guyanensis* belonging to the Euphorbiaceae family afforded 19 diterpenoids but only compound **180** exhibited moderate antiviral activity against Chikungunya virus (IC_{50} = 14 μM).[130] Diterpenoids jatropholones A and B, isolated from the rhizomes of *Jatropha isabelii* the Euphorbiaceae family, have a skeleton of a rare type. Their synthetic derivatives on the hydroxy group, ether **181** and ester **182**, exhibit antiherpetic activity, showing complete inhibition of HSV-1 strains in Vero cells at a concentration of 75 μM, as well as an immunomodulatory effect.[26]

9. Dolabellane and dolastane type diterpenoids

Dolabellane diterpenoids originate from both marine and terrestrial sources. The seeds of *Nigella damascena* of the Ranunculaceae family furnished dolabellane diterpenoids, among which compound **183** (Fig. 37) showed the highest antiviral activity (35%) against herpes simplex virus type 1 at a concentration of 10 μM, comparable with the effect of the known triterpene, oleanolic acid (42%).[131] Dolabelladienetriol (**184**) isolated from the marine brown algae *Dictyota pfaffii* and *Dictyota friabilis* inhibits HIV-1 replication in cell culture in the range from 20 to 99% in concentrations from 0.15 to 14.4 μM, respectively,[132] and also activity of HIV-1 reverse transcriptase (IC_{50} = 16.5 μM).[133] It was suggested that the presence of a substituent with an aromatic nucleus at the double bond in such a molecule could enhance its biological activity. Dolabelladienetriol showed low toxicity and safety of a dose up to 50 mg kg^{-1} in mice.[134] Previously unknown compounds **185** (IC_{50} = 2.9 μM) and **186** (IC_{50} = 4.1 μM) isolated from marine brown algae *Dictyota pfaffii* displayed higher anti-HIV-1 inhibitory activity than dolabelladienetriol (IC_{50} = 6.16 μM), with low cytotoxicity (CC_{50} > 1345 μM).[135] Carribean soft corals *Eunicea laciniata* were the source of a dolabellane diterpenoid, from which the products of epoxydation (**187**) and allylic oxidation (**188**) were isolated.[136] Compounds **187** and **188** exhibited significant anti-HIV-1 activity with IC_{50} values of 0.73 μM (SI = 2315) and 0.69 μM (SI = 1420), respectively. Diterpenoid **187**, isolated in small amounts from an extract of *Eunicea laciniata*, also inhibited replication of herpes simplex virus 1 (by 74% at a concentration of 50 μM) in infected cells with low cytotoxicity (CC_{50} = 959 μM) and showed activity close to that of acyclovir.[137] Five diterpenoids including compounds **187** and **189** were derived from the extract of corals *Eunicea laciniata* and *Eunicea asperula*.[138] These compounds and also their derivatives, the products of reduction, oxidation and acylation reactions, were tested for their activity against Zika and Chikungunya viruses. At a concentration of 20 μM, compounds **190** and **191** showed almost complete (99%) inhibition of Zika virus replication, and compounds **189**, **192** and **193** showed almost complete (⩾98%) inhibition of Chikungunya virus replication in Vero cells. High antiviral activity against Zika virus was observed in compounds **190** (IC_{50} = 0.9 μM, SI = 830) and **191** (IC_{50} = 1.2 μM, SI = 480), while compounds **189** (IC_{50} = 1.2 μM, SI = 440), **192** (IC_{50} = 0.7 μM, SI = 1440) and **193** (IC_{50} = 1.2 μM, SI = 83) showed potency against Chikungunya virus.

Dolastane type compounds and dolabellanes are structurally related bi- and tricyclic diterpenes. Derivative **194**, produced by the reaction of diterpenoid **189** with *p*-tolue-

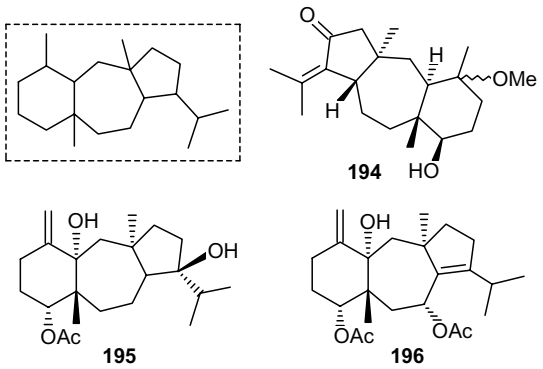


Compound	HIV-1		Compound	ZIKV		CHIKV	
	IC_{50}, μM	SI		IC_{50}, μM	SI	IC_{50}, μM	SI
184	6.16	> 218	**189**	–	–	1.2	440
185	2.9	> 463	**190**	0.90	830	–	–
186	4.1	> 328	**191**	1.2	480	–	–
187	0.73	2315	**192**	8.9	110	0.70	1440
188	0.69	1420	**193**	–	–	1.2	83

Figure 37. Dolabellane-type skeleton (in the frame) and structures and antiviral activity of dolabellane diterpenoids **183**–**193**.[132, 133, 135–138]

nesulfonic acid in methanol, exhibited complete inhibition of Zika virus replication at 20 μM, and also high antiviral activity against this virus with IC_{50} = 1.8 μM and SI = 410 values (Fig. 38).[138] Based on the preliminary studies it can be assumed that diterpenoids **189**, **193** and **194** could be promising drugs for early treatment of arboviral infections.

A crude extract of the marine brown seaweed *Canistrocarpus cervicornis* possessed activity against Zika and Chikungunya viruses.[139] Dolastane type diterpenoid **195**, isolated from this extract showed higher inhibitory activity against Zika (IC_{50} = 0.75 μM, SI = 1246) and Chikungunya (IC_{50} = 1.3 μM, SI = 730) viruses than the extract and reference drug ribavirin. A synergistic effect in inhibiting the replication of both viruses was found for the combination of this extract or compound **195** and ribavirin. Compounds **195** and **196**, isolated from a dichloromethane extract of the alga *Canistrocarpus cervicornis*, inhibited HIV-1 replication in a dose-dependent manner with IC_{50} values of 0.79 μM (SI = 1177) and 0.35 μM (SI = 5457), respectively.[140] These compounds also showed significant virucidal effect against HIV-1 of up to 87 and 99%, respectively, at a concentration of 25 μM (see †). Crude dry extract of the alga *Canistrocarpus cervicornis* showed marked inhibition of herpes simplex virus 1 replication with low cytotoxicity. Antiviral efficacy of the ointment containing 2% of the extract, was evaluated in mice.[141] These findings made it possible to argue that this extract could be useful in reducing the severity of skin lesions caused by herpes simplex virus type 1. Activity of compounds **195** and **196** against human herpes virus 1 and bovine herpes virus 5 was also studied.[142] Derivative **196** (IC_{50} = 6.3 μM, SI ⩾ 101) proved to be much more potent against human herpes virus 1 than diterpenoid **195** (IC_{50} = 120 μM, SI ⩾ 7.5), and at a concentration of 50 μM, both these compounds inactivated this virus almost completely, and bovine herpes virus 5 by 60%.



Compound	HIV-1		ZIKV		CHIKV	
	IC_{50}, μM	SI	IC_{50}, μM	SI	IC_{50}, μM	SI
194	–	–	1.8	410	–	–
195	0.79	1177	0.75	1246	1.3	730
196	0.35	5457	–	–	–	–
Ribavirin	–	–	4.0	75	2.4	122

Figure 38. Dolastane-type skeleton (in the frame), structures and antiviral activity of dolastane diterpenoids **194**–**196**.[138–140]

10. Clerodane type diterpenoids

Clerodane type diterpenoids represent rather large group of secondary metabolites derived from plants of various species, as well as from fungi and sea sponges. Neoclerodane type diterpenoids have the same absolute configuration as

† Percent inhibition of the virus at a certain concentration is given.

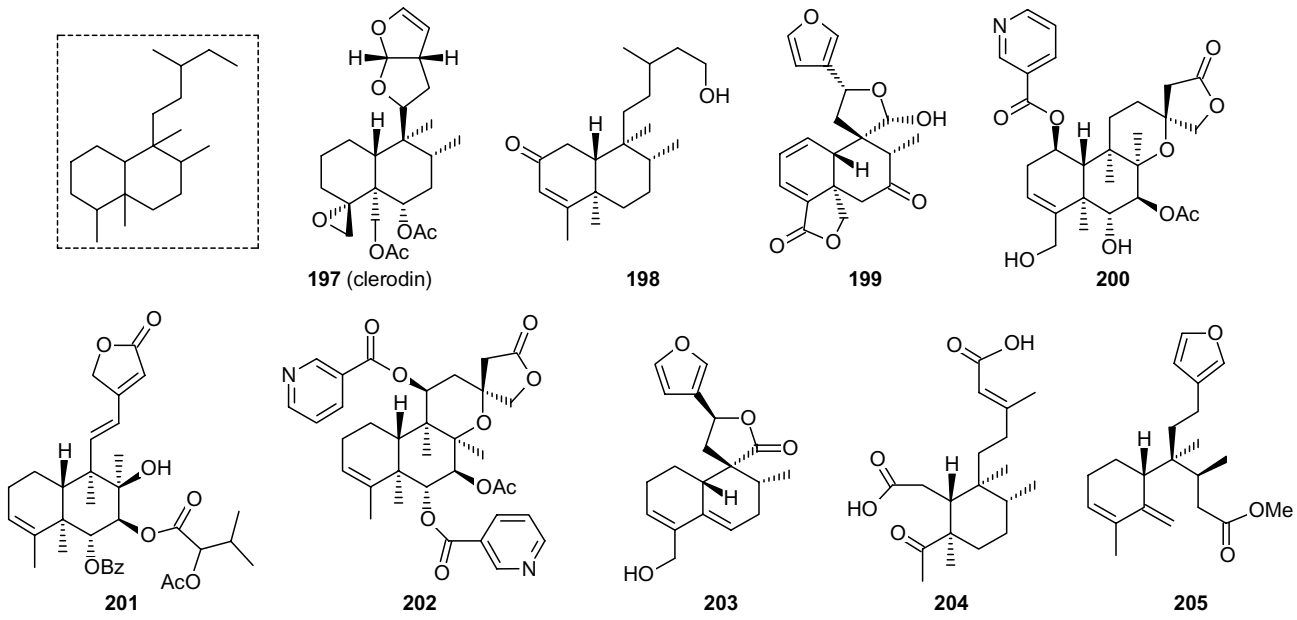


Figure 39. Clerodane type skeleton (in the frame) and structures of clerodane diterpenoids **197**–**205**.

the first representative of the clerodan series, clerodin (**197**), isolated from the plant *Clerodendrum infortunatum* of the Labiatae family and having potential for use as a natural pesticide (Fig. 39).[143]

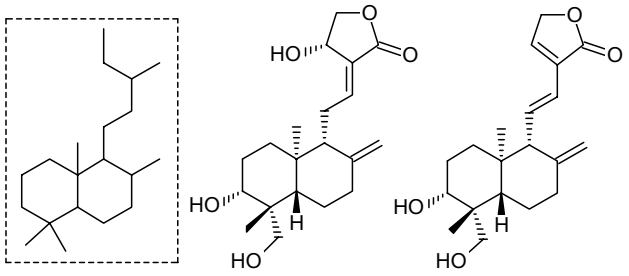
Novel cassane type diterpenoids and 15-hydroxy-3-cleroden-2-one (**198**) were isolated from the roots of *Erythrophleum fordii* of the Leguminosae family.[144] Compound **198** showed moderate antiviral activity against influenza A virus H3N2 with IC_{50} = 11.1 μM and SI = 4.3 values. Several *neo*-clerodane diterpenoids were isolated from *Salvia dugesii* of the Labiatae family.[145] Compound **199** displayed activity against influenza virus H1N1 (IC_{50} = 9.4 μM, SI = 4.8). Biotransformation of the *neo*-clerodane diterpenoid derived from *Scutellaria barbata* of the Labiatae family gave novel metabolites,[146] among which compound **200** exhibited activity against influenza virus H1N1 showing significant inhibitory potency (54.8%) against this virus at a concentration 20 μM compared to that of ribavirin (49.5%). An extract of *Scutellaria barbata* afforded 26 *neo*-clerodane diterpenoids.[147] All isolated compounds were evaluated for their inhibitory activity against Epstein–Barr virus (or human herpes virus type 4) lytic replication leading to the development of infectious mononucleosis and tumours. Previously unknown compound **201** was the most potent (IC_{50} = 3.2 μM, SI = 46.1), and derivative **202** showed the highest selectivity index (109.2) and IC_{50} = 16.4 μM.

An ethyl acetate extract of the leaves of *Teucrium flavum* of the Labiatae family demonstrated marked inhibitory effect against HIV-1 reverse transcriptase activity. From this extract, several compounds were isolated including 19-*nor*-clerodane type diterpenoid glycoside.[148] Although the latter compound proved to be inactive, its hydrolysis with diluted sulfuric acid gave 3 novel clerodane type diterpenoids, which showed their biological activities as HIV-1 reverse transcriptase inhibitors. Compound **203** with an IC_{50} value of 9.1 μM was the most potent. Clerodane type diterpenoids were also isolated from the roots of *Polyalthia laui* of the Annonaceous family.[149] These compounds were tested as anti-HIV-1 agents, among which compound **204** (IC_{50} = 12.2 μM, SI > 16.4), representing 3,4-*seco*-norclerodane, showed the highest activity. Six clerodane diterpenoids were isolated from the extract of the marine sponge *Raspailia bouryesnaultae*, collected in Brazil.[150] Moderate inhibitory activity against herpes simplex virus 1 was discovered in 5,6-*seco*-clerodane **205** (IC_{50} = 52.4 μM, SI = 1.9).

11. Labdane type diterpenoids

Labdane and clerodane diterpenoids have similar structures. The former compounds display a broad spectrum of biological activities, *e.g.*, act as modulators of NF-κB pathway, nitric oxide and arachidonic acid metabolism, therefore, such compounds can be considered as potential anti-inflammatory agents.[151] Of special interest is the lactone andrographolide (**206**), an extremely bitter substance, isolated in the beginning of the previous century from the stems and leaves of *Andrographis paniculata* of the Acanthaceae family (Fig. 40). Due to binding to various protein targets *via* covalent interactions, andrographolide possesses diverse pharmacological activities. Clinical trials demonstrated the viability of using this compound for preventing and treatment of primary progressive multiple sclerosis, oncological pathologies, acute tonsillitis, acute bronchitis and migraine.[152]

There have been numerous examples of activities of andrographolide against various viruses, which allows to identify it as a potent antiviral agent.[153,154] Thus, compound **206** has attracted attention as a therapeutic agent against Chikungunya virus showing a marked inhibition of infection caused by this virus and a decrease in the activity of the virus.[155] The results of the study[156] showed that andrographolide had significant antiviral activity against Denge virus serotype 2 in HeLa and HepG2 cell lines, lowering both the levels of cellular infections and the virus output, with $IC_{50} \approx 22$ μM. Compound **206** can control hepatitis C virus replication *via* activating p38 MAPK phosphorylation.[157] Andrographolide possesses antiviral



206 (andrographolide)

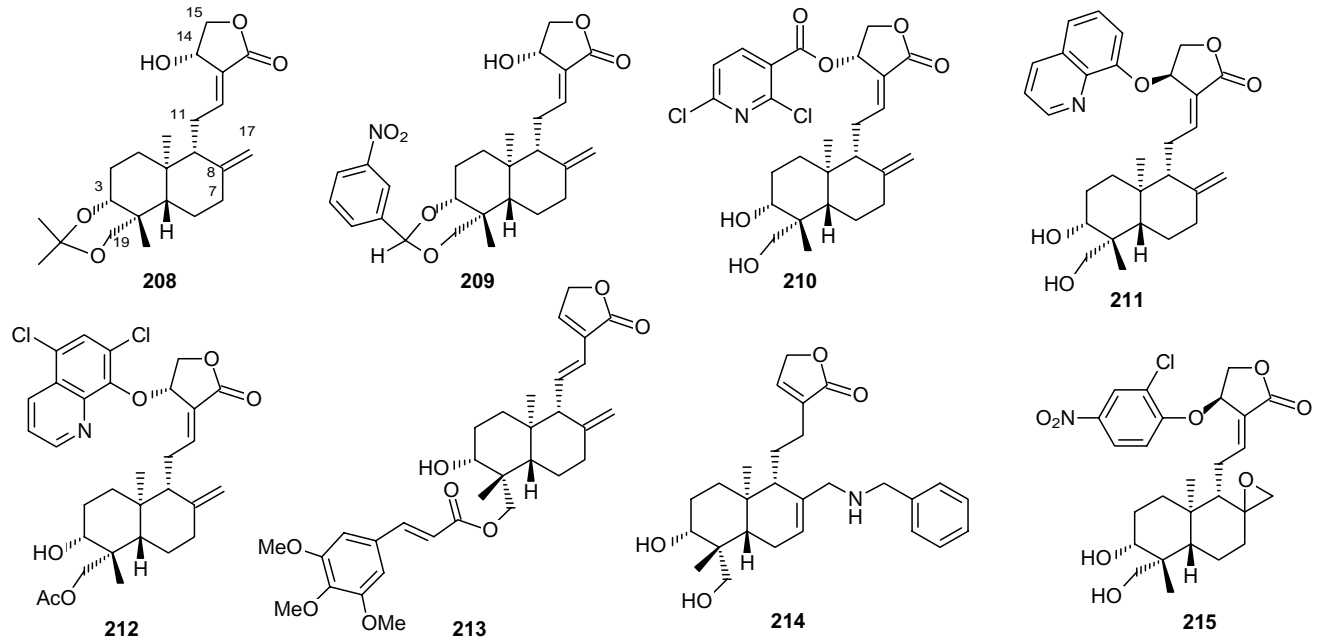
207 (14-deoxy-11,12-didehydroandrographolide)

Figure 40. Labdane-type skeleton (in the frame), structures of andrographolide (**206**) and 14-deoxy-11,12-didehydroandrographolide (**207**).

activity against influenza A virus H1N1, and it was established that the mechanism of its action is associated with the inhibition of viral-induced activation of the RIG-I-like receptor signaling pathway.[158] Given the safety of andrographolide demonstrated in clinical trials and based on preliminary studies, this diterpenoid can be used to alleviate the symptoms of COVID-19.[159]

Another major diterpenoid of *Andrographis paniculata*, 14-deoxy-11,12-didehydroandrographolide (**207**), also possesses antiviral activity and low toxicity. This compound showed the marked effect *in vitro* against H1N1, H3N2 and H5N1 strains of A influenza virus.[160] 14-Deoxy-11,12-didehydroandrographolide showed activity against influenza A virus (H5N1 strain), and also lowered the the intensity of expression of pro-inflammatory cytokines. In the *in vivo* studies, this diterpenoid protected mice lethally challenged with highly pathogenic A influenza virus H5N1 at a daily dose of 500 or 1000 mg kg^{-1}, reducing the mortality and weight loss.[161] Moreover, compound **207** markedly alleviated lung histopathology and significantly inhibited pro-inflammatory cytokine expression.

Various pharmacological activity of andrographolide could not but arouse interest in the preparation and study of the activity of its derivatives. For example, 3,19-isopropylideneandrographolide (**208**) proved itself as a promising antiviral agent for herpes simplex virus type 1, in contrast to andrographolide and compound **207** (Fig. 41).[162] Diterpenoid **208** showed complete inhibition of replication of herpes simplex virus type 1 in Vero cells after infection. In a study,[163] the increased activity against HIV-1 was found for andrographolide (IC_{50} = 0.59 μM, SI = 2875) and its derivatives **209** (IC_{50} = 0.51 μM, SI = 1460) and **210** (IC_{50} = 0.83 μM, SI = 12 474). The results of additional *in vitro* experiments and computational simulation data led to the conclusion that andrographolide derivatives may be promising agents for the prevention of HIV infection. Among compounds derived from andrographolide and containing quinoline moiety at the 14-positioned oxygen atom, derivatives **211** (IC_{50} = 1.3 μM, SI ⩾ 16.1) and **212** (IC_{50} = 4.5 μM, SI ⩾ 18.9) were the most potent against Zika virus.[164] According to the authors, combining the andrographolide molecule with the quinoline unit is a promising strategy for creating drugs to combat this virus. Among 48 various derivatives obtained *via* esterification,



208 **209** **210** **211** **212** **213** **214** **215**

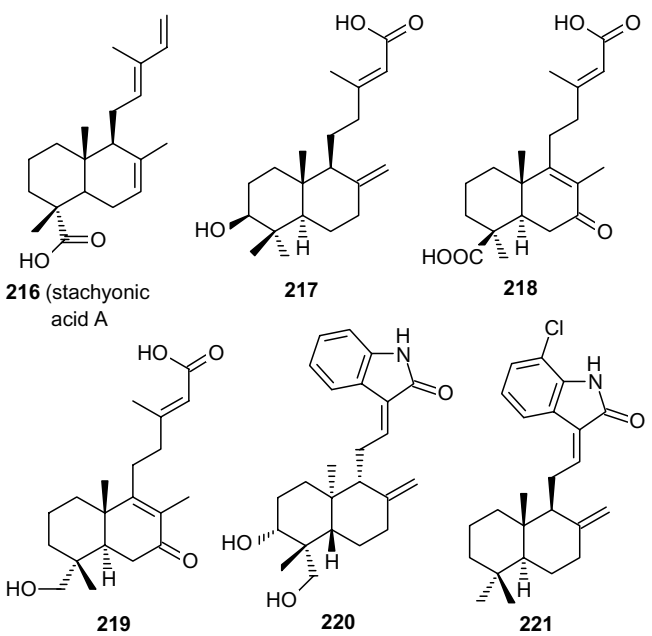
Compound	HIV-1		HBV	
	IC_{50}, μM	SI	IC_{50}, μM	SI
206	0.59	2875	54.1	3.7
207	–	–	22.6	8.7
209	0.51	1460	–	–
210	0.83	12 474	–	–

Compound	ZIKV		HBV		H3N2	
	IC_{50}, μM	SI	IC_{50}, μM	SI	IC_{50}, μM	SI
211	1.3	16.1	–	–	–	–
212	4.4	18.9	–	–	–	–
213	–	–	10.3	> 165	–	–
214	–	–			278	7.9

Figure 41. Structures and antiviral activity of andrographolide derivatives **208**–**215**.[162–167]

oxydation, dehydration and other transformations of compounds **206** and **207**, the highest inhibitory ability towards DNA replication of hepatitis B virus was demonstrated by agent **213** (IC_{50} = 10.3 μM, SI >165), the starting compound **207** showing moderate activity.[165] It was noted that 19-O-substituted compounds with the 3-positioned free hydroxy group has the strongest antiviral activity against hepatitis B virus. The presence of a double bond between C(8) and C(17) atoms, two conjugated double bonds and a methylene unit at the position 15 provide higher antiviral activity. Andrographolide gave rise to two series of compounds differing in the endocyclic double bond position.[166] Among the resultant compounds, derivative **214** showed low activity against influenza A virus H3N2 (IC_{50} = 278 μM, SI = 7.9). It was observed that to achieve higher antiviral activity, an endocyclic double bond between carbon atoms at positions 7 and 8 is required. Moreover, (14*S*)-(4-nitro-2-chlorophenyl)-8(*R*/*S*),17-epoxyandrographolide (**215**), representing a mixture of two diastereomers, effectively inhibited an infection caused by human enterovirus type 71.[167]

Stachyonic acid A (**216**) (Fig. 42) was isolated from the herb *Basilicum polystachyon* of the Labiatae family and showed significant inhibitory activity (IC_{50} = 1.4 μM) against Dengue virus in Vero cells with low cytotoxicity (SI = 63), in contrast to andrographolide (IC_{50} = 51 μM).[168] Compound **216** also demonstrated antiviral effect on West Nile virus (IC_{50} = 1.2 μM), influenza A viruses H1N1 (IC_{50} 4.1 μM) and H3N2 (IC_{50} 18 μM), while andrographolide showed low activity when interacting with these viruses.[169] Therefore, stachyonic acid A can be considered promising antiviral agent with a broad spectrum of activity and low cytotoxicity. Eight labdane type diterpenoids were isolated from the fruits of *Forsythia suspensa* of the Oleaceae family.[170] These compounds displayed similar marked activity against influenza A virus H1N1 (with the IC_{50} values in the range of 18.4–26.2 μM) and respiratory syncytial virus (IC_{50} from 10.5 to 14.4 μM), with compounds **217**–**219** being slightly more active.



216 (stachyonic acid A) **217** **218** **219** **220** **221** **222**

Compound	H1N1	CHIKV	
	IC_{50}, μM	IC_{50}, μM	SI
216	4.1	–	–
217	19.9	–	–
218	18.4	–	–
219	18.6	–	–
220	–	5.52	14
221	–	1.55	83

Figure 42. Structures of labdane-type diterpenoids **216**–**219**, labdane-oxindole hybrides **220**, **221** and sclareolide (**222**), and their antiviral activities.[170, 171]

Andrographolide used as a scaffold for the synthesis of novel compounds with anti-Chikungunya virus activity.[171] Among 72 analogues of andrographolide, compound **220**, prepared *via* oxidation of the substrate on the C(12)=C(13) double bond followed by condensation of the intermediate aldehyde with oxindole, proved to be a promising inhibitor of this virus (IC_{50} = 5.5 μM). It was found that the oxindole ring favours antiviral activity in the compound. As a result of further optimization of the structure, compound **221** was obtained based on sesquiterpene (+)-sclareolide (**222**), which was a potent inhibitor of two human strains of Chikungunya virus with IC_{50} values of 1.55 μM (SI = 83) and 0.14 μM (SI = 714).

12. Other diterpenoids

In the last section of this review, other diterpenoids with pronounced antiviral activity should be mentioned, whose structure does not allow them to be attributed to the above types. For example, diterpene tetracyclic cage alcohols, wickerols A (**223**) and B (**224**), having a unique tetracyclic carbon skeleton, produced by fungi *Trichoderma atroviride* (Fig. 43). Wickerols A (IC_{50} = 0.24 μM, SI = 100) and B (IC_{50} = 16 μM, SI = 20) showed anti-H1N1 potency but were inactive against influenza A (H3N2 strain) and B viruses.[172]

Cage structures appear to be a promising platform for the design of antiviral agents.[173, 174] An effective five-step synthesis of wickerol A was described. [175]. Icetexane type diterpenoids were isolated from the Tibetan plant *Perovskia atriplicifolia* of the Labiatae family.[176] Among these metabolites, compounds **225** and **226** were identified, which suppressed replication of hepatitis B virus DNA with IC_{50} values of 13.8 μM (SI = 154) and 20.7 μM (SI = 138), respectively. An ethyl acetate extract of the stem bark of *Stillingia lineata* of the Euphorbiaceae family exhibited significant anti-Chikungunya virus activity.[177] Among diterpenoids isolated from this extract, only compound **227** possessing flexibilane skeletone showed effective and selective inhibition of virus replication (IC_{50} = 7 μM, SI = 8.8).

Briarane type diterpenoids were derived from the gorgonial coral *Ellisella*. Compound **228** displayed the highest inhibitory effect (IC_{50} = 5.2 μM, SI = 20) on the activity of hepatitis B virus replication in HepAD38 cells. This metabolite inhibits covalently closed circular viral DNA and can be used as a promising drug in the hepatitis B therapy.[178] *Seco*-cembranoid **229** isolated from the soft coral *Lobophytum crassum* proved to be active against cytomegalovirus or human herpes virus type 5 with an IC_{50} = 5.0 μM.[179] Nine novel prenylbisabolane diterpenoids isolated from the leaves of *Claoxylon polot* of the Euphorbiaceae family,[180] showed moderate antiviral activity against Coxsackie B3

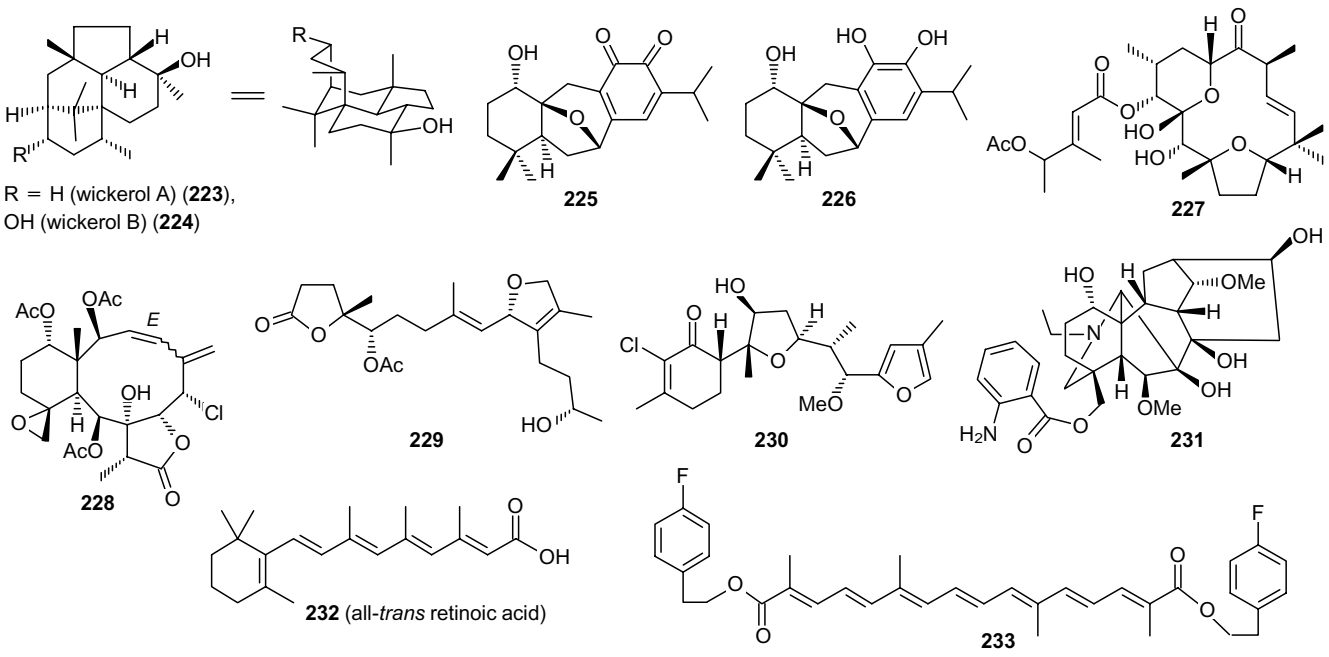


Figure 43. Structures of diterpenoids **223**–**233** possessing antiviral activity.

virus, with compound **230** being the most potent (IC_{50} = 6.0 μM, SI = 11.6).

Roots and stems of *Delphinium ajacis* of the Ranunculaceae family afforded diterpenoid alkaloids.[181] Among these derivatives, the most noticeable activity against respiratory syncytial virus was observed in compound **231** (IC_{50} = 10 μM, SI > 9.9). Preliminary findings suggest that diterpenoid **232**, representing an all-*trans* retinoic acid, can be considered as a potential therapeutic agent against SARS-CoV-2.[182]

Crocetin is a natural dicarboxylic acid, which can be classified by its structure as carotenoids and acyclic diterpenoids. Various esters of this acid were synthesized, where ester **233** showed the highest potency against tobacco mosaic virus: at 0.5 mg mL^{-1}, its activity was markedly higher than that of ribavirin and natural crocetin esters.[183]

13. Conclusion

Summing up the review of the state-of-the-art literature on diterpene compounds and their derivatives possessing antiviral activity, it should be noted that dozens of such compounds are currently known that can be used as antiviral agents. Naturally occurring diterpenoids and their synthetic analogues have antiviral effect on viruses such as Zika virus, influenza viruses, human papilloma virus, hepatitis B and C viruses, Coxsackie virus, human respiratory syncytial virus, HIV-1 and HIV-2, coronaviruses, Dengue, Epstein–Barr, Sindbis, Chikungunya and tobacco mosaic viruses. Diterpenoids are of great interest to researchers as available compounds for studying the biological activity and mechanisms of action of low-molecular-weight metabolites, and also for developing new antiviral drugs derived therefrom. The key objective of specialists in the field of synthetic organic and medicinal chemistry involved in the modification of natural compounds is to understand the relationship between the chemical structure of a molecule and its various biological activities. Some of such compounds, *e.g.*, gnidimacrin, prostratin, ingenol, andrographolide, *etc.*, possess unique pharmacological activity and pronounced antiviral properties. However, even for them there is no way to identify clear relationships with the structure. Thus, for andrographolide derivatives to display pronounced antiviral activity against hepatitis B, Zika, Chikungunya and influenza A H3N2 viruses, various modifications of the skeleton of the starting molecule should be carried out. For example, the literature data suggest that the presence of the 5-positioned free hydroxyl group in such structures is necessary for the pronounced anti-HIV-1 activity to occur, however, the effect of other substituents is not so obvious. The available examples of increased post-modification activity are generally valid within the framework of a particular study and are limited both to a small number of compounds and to a narrow range of viruses being studied. Undoubtedly, further accumulation of experimental material will help to identify certain structure–activity relationships. At the moment, the mechanisms of action of only some diterpenoids that are active against a large number of viruses have been studied, and the most detailed is the human immunodeficiency virus.

It should also be noted that for a wider application of these compounds, one should not only focus on their biological activity, but also consider the availability of biological raw materials. Resin acid derivatives are the most available among terpenoids and it can be assumed that, most likely, these compounds are the most promising scaffolds for the synthesis of novel derivatives with antiviral activity. In terms of chemical modifications of abietane and kaurane type compounds, the transformation of the carboxyl group into an isocyanate or primary amino group should be considered as the most effective way. However, it is now impossible to predict which transformations will lead to the creation of new effective antiviral agents.

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14. List of acronyms

Following acronyms and designations are used in the review:

APOBEC3G (apolipoprotein B mRNA editing enzyme, catalytic subunit 3G) — human enzyme that plays an important role in innate antiviral immunity;

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

CHIKV — Chikungunya virus;

CMV — cytomegalovirus;

CVB2, CVB3, CVB6 — Coxsackie virus B2, B3, B6;

DENV-2 — Dengue virus type 2;

FDA — Food and Drug Administration;

H1N1, H3N2, H5N1 — serotypes of influenza A virus;

HBsAg — hepatitis B surface antigen;

HBV — hepatitis B virus;

HCV — hepatitis C virus;

HIV-1 — human immunodeficiency virus type 1;

HIV-2 — human immunodeficiency virus type 2;

HRSV — human respiratory syncytial virus;

HRV3 — human rhinovirus 3 type;

HSV-1 — herpes simplex virus type 1 (or human herpsevirus type 1);

HSV-2 — herpes simplex virus type 2 (or human herpsevirus type 2);

IC_{50} — half-maximal inhibitory concentration;

JAK-STAT (the Janus kinase/signal transducer and activator of transcription) — a signaling pathway representing a chain of interactions between proteins inside the cell;

NF-κB — universal transcription factor;

p38 MAPK (mitogen-activated protein kinase) — a class of protein kinases that respond to stress stimuli;

PIV3 — parainfluenza virus type 3;

PKCθ/MEK (protein kinase C-theta/mitogen-activated protein kinase kinase) — signaling pathway for latent HIV reactivation;

P-TEFb — positive transcription elongation factor b;

RIG-I (retinoic acid-inducible gene-I) — intracellular receptor involved in the antiviral response of the body's innate immune system;

SARS-CoV-2 — COVID-19 causative agent;

SI — selectivity index;

VZV — varicella-zoster virus;

ZIKV — Zika virus.

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