Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol.24*
2000 Elsevier Science B.V.

NATURAL PRODUCTS AS ANTIVIRAL AGENTS

KHALID A. EL SAYED

Medicinal, Aromatic and Poisonous Plants Research Center, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

ABSTRACT: Since the ancient times, natural products have served as a major source of drugs. About fifty percent of today's pharmaceutical drugs are derived from natural origin. Interest in natural products as a source of new drugs is growing due to many factors that will be discussed in this article. Viruses have been resistant to therapy or prophylaxis longer than any other form of life. Currently, there are only few drugs available for the cure of viral diseases including acyclovir which is modeled on a natural product parent. In order to combat viruses which have devastating effects on humans, animals, insects, crop plants, fungi and bacteria, many research efforts have been devoted for the discovery of new antiviral natural products. Recent analysis of the number and sources of antiviral agents reported mainly in the annual reports of medicinal chemistry from 1984 to 1995 indicated that seven out of ten synthetic agents approved by FDA between 1983-1994, are modeled on a natural product parent. It has been estimated that only 5-15% of the approximately 250, 000 species of higher plants have been systematically investigated for the presence of bioactive compounds while the potential of the marine environment has barely been tapped. The aim of this review is to provide an overview on the central role of natural products in the discovery and development of new antiviral drugs by displaying 340 structures of plant, marine and microbial origin that show promising *in vitro* antiviral activity.

INTRODUCTION

Natural Products as a Source for New Drugs: Merits and Obstacles

Since the ancient times, natural products have served as a major source of drugs. About fifty percent of today's pharmaceutical drugs are derived from natural origin [1]. The growing interest in natural products as a source of new drugs can be attributed to many factors including urgent therapeutic needs, the wide range of both chemical structures and biological activities of natural secondary metabolites, the adequacy of bioactive natural products as biochemical and molecular probes, the development of recent techniques to accurately detect, isolate and structurally characterize the bioactive natural products and advances in solving the demand for supply of complex natural products [1]. Historically, the majority of the natural product-based drugs including cyclosporine, paclitaxel and camptothecin derivatives were first discovered

* Present address: Department of Pharmacognosy, School of Pharmacy, University of Mississippi, P.O. Box 7624, University, MS 38677, U.S.A.

by traditional cell-based *in vitro* assays before their real molecular biological targets were identified [2]. These cellular biological responses of natural products are likely to be associated with the inherent properties of secondary metabolites for the defense of their producing organisms [2].

Infectious viral diseases remain a worldwide problem. Viruses have been resistant to therapy or prophylaxis longer than any other form of life due to their nature because they totally depend on the cells they infect for their multiplication and survival. This peculiar characteristic has rendered the development of effective antiviral chemotherapeutic agents very difficult. Currently, there are only few drugs available for the cure of viral diseases including acyclovir (**1**), the known antiherpetic drug which is modeled on a natural product parent. In order to combat viruses which have devastating effects on humans, animals, insects, crop plants, fungi and bacteria, many research efforts have been devoted for the discovery of new antiviral natural products. Although the search for naturally occurring products which can interfere with viral infections began with the successful isolation of antibiotics from microorganisms but it has not been as intensive as that of synthetic antiviral agents [3]. This is mainly due to the tendency of most virologists who adopt a rational design of antiviral agents rather than toward empiricism especially with the progress in knowledge of viral replication [3]. Moreover, there are some problems arising from the screening of crude extracts, as well as with the purification and identification of the antiviral components from these crude extracts. These problems became less intense with the recent advances in different chromatographic and spectroscopic technologies. Many natural and synthetic compounds were found to show *in vitro* antiviral activity but were much less effective when tested *in vivo*. This could be attributed to difficulty in drug transportation to the cells of the infected tissue especially if these tissues become inflammed due to infection. Many antivirally active compounds are too toxic for therapeutic applications. However, natural products remain the best resource for chemically diversed new lead entities that could serve for future development as potent and safe antiviral agents. Recent analysis of the number and sources of antiviral agents reported mainly in the annual reports of medicinal chemistry from 1984 to 1995 indicated that seven out of ten synthetic agents approved by FDA between 1983-1994, are modeled on a natural product parent [4]. These drugs are: famciclovir (**2**), ganciclovir (**3**), sorivudine (**6**), zidovudine (7), didanosine (**8**), zalcitabine (**9**) and stavudine (**10**) [4].

The aim of this review is to provide an overview on the central role of natural products in the discovery and development of new antiviral drugs.

History and Definition of the Word "Virus"

The original Latin meaning of "virus" is "poison", "venom" or "slime" [5]. The word "virus" was also used figuratively in the sense of "virulent or bitter feeling", "stench" or "offensive odor" [3]. In the late 1800s, the term "virus" was bestowed on a newly discovered class of pathogens, smaller than bacteria being studied by Louis Pasteur and others of that era [6]. As late as 1907, "virus" was defined as "the poison of an infectious disease especially found in the secretion or tissues of an individual or animal suffering from infectious diseases [5]. In the early decades of the twentieth century, viruses were identified as infectious agents that were filterable and invisible in the light microscope which superficially distinguished them from most familiar microorganisms [5]. Today, viruses are defined as noncellular infectious agents that vary in size, morphology, complexity, host range and how they affect their hosts [7]. However, they share three main characteristics in common: a) A virus consists of a genome, either RNA or DNA core (its genetic material) which is surrounded by a protective protein shell. Frequently this shell is enclosed inside an envelope (capsid) that contains both proteins and lipids. b) A virus can be replicated (multiplied) only after its genetic material enters a host cell. Viruses are absolutely dependent on the host cells' energy-yielding and protein-synthesizing machineries and hence they are parasites at the genetic level. c) A virus's multiplication cycle includes the separation of its genomes from its protective shells as an initial step [7]. When a virus is outside the host cell, it is considered no more alive than a chromosome [6].

The Multiplication Cycle

The interval between successive mitosis of the individual cell is divided into three periods [7]:

1- The G1 period precedes DNA replication. Its average duration is 12 hours.
2- The S period during which DNA replicates. Its average duration is 8 hours.
3- The G2 period in which the cell prepares for the next mitosis. Its average duration is 4 hours.

RNA and protein are not synthesized while mitosis proceeds, i.e., during the metaphase which is between G2 and G1 periods but are otherwise synthesized throughout the multiplication cycle [7]. Non-growing cells are usually arrested in the G1 period; the resting state is referred to as G0. Under normal growth conditions, cells of a growing culture multiply in an unsynchronized manner, hence cells at all stages of the cycle are present. The aging of cells starts after about 50 passages by

slowing their growth rate. The amount of time they spend in G0 after each mitosis gradually increases. The chromosomal complement changes from normal diploid to aneuploid pattern, supernumerary chromosomes and it finally fragmented and the cell dies. Malignant tissues give rise to aneuploid cell lines that have infinite life spans and are known as continuous cell lines.

Patterns of Macromolecular Biosynthesis

The main feature of normal animal cell is its compartmentalization [7]. The DNA of the animal cell is restricted to the nucleus at all cell cycle stages except during metaphase when no nucleus exists. The synthesis of RNA occurs in the nucleus and most of it remains there, but messenger RNA and transfer RNA migrate to the cytoplasm. Ribosomal RNA is synthesized in the nucleolus; the two ribosomal subunits are partly assembled in the nucleolus and nucleus then migrate to the cytoplasm. All protein synthesis proceed in the cytoplasm. The mitochondria, which is located only in the cytoplasm, contains DNA-s, RNA- and protein-synthesizing systems of their own [7].

Viral Replication

Viruses replicate in different ways. In all cases, the viral DNA or RNA is copied repeatedly. Viral proteins are synthesized inside a suitable host cell where many new viral particles are assembled [6]. Generally viruses replicate through the following stages [3,6,7]:

1- The virus chemically recognizes and attaches to appropriate host cell. This step is very specific, i.e., specific virus sites will bind to appropriate cellular receptor sites which are presumably glycoproteins. The organs of cell attachment of some viruses are protrusions from their outer surface which called spikes. In viruses lacking spikes, complex polypeptide binding sites are involved.
2- The whole virus or its genetic material alone (DNA or RNA) enters the cell's cytoplasm (penetration and uncoating). A virus may have different penetration mechanisms in the host cell. For enveloped virus, fusion of membrane sometimes occurs. Most viruses are introduced into the cell by a kind of phagocytosis named viropexis. Virus particles are transported along the network of cytoplasmic microtubules to a specific cell site where subsequent replication takes place. Uncoating results in the liberation of viral nucleic acids into the cell which makes them sensitive to nucleases.
3- Information contained in the viral DNA or RNA directs the host cell to replicate viral nucleic acids and synthesizes viral enzymes and

capsid proteins, which are incorporated into the host's plasma membrane.

4- These viral nucleic acids, enzymes and capsid proteins are assembled into new viral particles (genomes) together with their associated RNA or DNA polymerase.

5- The newly formed viral particles are released from the infected cell.

Viruses usually replicate by lytic or temperate pathways. In the lytic pathway, stages 1-4 from above proceeds quickly and the virus is released as the host cells undergo lysis, ruptures and dies after loss of its contents. In temperate pathways, the virus does not kill the host cell but the infection enters a period of latency, in which viral genes remain inactive inside the host cell. In some cases of latency the viral genes become integrated into the host's DNA, replicated along with it and passed along to all daughter cells. In time, damage to the DNA or some other event may activate transcription of the viral genes therefore new viral particles can be produced and infected cells are destroyed [6]. Proposed targets of some specific antiviral chemotherapy are illustrated in Figure 1 and can be summarized as [3]:

1- Attachment (adsorption) of the viral particle to the host cell.
2- Penetration of the host cell by infectious viral particles.
3- Particles uncoating, release and transport of viral nucleic acid and core proteins.
4- Nucleic acid polymerase release and/or activation.
5- Translation of m-RNA to polypeptides which are early proteins.
6- Transcription of m-RNA.
7- Replication of nucleic acids.
8- Protein synthesis (late proteins).
9- Viral polypeptides cleavage into useful polypeptides for maturation.
10- Morphogenesis and assemblage of viral capsids and precursors.
11- Encapsidation of nucleic acid. 12- Envelopment. 13- Release.

Viral Proteins

Proteins represent the main viral component. Proteins are the sole constituent of capsids, the major component of envelopes and also they are associated with the nucleic acids of many viruses as core proteins [7]. Viral proteins have a wide range of molecular weight ranging from 10,000-150,000 daltons. Viral proteins also vary in number, some viruses posses as few as three species while others contains up to 50 protein species. All members of the same virus family display almost the same highly characteristic electrophoretic protein patterns [7].

Glycoproteins: Viral envelopes usually contain glycopoteins in the form of oligomeric spikes or projections. The carbohydrate moieties of

glycoproteins are formed of oligosaccharide (10-15 monosaccharide units) which are linked to the polypeptide backbone through *N*- and *O*-glycosidic bonds involving asparagine and serine or threonine, respectively. Their main components are: galactose and galactosamine, glucose and glucoseamine, fucose, mannose and sialic acid which always occupies a terminal position [7].

Example of some viral proteins with specialized functions are:

Hemagglutinins: Many animal viruses (e.g., ortho- and paramyxoviruses) agglutinate the red blood cells of certain animal species. This means that these red cells contain receptors for certain surface components of viral particles that act as cell attachment proteins which are glycoproteins and known as hemagglutinins. Viral hemagglutinins could be used in their quantitative measurement [7].

Enzymes: Animal viral particles often contain enzymes (Table 1). These enzymes are virus-specific. In addition to the enzymes summarized in Table 1, viruses often contain other enzymes. Among them are the enzymes that modify both ends of m-RNA molecules synthesized by their capping enzymes and poly(A) polymerases. Protein kinases, deoxyribonucleases, DNA-dependent phosphohydrolases and topoisomerases are also often present in viruses [7].

Apoptosis in Viral Infections [8]

Homeostasis of cell numbers in multicellular organisms is maintained by a balance between cell proliferation and physiologic (programmed) cell death. Apoptosis is a process by which cells undergo physiologic death in response to a stimulus and it is a predictable series of morphologically defined events. It is divided into two stages namely, the breakdown of the nucleus and alteration of the cell shape and the plasma membrane permeability. The consequences of apoptosis are the fragmentation of nuclear DNA, the zeiosis (boiling) of the cytoplasm associated with the blebbing and increased granularity of the plasma membrane and fracturing of the cell into subcellular DNA-containing apoptotic bodies. Apoptosis process is different from necrotic cell death by involvement of lysosomal enzyme leakage into the cytoplasm, the swelling of the cell and the actual rupture of the plasma membrane. Necrosis is often induced by agents that affect membrane integrity, generalized protein synthesis, or energy metabolism [9]. Apoptosis can be induced by a variety of stimuli, e.g., steroids, cytokines, DNA-damaging agents, growth factor withdrawal and in case of T or B cells, antigen-receptor engagement. Apoptosis is also a mechanism by which cytotoxic lymphocytes kill their targets. Many viruses can induce apoptosis in infected cells while many other viruses especially transforming viruses, can inhibit apoptosis and allow for cell transformation. The nuclear changes during apoptosis induce chromatin

Table 1. Enzymes in Animal Viruses [7]

Virus	Enzyme
DNA Viruses:	
Poxyvirus	DNA-Dependant RNA polymerase Messenger-RNA capping enzyme Poly(A) polymerase Nucleasess DNA-Dependant nucleotide phosphohydrolase Topoisomerase Protein kinase
Herpesvirus	None
Adenovirus	None
Papovavirus	None
Hepatitis virus	DNA Polymerase
Parvovirus	None
RNA Viruses:	
Picornavirus	None
Calicivirus	None
Togavirus	None
Flavivirus	None
Coronavirus	None
Reovirus	RNA-Dependant RNA polymerase Nucleotide phosphohydrolase Messenger-RNA capping enzyme
Rhabdovirus	RNA-Dependant RNA polymerase
Paramyxovirus	Neuraminidase RNA-Dependant RNA polymerase
Orthomyxovirus	Neuraminidase RNA-Dependant RNA polymerase
Bunyavirus	RNA-Dependant RNA polymerase
Arenavirus	RNA-Dependant RNA polymerase
Retrovirus	RNA-Dependant DNA polymerase (reverse transcriptase) Ribonuclease H Endoribonuclease Protein-cleaving enzyme Protein kinase

condensation into several segments. The nuclear DNA is fragmented into oligonucleosomal-sized pieces [8]. This process involves the activation of endogenous endonuclease(s) in the cell programmed to die. Changes in accessibility of DNA to nucleases is mediated by topoisomerases which can induce conformational changes in DNA by making strand cuts. An increase in intracellular calcium ions is observed in cells undergoing apoptosis. Therefore, extracellular calcium-chelating agents can block a variety of apoptotic forms. The endonucleases associated with DNA fragmentation are Ca^{++} dependent.

Classification of Viruses

Viral strains that are distinctly different in more than one gene, excluding mutants and variants, are designated species. Species that are apparently genetically similar are grouped into genera. These genera are grouped into families based on morphology, physical and chemical nature of viral component and on molecular strategies used by viral genomes to express themselves and replicate [6]. Viruses are classified into four major different classes:

Bacteriophages

A class of viruses that infect bacterial cells. Despite bacteriophages could have adverse effects on the host cell, they could also be used as research tools in early experiments designed to reveal whether DNA or proteins are the molecules of inheritance and in genetic engineering. Replication of bacteriophages can proceed by either lytic or temperate pathways [6].

Plant Viruses

Viruses cause several hundred infectious diseases to many plants after successfully penetrating their cell walls, reducing the yield of a variety of crops including tobacco, potatoes, tomatoes, as well as many other vegetables, inducing serious economic damages. Some insects that feed plants assist in viral infection. Viral particles may be clinging to these insects' piercing or sucking devices and when these devices penetrate plant cells, infection occurs. Most plant viruses are RNA viruses. Outward symptoms of infection include mottled and blistered leaves, misshapen or abnormally small fruits, tumors on roots and color change in flowers. Examples of some common RNA viruses and their target plants are: Closterovirus (Beet), Comovirus (Cowpeas), Cucumovirus (Cucumber), Hordeivirus (Barley), Potaxvirus (Potatoes) and Tobamovirus (Tobacco mosaic virus, Tobacco) [6]. Examples of DNA viruses and their plant targets are: *Caulimovirus* (Cauliflower) and *Geminivirus* (Maize) [6].

Table 2. Classification of Animal Viruses [6,7,10]

Virus	Disease
DNA Viruses:	
Adenoviruses	Respiratory infections
Herpesviruses:	
H. simplex type I	Oral herpes, cold sores
H. simplex type II	Genital herpes
Varicella-zoster	Chickenpox, shingles
Epstein-Barr	Infectious mononucleosis, implicated in some cancer
Papovaviruses	Benign and malignant warts
Parvoviruses	Roseola (fever, rash) in children, aggravates sickle-cell anemia
Poxyviruses	Smallpox, cowpox
RNA Viruses:	
Picornaviruses:	
Enteroviruses	Polio, hemorrhagic eye disease, hepatitis A (infectious hepatitis)
Rhinoviruses	Common cold
Togaviruses	Encephalitis, dengue fever, yellow fever
Paramyxoviruses	measles, mumps
Rhabdoviruses	Rabies
Coronaviruses	Respiratory infections
Orthomyxoviruses	Influenza
Arenaviruses	Hemorrhagic fevers
Reoviruses	Respiratory, intestinal infections
Retroviruses:	
HTLV I, II	Associated with cancer
HIV	AIDS, ARC
Filoviruses:	
Marburg virus	Marburg hemorrhagic fever
Ebola virus	Ebola hemorrhagic fever
Miscellaneous viruses:	
The Norwalk group of viruses	Gastroenteritis
Non-A, non-B Hepatitis	Post transfusion hepatitis
Delta hepatitis virus (HDV)	Hepatitis (requires HBV as a helper virus)
Chronic infectious neuropathic agents (CHINAs)	Kuru and Creutzfeldt-Jacob in human, scrapie in sheep

Animal Viruses

Many animal viruses infect humans and animals causing several serious diseases. Table 2 presents a summary of some animal viruses and the diseases they induce.

Viroids and Other Unconventional Agents

Viroids are plant pathogens which consist of naked strands or circles of RNA with no protein coat. Viroids are mere snippets of genes smaller than the smallest known viral DNA or RNA molecule and they can have damaging effects on citrus, avocados, potatoes and other crop plants. Apparently, enzymes already present in a host cell synthesize viroid RNA then use this new viroid RNA as a template for building new viroids.

Some unidentified infectious agents cause some rare fatal diseases of the nervous system including Scrapie in sheep and Kuru and Crutzfeldt-Jacob (mad cow) disease in humans. Probably these diseases are caused by infectious protein particles, tentatively named prions. Prions might be synthesized according to information in mutated genes. Researchers studying scrapie, have isolated the gene coding for altered forms of a protein in infected cells [6].

Measurement of Animal Viruses

Viruses are either measured as infectious units, i.e., in terms of their ability to infect, multiply and produce progeny or as viral particles, regardless of their function as infectious agents [7].

Titration of Viruses as Infectious Units

Titration means the measurement of the amount of virus in terms of the number of infectious unites per unit volume.

Plaque Formation [7]

Monolayers of susceptible cells are inoculated with small aliquots of serial dilutions of the virus suspension to be titrated. Whenever viral particles infect cells, progeny virus particles are produced, released and immediately infect adjoining cells. This process is repeated until after 2-12 incubation days or more. Areas of infected cells develop plaques that can be seen with a naked eye. Agar is frequently incorporated in the medium to ensure that the liberated progeny virus particles in the medium do not diffuse away and initiate separate or secondary plaques. The infected cells must differ in some recognizable manner from non infected ones, i.e., they must

be completely destroyed, become detached from the surface on which they grow or possess staining properties different from those of normal cells. The most common method to visualize plaques is to apply neutral red or crystal violet to the infected cell monolayers and then counting the number of non stained areas [7]. Titers are expressed in terms of number of plaque-forming units (PFU) per milliliter. There is a linear relationship (linear dose-response curve) between the amount of virus and the number of plaques produced which indicates that each plaque is produced by a single viral particle. The virus progeny in each plaque are clones. Virus stocks derived from single plaques are named "plaque purified" which is important in isolating pure virus strains. Plaque formation is the most desirable method of viral titration because it is economic and technically simple. However, not all viruses can be measured this way due to lack of host cells that can develop the desired cytopathic effects (CPE).

Focus Formation [7]

Many tumor viruses do not destroy cells in which they multiply and hence produce no plaques. They induce morphological changes and faster multiplication rate in the infected cells which are known as transformed cells. Colonies of the transformed cells are developed into large foci which are visible by naked eye. Assay by focus formation depends on counting the number of focus-forming units (FFU), which is analogous to plaque formation assay.

Serial Dilution End Point [7]

Some viruses destroy cells they infect but do not produce the necessary CPE for visible plaque formation. These viruses are titrated by serial dilution end point method. Serial dilutions of virus suspensions are inoculated into cell monolayers which are then incubated until the cell sheets show clear signs of cell's destruction. The end point is the dilution that gives a positive (cell-destroying) reaction and originally contains at least one infectious unit.

Enumeration of the Total Number of Viral Particles (Hemagglutination Assay)

Many animal viruses get adsorbed by red blood cells (RBCs) of various animal species. Each viral particle is a multivalent, i.e., it can adsorb more than one cell at a time. In practice, the maximum number of cells with which any particular virus can combine is two since RBCs are bigger than viral particles. In a virus-cell mixture in which the number of cells exceeds the number of viral particles, the small number of cell dimer that may be formed is generally undetectable. If the number of viral particles exceeds the number of cells, a lattice of agglutinated cells is formed that settles out

in a characteristic readily distinguishable manner from the settling pattern exhibited by unagglutinated cells [7]. Hemagglutination assay is the determination of the virus that will exactly agglutinate a standard number of RBCs. Because the number of viral particles required for this is readily calculated (slightly higher than the number of cells), hemagglutination is a highly accurate and rapid assay.

In Vitro *Antiviral Screening Assays* [11,12]

The viral infectivity in cultured cells is determined during virus multiplication in the presence of a single tested compound or extract or after extracellular incubation.

1- Plaque inhibition or reduction assays: Only for viruses which form plaques in suitable cell systems. Titration of a limited viruses number or residual viruses infectivity after extracellular action of the tested compound. The tested compound must be in a non-toxic dose or cytotoxicity should be eliminated by dilution or filtration before the titration.
2- Inhibition of viral-induced CPE: For viruses that induce CPE but do not form plaques in cell cultures. Determination of virus-induced CPE in monolayers cultured in a liquid medium, infected with a limited dose of virus and treated with a non-toxic dose of tested sample.
3- Virus yield reduction assay: Estimation of a virus yield in tissue cultures, infected with a given amount of virus and treated with a non-toxic dose of tested sample.
4- End point titration assay: Determination of viral titer reduction in the presence of two-fold dilutions of tested sample.
5- Assays based on measurements of specialized functions and viral products: For viruses that do not form plaques or induce CPE in cell cultures. Determination of virus specific parameters, e.g., hemagglutination and hemadsorption tests, inhibition of cell transformation and immunological tests detecting antiviral antigens in cell cultures. Reduction or inhibition of the synthesis of virus specific polypeptides in infected cell cultures, e.g., viral nucleic acids, viral genome copy numbers or the uptake of radio labeled precursors.

Current Antiviral Chemotherapy [13,14]

Research in antiviral chemotherapy started around early 1950's when the search for anticancer drugs revealed several new compounds that inhibit viral DNA synthesis, e.g., the pyrimidine analog idoxuridine which was

later approved as a topical treatment for herpes keratitis. Since then, research efforts were focused on both purine and pyrimidine nucleoside analogs [13]. With the emergence of AIDS epidemic, research on antiviral generally and specifically anti-HIV became highest priority. Many of these retrovirus proteins have been purified and characterized for the sake of designing drugs that would selectively inhibit some critical enzymes of HIV such as reverse transcriptase and protease which are required for the final packaging of this virus particle. Most current antiviral agents (purine and pyrimidine derivatives) target reverse transcriptase inhibition to block the transcription of HIV RNA genome to DNA and hence preventing synthesis of viral mRNA and proteins (Figure 1). Protease inhibitors affect the synthesis of late proteins and packaging (Figure 1). No currently available drugs target the early protein synthesis.

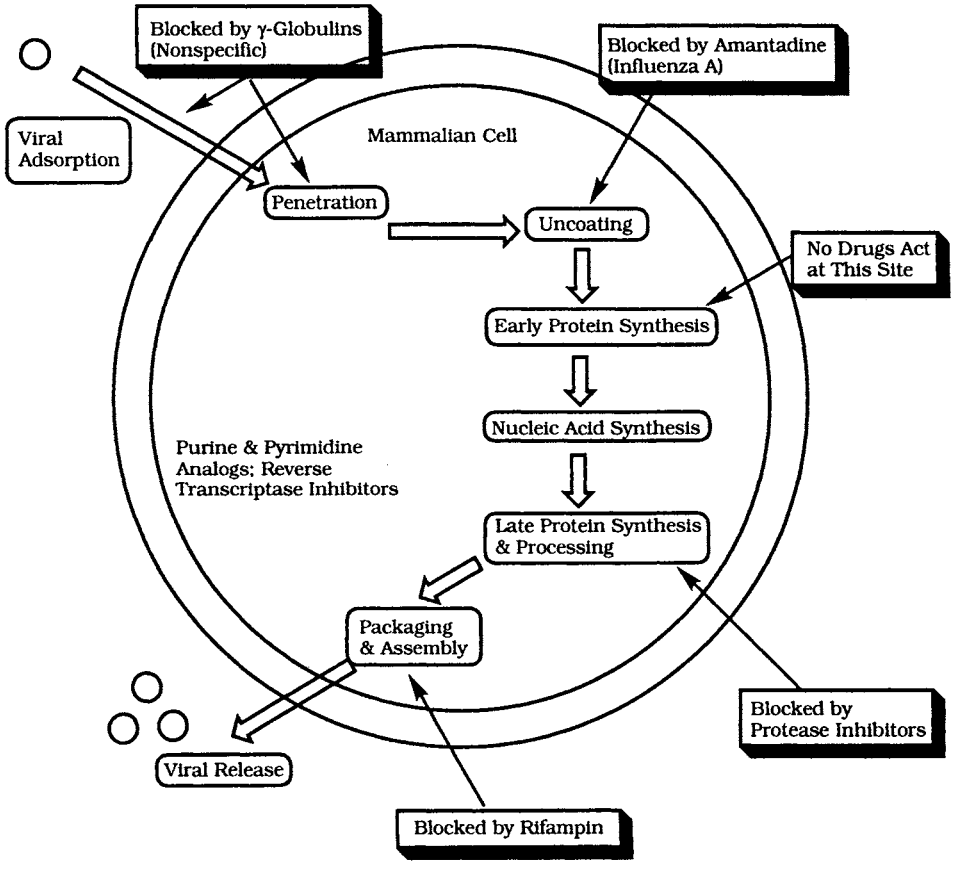


Fig (1). Major sites of action of current antiviral drugs.

Antiherpetic Drugs

1- Acyclovir (**1**) is an acyclic guanosine derivative which is very effective against *Herpes simplex* viruses (HSV)-1, -2 and *Varicella-zoster* virus (VZV). It also shows *in vitro* inhibitory activities against *Epstein-barr* virus (EBV), cytomegalovirus (CMV) and human herpes virus (HHV)-6. Acyclovir requires three phosphorylation steps for activation. It is first converted by the virus-specific thymidine kinase to monophosphate derivative (hence it is selective to the infected cells). Acyclovir monophosphate is then converted by the host's cellular enzymes to di- followed by triphosphate derivatives. Acyclovir triphosphate inhibits viral DNA synthesis by competitive inhibition of GTP for the viral DNA polymerase, irreversibly binding to DNA template and chain termination after incorporation to the viral DNA. Valacyclovir is the L-valyl ester of **1** which is rapidly transformed after ingestion to acyclovir. Resistance to acyclovir can be developed in HSV and VZV through alteration of viral thymidine kinase or DNA polymerase.

2- Famciclovir (**2**) is the diacetyl ester prodrug of 6-deoxy penciclovir, an acyclic guanosine analog. Famciclover is rapidly converted to its prodrug after oral ingestion. The latter is similar to **1** in the margin of activity. It is also active *in vitro* against HSV-1, -2, VZV, EBV and hepatitis virus B (HVB). Activation by phosphorylation is also accomplished by the virus-specific thymidine kinase. Unlike **1**, Penciclovir does not induce DNA chain termination. There is a cross resistance between **1** and penciclovir.

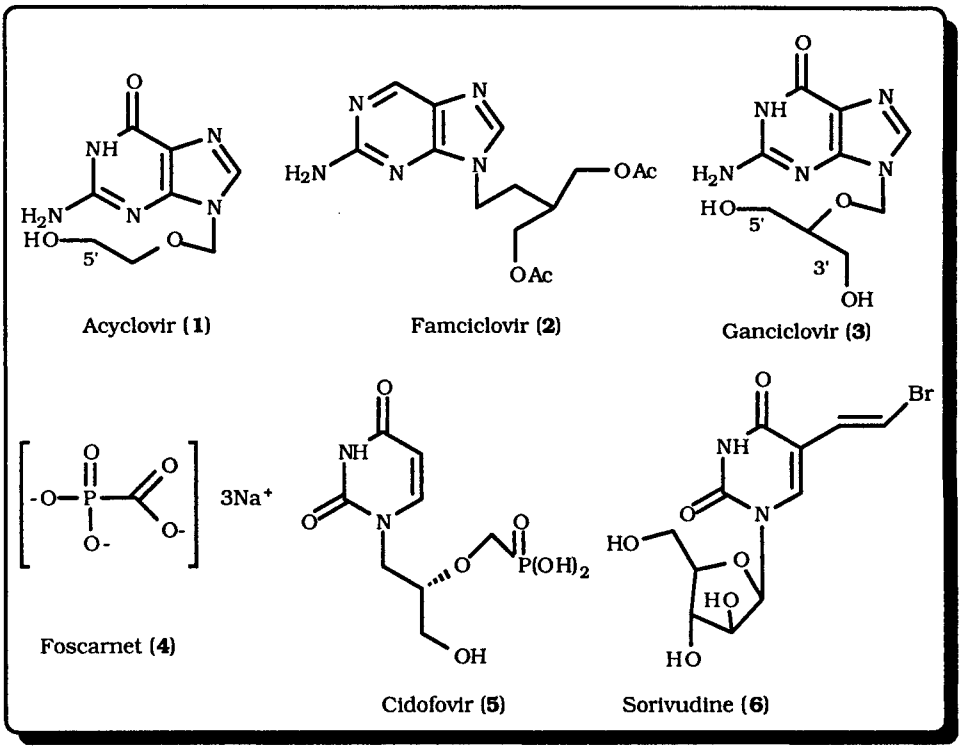
3- Ganciclovir (**3**) is a guanosine analog which also requires triphosphorylation for activation prior to inhibiting the viral DNA polymerase. Monophosphorylation is catalyzed by the virus-specific protein kinase phosphotransferase UL97 in CMV-infected cells and by thymidine kinase in HSV-infected cells. Ganciclovir is active against CMV, HSV, VZV and EBV. Its activity against CMV is 100 fold more than **1** [13].

4- Foscarnet (**4**) is an inorganic pyrophosphate derivative that inhibits viral DNA, RNA polymerases and HIV reverse transcriptase (RT) directly without the need of any activation steps. It is *in vitro* active against HSV, VZV, CMV, EBV, HHV-6, HBV and HIV. Resistance is developed due to mutation in the DNA polymerase gene [13].

5- Cidofovir (**5**) is a cytosine nucleotide analog which is active *in vitro* against CMV, HSV-1, -2, VZV, EBV, adenovirus and human papillomavirus. Phosphorylation of **5** is independent of viral infection [13].

6- Sorivudine (**6**) is an investigational pyrimidine nucleoside analog with an *in vitro* activity against VZV, HSV-1 and EBV. It requires activation through phosphorylation by the virus-specific thymidine

kinase. It competitively inhibits DNA polymerase but does not incorporate into viral DNA.



7- Trifluridine is a fluorinated pyrimidine nucleoside that inhibits viral DNA synthesis. It is *in vitro* active against HSV-1, -2, vaccinia virus (VV) and some advenoviruses. Incorporation of trifluridine phosphate into both viral and cellular DNA prevents its systemic use but not its topical use.

8- Vidarabine is an adenine arabinoside which shows *in vitro* activity against HSV, VZV and CMV. It is phosphorylated intracellularly by host enzymes to form ara-ATP which inhibits viral DNA polymerase. It is incorporated into both viral and cellular DNA and shows some animal teratogenicity [13].

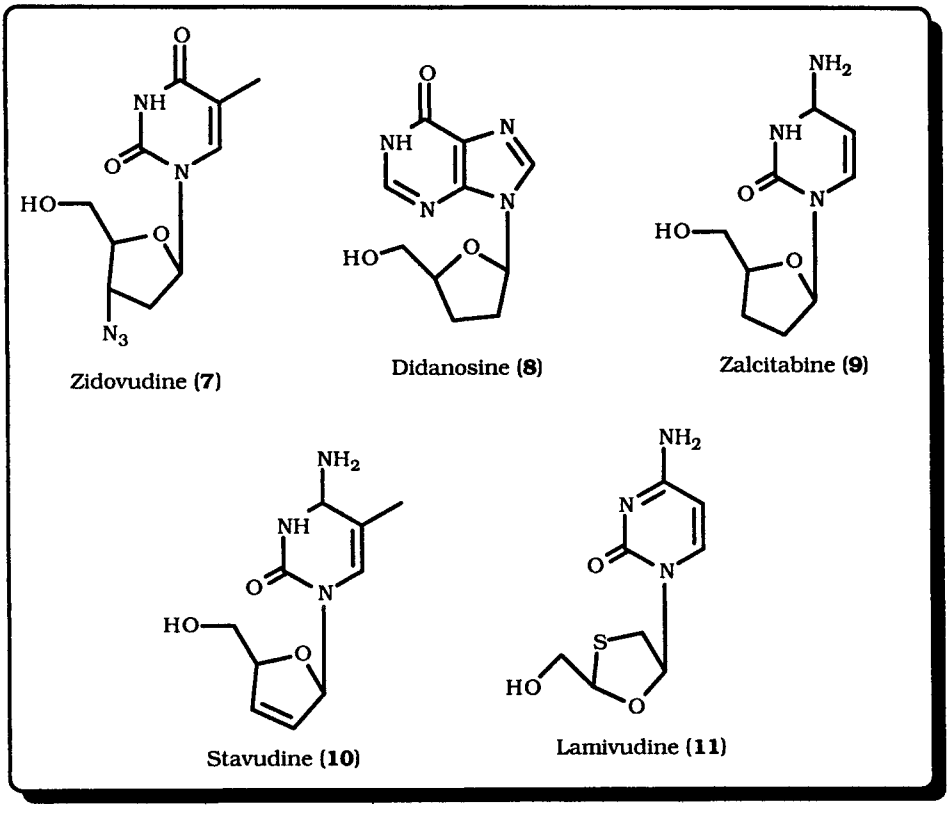
Antiretroviral Drugs [13]

1- Zidovudine (7) (previously azidothymidine, AZT) is a deoxythymidine analog that also requires anabolic phosphorylation for activation. It competitively inhibits deoxythymidine triphosphate for the RT. It also acts as a chain terminator in the synthesis of proviral DNA. It is active against HIV-1, HIV-2 and the

human T cell lymphotropic viruses. Resistance to **7** occurs due to mutation in RT gene.

2- Didanosine (**8**) is a synthetic analog of deoxyadenosine. It is anabolically activated to 2,3-dideoxyadenosine-5-triphosphate which inhibits viral replication as **7**. Resistance is typically associated with mutation at codon 74.

3- Zalcitabine (**9**) is a pyrimidine nucleoside that inhibits replication of HIV-1 in a similar mechanism to **7**. Mutation at codon 65 induces resistance which is associated with the decrease in susceptibility to **8** and **9**.



4- Stavudine (**10**) is a thymidine analog that also requires a metabolic activation as that of **7**. It is active against HIV-1.

5- Lamivudine (**11**) is a nucleoside analog which *in vitro* inhibits HIV-1 and HBV. It inhibits HIV-RT and shows synergistic effect with **7** against HIV-1. It requires metabolic phosphorylation as that of **7**. High level of resistance is developed by mutation at codon 184.

Protease Inhibitors [13]

1- Indinavir is a specific inhibitor of HIV-1 protease which is essential for the production of mature and infectious virions. It is currently clinically approved for treatment of HIV-1 infections.
2- Ritonavir is an inhibitor of HIV protease with high bioavailability. It is metabolized by the hepatic P450 cytochrome oxidase system and hence suffers from several drug interactions.
3- Saquinavir is a synthetic peptide-like analog that inhibits the activity of HIV-1 protease and prevents the cleavage of viral polyproteins.

Other Antiviral Agents

1- Amanatdine and Rimantadine are the 1-aminoadamantane hydrochloride and its α-methyl derivative. Both compounds are cyclic amines that inhibit the uncoating of the influenza A viral RNA within the infected host cell and hence prevent its replication. They are effective in prevention and treatment of influenza A infection in high risk individuals [13].
2- Interferones (INFs) are a family of multifunctional endogenous polypeptides that exerts non-specific antiviral activities through cellular metabolic processes involving the synthesis of both RNA and proteins [13-15]. There are four known varieties of INFs: INF-α, INF- ω, INF-β and INF-γ. In humans, the INF-α family is composed of eighteen genes, six of them are probably pseudogenes. There are six INF-ω genes, five of them are pseudogenes and a single INF-β gene. These three INF subtypes are designated as members of a super family of type I (or α/β) INFs. Unlike the rest of the other INFs, INF-γ is encoded in a single copy gene with three introns and is designated as type II INF. Each type acts as a potent complex antiviral, immunomodulatory and antiproliferative agent. INFs are not direct antiviral agents but they act by causing elaboration of effector proteins in infected cells which inhibits the viral penetration, uncoating, mRNA synthesis and translation or virion assembly and release. Their immunomodulatory effect may be additive to their antiviral effect. Three known enzymes are induced by INFs: 1- Protein kinase that leads to phosphorylation of elongation factor 2, which inhibits peptide initiation. 2- Oligoisoadenylate synthase, which leads to activation of RNAase and degradation of viral mRNA. 3- Phosphodiesterase, which degrades the terminal nucleotides of tRNA and thus inhibiting peptide elongation. Systemic INF-α is currently approved in US for the treatment of chronic HBV and HBC infections. It is also clinically approved for the treatment of AIDS-associated Kaposi's sarcoma and laryngeal papillomatosis.

3- Ribavirin [13] is a guanosine analog that is intracellularly phosphorylated by the host cell's enzymes. Despite its mechanism is not yet fully elucidated, it apparently interferes with the synthesis of guanosine triphosphate to inhibit capping of viral mRNA and some viral RNA-dependent polymerases. Its triphosphate derivative inhibits the replication of a wide range of RNA and DNA viruses including influenza A and B, parainfluenza, respiratory syncytial virus (RSV), paramyxovirus, HCV and HIV-1.

PLANTS AS ANTIVIRAL AGENTS

Introduction

Selection of Plants for Antiviral Screening

Four basic approaches are conducted for plant selection for antiviral screening assays: 1- Random collection of plants followed by mass screening. 2- Ethnomedical approach. 3- Literature-based follow up of the existing leads. 4- Chemotaxonomic approach [12]. The second and third approaches are the most favored ones because of their cost-effective applicability. The selection based on folkloric use proved five times higher percentage of active leads than other approaches. The random approach usually affords more novel compounds with antiviral activity. Combining ethnomedical, phytochemical and taxonomical approaches is considered the best compromise.

Selection of the In Vitro *Assays for Antiviral Screening of Natural Products*

Different cell culture-based assays are currently available and can be successfully applied for plant extracts and pure compounds. Antiviral agents that interfere with one or more viral biosynthetic dynamic processes are good candidates as clinically useful drugs. Virucidal agents that extracellularly inactivate virus infectivity are rather candidates as antiseptics. The key factors that determine the selection of the assay system are: simplicity, accuracy, reproducibility, selectivity and specificity [12]. After evaluation of the antiviral potency of a tested compound along with its cytotoxicity, the therapeutic index in a given viral system is calculated. The therapeutic index is defined as a ratio of the maximum drug concentration at which 50% of the normal cells growth is inhibited to the minimum drug concentration at which 50% (sometimes 90 or 99%) of the virus is inhibited. The relative potency of a new antiviral agent should be compared with an existing approved drug.

In Vivo *Testing of Antiviral Agents*

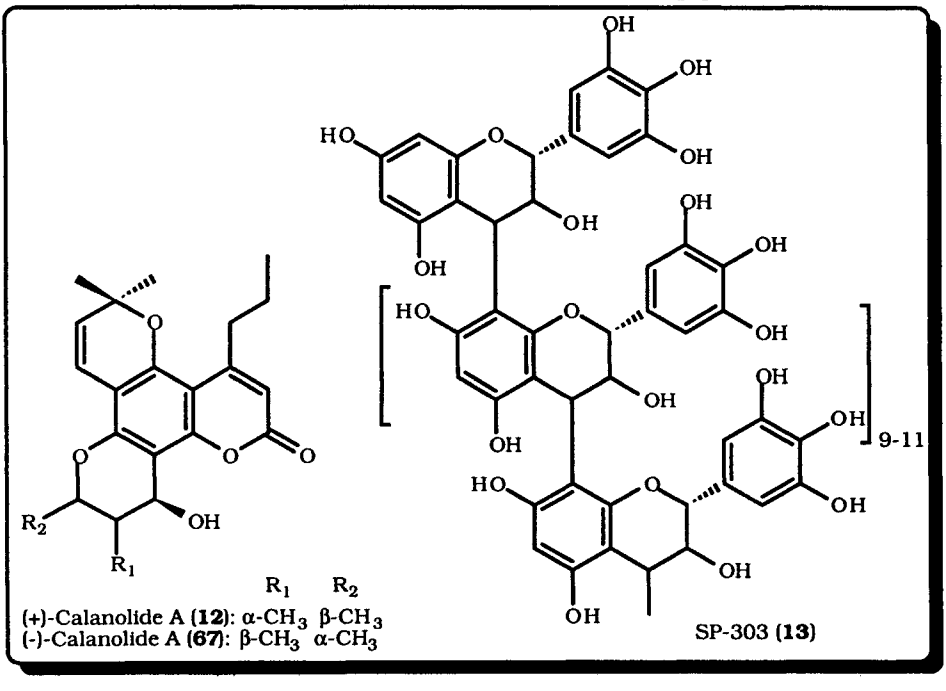
In vivo testing of any new *in vitro* active antiviral agent is considered the key step before any human clinical trials. This model should predict efficacy in human and should mimic the natural disease as close as possible. The therapeutic index of any antiviral agent to be *in vivo* tested should be adequate so that appropriate, non-toxic dose for the animal could be considered. Animal models are useful in:

1- Detecting the effectiveness of the candidate compound as a viral inhibitor without inducing a viral resistance.
2- Testing if the compound is reachable to the target organ without stability problems.
3- Checking if the compound is well excreted and does not interfere with an animal's metabolic processes.
4- Proving that the compound will resist and will not adversely affect the immune system [12].

Two useful animal models are usually employed: heterologus or homologus. In heterologus systems, a disease is induced by a virus from an animal origin in an experimental animal that mimics the human disease. Examples of such systems are *Herpes encephalitis* induced by a human virus, HSV-1 in rodents including mice, rats and hamsters as well as genital herpes induced by HSV-2 in mice, guinea pigs and monkeys. In case of host specific viruses, a homologus system is conducted. For example CMV infection is host specific, i.e., human CMV only infects humans and mice CMV only infects mice. To study a human CMV-induced disease in an animal model, the homologus virus of that animal must be used. However, it is uncertain whether animal models can be developed for all human viral infections. Some viruses are without convenient models, e.g., HBV and human papilloma virus which can be studied in non-human mammals only.

Several reviews have been published dealing with natural products-derived antiviral compounds [11,12,16-23]. Presently, there are only two plant-derived compounds under clinical development [2]. (+)-Calanolide A (**12**) is a C22 coumarin isolated from the Malaysian rainforest tree, *Calophyllum langigerum* by the U.S. National Cancer Institute [2]. It shows a potent HIV-RT inhibitory activity [2]. *In vitro* studies of **12** demonstrated activity against HIV-1 including AZT and other non-nucleoside RT inhibitors-resistant strains. It also shows synergistic anti-HIV activity in combination with nucleoside RT inhibitors: **7**, **8** and **9** [2]. To overcome the difficulty of supply of **12**, its total chemical synthesis was accomplished [2]. In June 1997, clinical development of **12** was started as a potential drug for treatment of AIDS. A single -center 7-month U.S. phase Ia clinical trial of **12** was started to assess its safety and

tolerability [2]. SP-303 (**13**) is a mixture of natural oligomeric proanthocyanidins up to a molecular weight 2100 daltons. It is isolated from the latex of a Latin American plant *Croton lechleri* [2]. It shows potent *in vitro* activity against HSV and other varieties of DNA and RNA viruses. Virend, which is the topical formulation of **13**, is evaluated in phase II clinical trials for the treatment of genital herpes in combination with acyclovir. These trials were later suspended as they proved virend to have no additional benefit over using oral acyclovir alone. Provir, the oral formulation of SP-303, is proved to be safe and well tolerated in phase I trials but ineffective in phase II for the treatment of RSV since there was no adequate absorption by patients. However, provir was proved effective in symptomatic treatment of traveler's diarrhea through restoration of normal bowel function and prevention of recurrences [2].



Plant-Derived Antiviral Compounds

Alkaloids

Alkaloids are heterogeneous group of compounds linked by the common possession of a basic nature, containing one or more nitrogen atoms usually in combinations part of heterocyclic system [11]. Their precursors are usually amino acids and they exert certain biological activities. Many

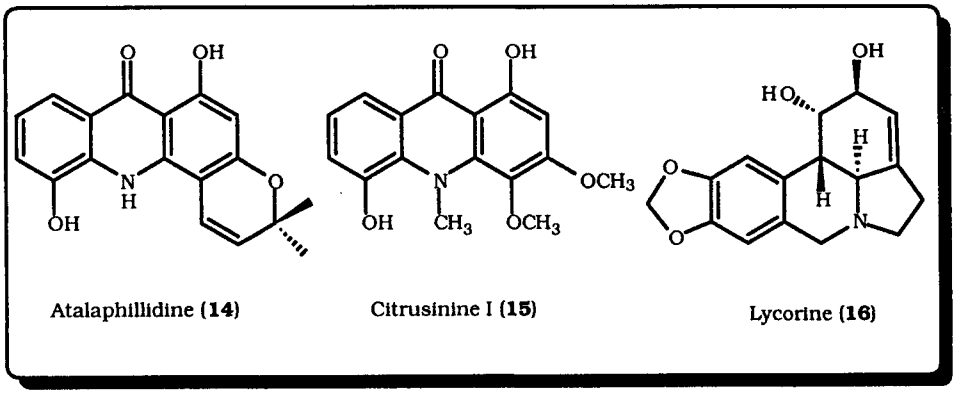
alkaloids are also found in animals and humans where they could exert a profound pharmacological activity [11]. Table 1 illustrates various alkaloids with activity against many animal viruses.

Table 3. Antiviral Plant-Derived Alkaloids

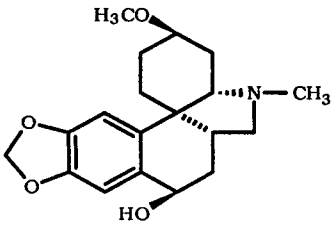
Alkaloid: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Acridone: Atalaphillidine (**14**), Citrusinine I (**15**)	*Atalantia monophylla* *Citrus* sp.	HSV	Virus-coded riboucleoside reductase Viral DNA-synthesis	[12]
Amaryllidaceae: Lycorine (**16**), Pretazettine (**17**)	*Clivia miniata* *Narcissus tazetta*	HSV	Cytotoxic Protein synthesis	[24,25, 16]
Aporphine: Oliverine (**18**), Pachystaudine (**19**), Oxostephanine (**20**)	*Polyalthia oliveri* *Pachypodanthium staudi* *Stephania Japonica*	HSV	Late protein synthesis Assembly of virions	[26]
Benzophenanthridine: Chelidonine (**21**), Fagaronine (**22**), Nitidine (**23**)	*Chelidonium majus* *Fagara xanthoxyloides* *Xanthoxylium* sp.	HSV HIV-RT	Cytotoxic/ Cell protein synthesis	[27-29]
β-Carboline: Brevicollin (**24**), 6-Canthinone (**25**), Harmine (**26**), Harmane (**27**), Harmol (**28**)	About 26 families	SV, MCMV	Late protein synthesis Viral replication	[11]
Chromone: Schumannificine (**29**)	*Schumaniophyton magnificum*	HIV	Irreversible binding to gp120	[12]
Flavonoid: O-Demethyl-buchenavianine (**30**)	*Buchenavia capitata*	HIV	Cytotoxic	[30]
Indole: Camptothecin (**31**), 10-OMe-camptothecin	*Camptotheca acuminata*	HSV	Cytotoxic DNA topoisomerase	[12, 31]
Indolizidine: Castanospermine (**32**), Alexine	*Castanospermum australe* *Alexia leiopetala*	HIV	Glucosidase I	[32-34]
Naphthylisoquinoline: Michellamines A, B (**33**), C	*Ancistrocladus korupensis*	HIV	HIV-induced cell killing HIV-RT	[35, 36]

(Table 3). contd.....

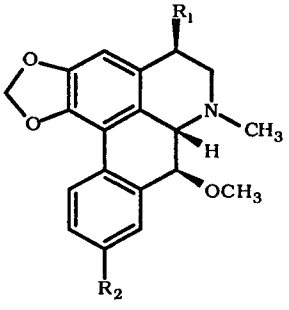
Alkaloid: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Opium: Morphine (**34**), Codeine (**35**), Papaverine (**36**)	*Papaver somniferum*	HSV	Non-specific at subtoxic concentration	[16]
Phenanthroquinozolizidine: Cryptopleurine (**37**)	*Boehmeria cylindrica*	HSV	Cytotoxic/ cell protein synthesis	[37]
Piperidine: 1-Deoxynojirimycin (**38**), 1-Deoxymannojirimycin (**39**), α-Homonojirimycin (**40**)	*Omphalea diandra*	HIV	Glucosidase I Mannosidase I	[12, 38]
Protoberberine: Berberine (**41**), Columbamine (**42**), Palmatine (**43**)	*Corydalis cava*	HIV-RT	HIV-RT	[29, 39]
Pyrrolizidine: Australine (**44**)	*Castanospermum australe*	HIV	Glucosidase I	[12]
Quinoline/Isoquinoline: Emetine (**45**), Psychotrine (**46**), Buchapine (**47**)	*Cephalis ipecacuanha* *Haplophylum tuberculatum* *Euodia oxburghiana*	HSV HIV-RT HIV-RT	Cytotoxic/Prote in synthesis HIV-RT HIV-RT	[16, 29, 40]
Tropane: Atropine (**48**), Scopolamine (**49**)	*Atropa belladona* *Datura stramonium*	HSV	Viral protein glycosylation Non-specific at subtoxic concentration	[16, 41]



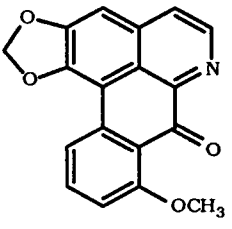
Atalaphillidine (**14**) Citrusinine I (**15**) Lycorine (**16**)



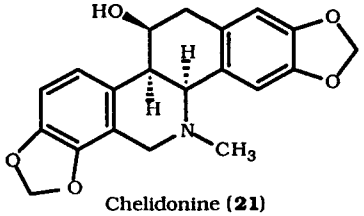
Pretazettine (**17**)



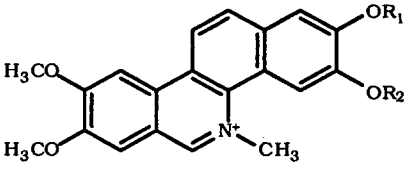
Oliverine (**18**) R_1 = H; R_2 = H
Pachystaudine (**19**) R_1 = OH; R_2 = OCH_3



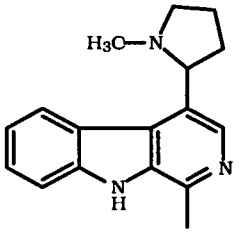
Oxostephanine (**20**)



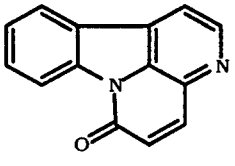
Chelidonine (**21**)



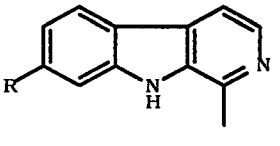
Fagaronine (**22**) R_1 = H; R_2 = CH_3
Nitidine (**23**) R_1 = R_2 = CH_2



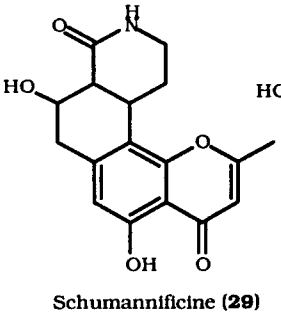
Brevicollin (**24**)



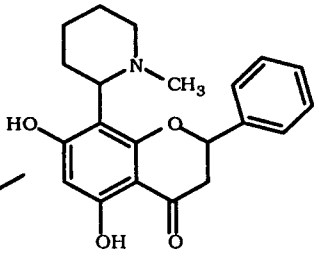
6-Canthinone (**25**)



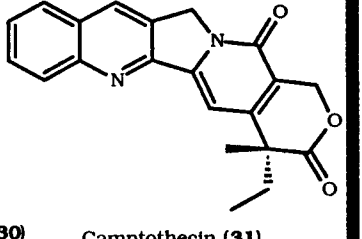
Harmine (**26**) R = OCH_3
Harmane (**27**) R = H
Harmol (**28**) R = OH



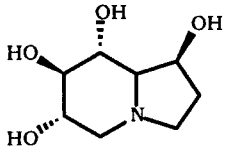
Schumannificine (**29**)



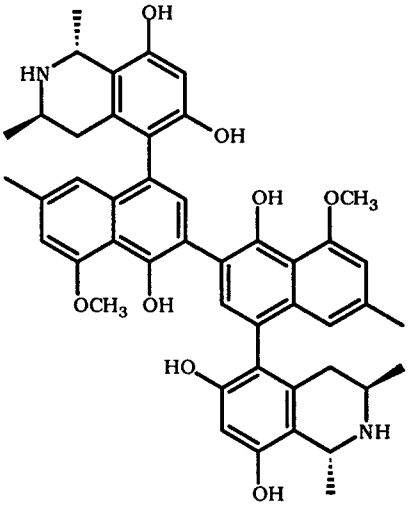
O-Demethylbuchenavianine (**30**)



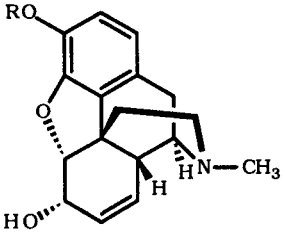
Camptothecin (**31**)



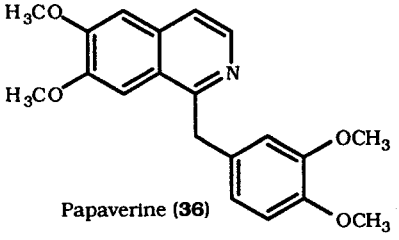
Castanospermine (**32**)



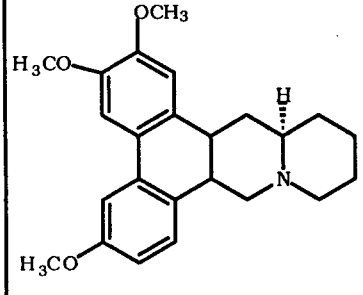
Michellamine (**33**)



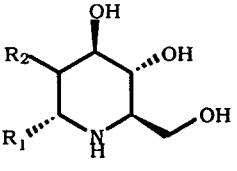
Morphine (**34**) R = H
Codeine (**35**) R = CH_3



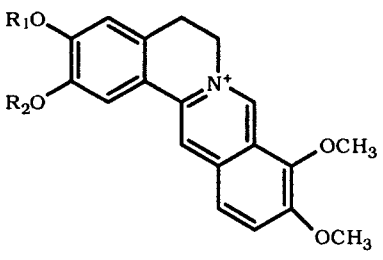
Papaverine (**36**)



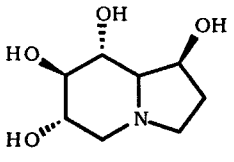
Cryptopleurine (**37**)



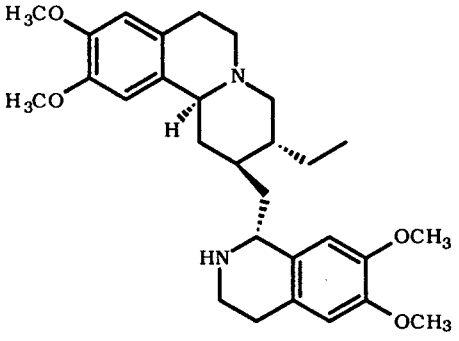
1-Deoxynojirimycine (**38**):
R_1 = H, R_2 = α-OH
1-Deoxymannojirimycin (**39**):
R_1 = H, R_2 = β-OH
α-Homonojirimycin (**40**):
R_1 = CH_2OH, R_2 = α-OH



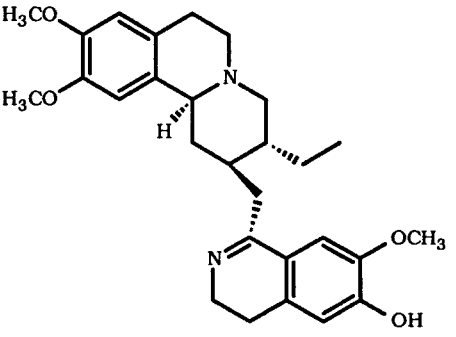
Berberine (**41**) R_1, R_2 = -CH_2-
Columbamine (**42**) R_1 = CH_3, R_2 = H
Palmatine (**43**) R_1 = R_2 = CH_3



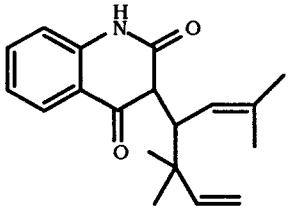
Australine (**44**)



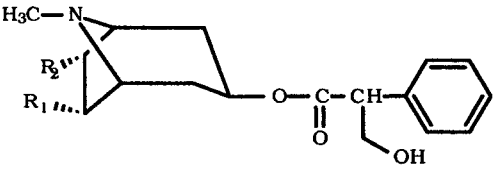
Emetine (**45**)



Psychotrine (**46**)



Buchapine (**47**)



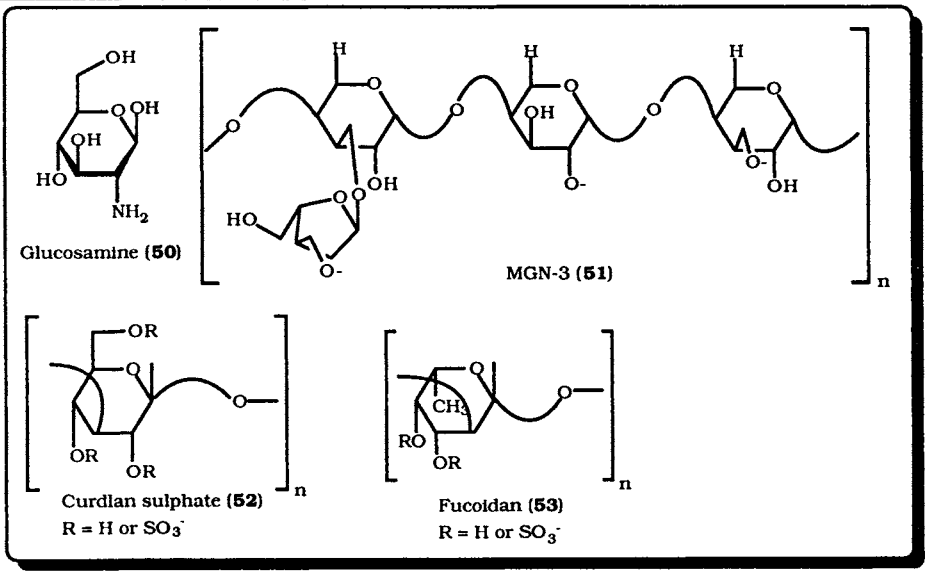
Atropine (**48**) R_1 = R_2 = H
Scopolamine (**49**) R_1, R_2 = Epoxy

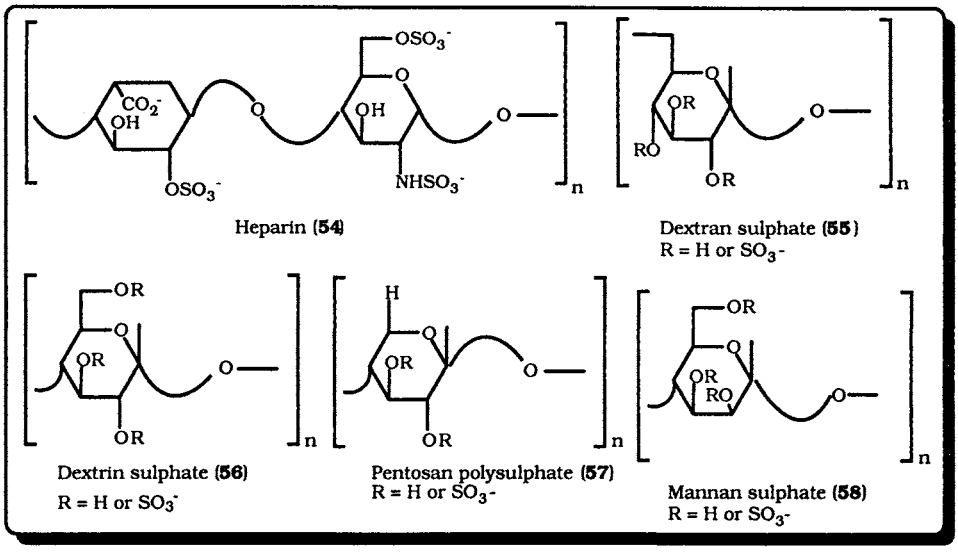
Carbohydrates

Many plant-derived carbohydrates exhibited *in vitro* inhibitory activities against HIV, HIV-RT, CMV and HSV. Table 4 summarizes the antiviral activity of plant and some non-plant carbohydrates.

Table 4. Antiviral Plant-Derived Carbohydrates

Carbohydrate: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Monosaccharides:				
Glucosamine (**50**)	*Glycine max.* & *Dahlia* sp.	HSV	Gylycolipid and glycoprotein syntheses	[18]
Polysaccharides:				
Arabinoxylans: MGN-3 (**51**)	Rice bran enzymatically modified with *Hyphomycetes mycelia*	HIV	HIV replication, Syncytia formation, Increase T & B cell mitogen response	[42]
Sulphated polysaccharides:				
Acemannan, Prunellin, Sea algal extract (SAE) γ-carrageenan, Curdlan sulphate (**52**) Fucoidan (**53**)	*Aloe* sp., *Alternanthera philoxeroides*, *Chondrus crispus*, *Gigartina* sp., *Prunella vulgaris*, *Schizymenia dubyi*, *S. pacifica*, *Viola yedoensis*	HIV HIV	Interaction with gp120, Blocking the binding of gp120 to CD_4 receptor, Virus attachment, Syncytium formation, Immunostimulation: Acemannans	[12] [18] [43-45]
NON PLANT ORIGINS:				
Heparin (**54**), Dextran sulphate (**55**), Dextrin sulphate (**56**), Pentosan polysulphate (**57**), Mannan sulphate (**58**)				
Lectins:				
Mannose specific lectins	*Cymbidium hybrid*, *Epipactis helleborine*, *Hippeastrum hybrid*, *Listeria ovata*, *Machaerium biovulatum*, *M. lunatus*, *Gerardia savaglia*	HIV CMV	Cell fusion of HIV replication, Syncytium formation.	[12] [46]





Chromones, Coumarins and Flavonoids

Chromones, furanocoumarins and flavonoids are common constituents in many plant families. Coumarins are specifically abundant in the families Rutaceae and Umbelliferae [11]. The yield could sometimes reach up to 1% of the dry plant weight. Table 5 illustrates various antiviral activities of chromones, coumarins and flavonoids.

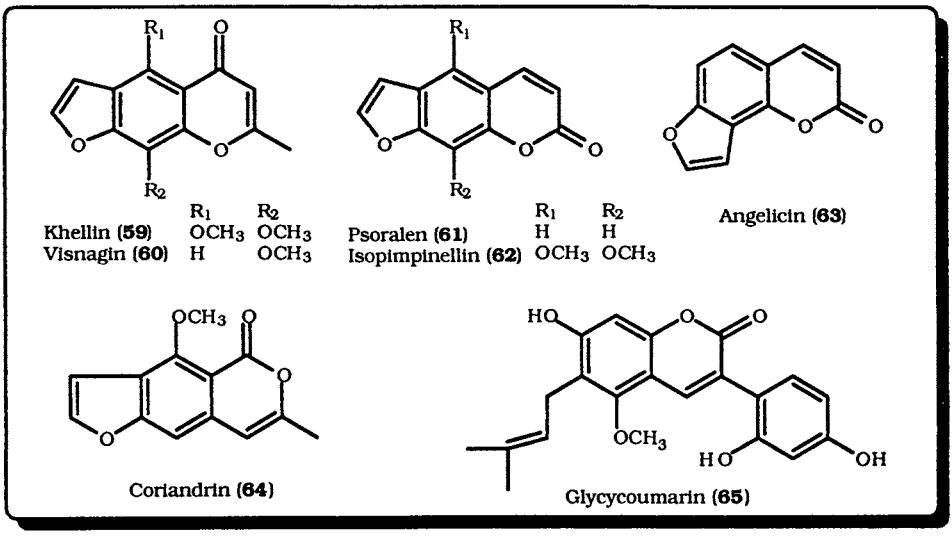
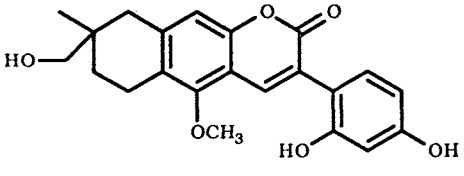


Table 5. Antiviral Plant-Derived Chromones, Furanocoumarins and Flavonoids

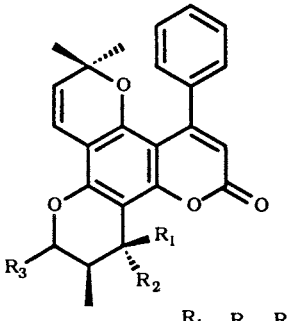
Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Chromones and Coumarins:				
Khellin (**59**), Visnagin (**60**), Psoralen (**61**), Isopimpinellin (**62**), 8-Methoxypsoralen, Angelicin (**63**), Coriandrin (**64**)	*Ammi* species (Umbelliferae) *Coriandrum sativum*	DNA, RNA viruses and Bacteriophages HIV	Cross linking viral DNA Adds to viral pyrimidines (in DNA) and uridines (in RNA), forming cycloadduct	[11] [21]
Glycycoumarin (**65**), Licopyranocoumarin (**66**)	*Glycyrrhiza glabra*	HIV	Giant cell formation	[47]
Calanolides A (**12**), B (**67**) (Costatolide), Soulattrolide (**68**), Inophyllums A (**69**), B, C, D (**70**) and E	*Calophyllum langigerum* *C. teysmannii* *C. inophyllum*	HIV-RT	HIV-RT	[48] [49] [50] [12]
Flavonoids:				
Anthocyanins: Cyanidin (**71**), Pelargodin (**72**)	Many sp.	HSV	Virucidal	[12]
Catechins: Catechin (**73**)	Many sp.	HSV	Virucidal	[12]
Flavanones/ Dihydroflavano-ls: Naringin (**74**), Hesperetin (**75**), Taxifolin (**76**), Dihydrofisetin	Many sp.	HSV	Virucidal	[12]
Flavones/Flavonols:				
Apigenin (**77**), Luteolin (**78**),	Many sp.	HSV	Virucidal	[12,
Luteolin-7-glucoside, Morin,	*Plantago* sp.	HIV-RT	HIV-RT	21]
Quercetin (**79**),	*Euphorbia grantii*	Picornavirus, e.g., rhino &		[51] [52]
Quercetagistrin,	*Agastache rugoza*	coxsackie V.	Giant cell formation	[53]
Quercimeritrin, Quercetrin,	*Callicarpa japonica*	HSV-1, CMV & Poliovirus		[54] [55]
3-Methoxyflavones, 4',5-Dihhydroxy-3,3',7-trimethoxyflavone (**80**)	*Glycyrrhiza glabra*	HIV	Viral replication, synergistic with acyclovir	[56] [57]
5,6,7-Trimethoxyflavone	Many sp.	HIV	Selective interaction with gp120	[47]
Glycyrrhizoflavone (**81**)	Many sp.	HIV-RT	HIV-RT	[12,
Myricetin (**32**), Kaempferol (**83**), & their 3-*O*-glucosides				21]
Baicalein (**84**),				[58]
6-Hydroxyluteolin (**85**),				
Pedalitin (**86**),				
Scutellarein (**87**), Quercetagetin (**88**), Gossypetin (**89**),				
6-Hydroxykaempferol (**90**)				
Isoflavones/Isofalvonols:				
5-*O*-Methylgenistein-7-glucoside (**91**)	*Ulex europaeus*	HSV	Uknown	[59]
Isolicoflavonol (**92**)	*Glycyrrhiza glabra*	HIV	Giant cell formation	[47]

(Table 5). contd.....

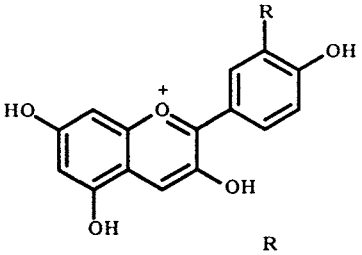
Type & Name	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Chalcones: Licochalcone A (**93**)	*Glycyrrhiza glabra*	HIV	Giant cell formation	[47]
Flavans: (-)-Epicatchin-3-*O*-gallate (**94**), Epicatchin (**95**),	Many sp.	HIV	Selective interaction with gp120	[12]
Biflavones: Amentoflavone (**96**)	*Vibumum prunifolium*	HIV-RT	HIV-RT	[12]
Flavanone-Xanthone: Swertifrancheside (**97**)	*Swertia franchetiana*	HIV-RT	HIV-RT	[60]



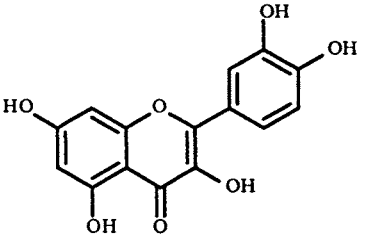
Licopyranocoumarin (**66**)



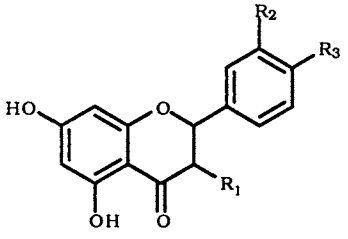
	R_1	R_2	R_3
Soulattrolide (**68**)	OH	H	α-CH_3
Inophyllum A (**69**)	OH	H	β-CH_3
Inophyllum D (**70**)	H	OH	β-CH_3



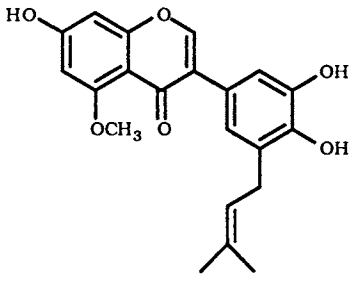
	R
Cyanidin (**71**)	OH
Pelargodin (**72**)	H



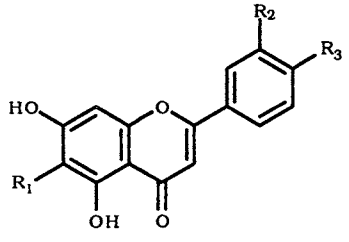
Catechin (**73**)



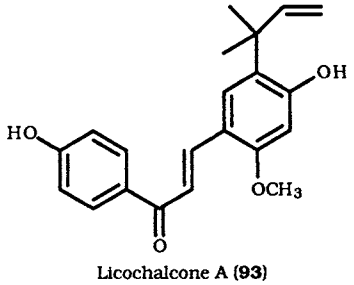
	R_1	R_2	R_3
Naringin (**74**)	H	H	OH
Hesperetin (**75**)	H	OH	OCH_3
Taxifolin (**76**)	OH	OH	OH



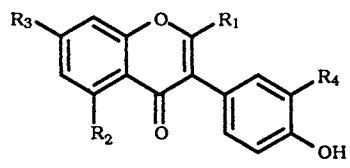
Glycyrrhizoflavone (**81**)



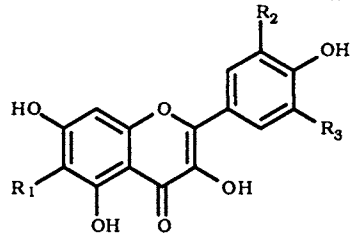
	R_1	R_2	R_3
Apigenin (**77**)	H	H	OH
Luteolin (**78**)	H	OH	OH
Baicalein(**84**)	OH	H	H
6-Hydroxyluteolin (**85**)	OH	OH	OH
Pedalitin (**86**)	OH	CH_3	OH
Scutellarein (**87**)	OH	H	OH



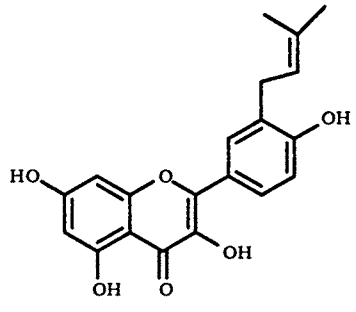
Licochalcone A (**93**)



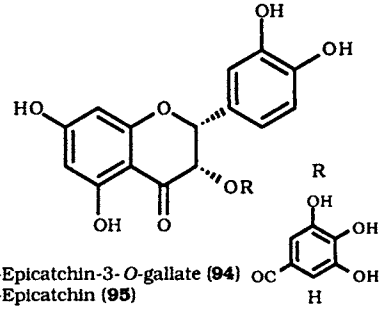
	R_1	R_2	R_3	R_4
4',5-Dihydroxy-3,3',7-trimethoxy flavone (**80**)	OCH_3	OH	OCH_3	OCH_3
5-*O*-Methylgenistein-7-glucoside (**91**)	H	OCH_3	O-Glc.	H



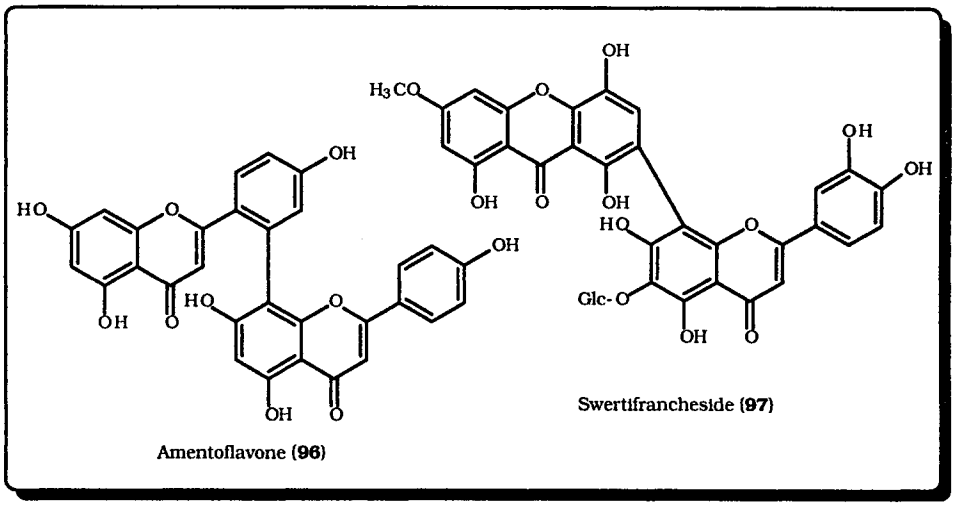
	R_1	R_2	R_3
Quercetin (**79**)	H	OH	H
Myricetin (**82**)	H	OH	OH
Kaempferol (**83**)	H	H	H
Quercetagetin (**88**)	OH	OH	H
Gossypetin (**89**)	H	OH	OH
6-Hydroxykaempferol (**90**)	OH	H	H



Isolicoflavonol (**92**)



(-)-Epicatchin-3-*O*-gallate (**94**)
(-)-Epicatchin (**95**)



Lignans, Phenolic, Quinone/Xanthone and Phenylpropanoid Compounds

Lignans are widespread secondary metabolites in plant kingdom. They occur in many parts of plants especially wood, resin and bark trees [11]. They are also found in many roots, leaves, flowers, fruits and seeds [61]. There is an evidence that lignans play a major role in plant-plant, plant-insect and plant-fungus interactions [11]. The chemical structures of

Table 6. Antiviral Plant-Derived Lignans, Phenolics, Quinone/Xanthones and Phenylpropanoids

Lignan/: Type & Name Phenolic/quinone/Xan-thone	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Lignans:				
α-Peltatin (**98**), Podophyllo-toxin (**99**) & its deoxy analog (-)-Arctigenin (**100**), (-)-Trachelogenin (**101**), 3-*O*-Demethylarcetagenin, High M. Wt. Compounds KS-6 & KS-7-Rhinacanthins F (**102**) & E (**103**) Termilignan (**104**), Thannilignan (**105**), Anolignan (**106**) Justicidin A (**107**), B, C and their 6'-*O*-glucosides, D, Diphyllin, Diphyllin aposide	*Podophyllum peltatum* *Amanoa oblongifolia* *Forsythia intermedia* *Ipomea cairica* *Pinus* sp. *P. parviflora* *Rhinacanthus nasutus* *Terminalia bellerica* *Justicia procumbens*	HSV HIV Influenza A HIV-1 VSV	Cytotoxic, disruption of cellular microtubules, early stage of replication. Suppression of integration of proviral DNA into cellular genome. Replication/micro-tubule formation, nucleic acid metabolism. HIV-RT Unkown	[62] [63, 64] [65] [66, 67] [68] [69] [70]
Phenolics:				
Benzoic acid derivatives: Woodorien (**108**)	*Woodwardia orientalis*	HSV	Uknown	[59]

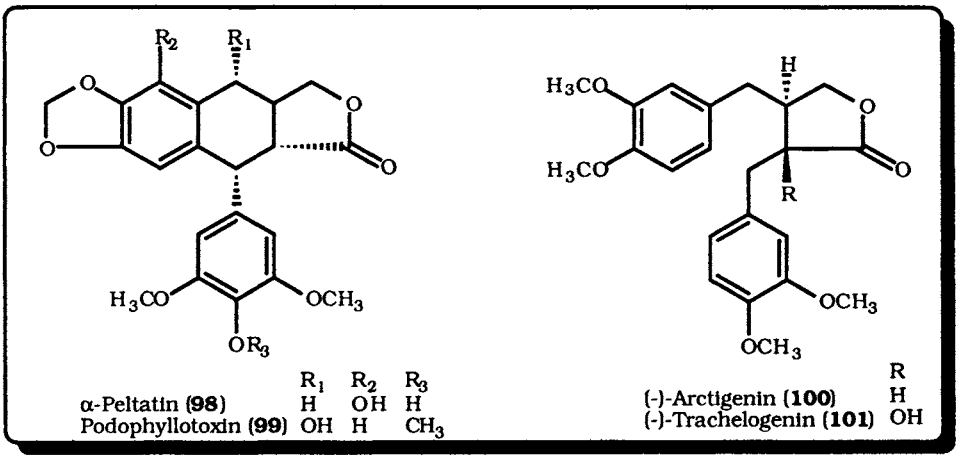
(Table 6). contd.....

Lignan/: Type & Name Phenolic/quinone/Xan-thone	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Binaphthalenes: (-)-Gossypol (**109**) & its analogs	*Gossypium* sp.	HIV	Virucidal	[71, 72]
Caffeic acid derivatives: Caffeic acid (**110**), Chlorogenic acid (**111**) & its butyl ester, Rosmarinic acid (**112**), KOP (Caffeic acid oxidised polymer). 3,4,5-Tri-*O*-caffeoyl-quinic acid, 4,5-Di-*O*-caffeoylquinic acid, Synapoic acid	Many sp. *Securidaca longipedunculata*	HSV HIV	Virucidal, Cellular DNA metabolism. Binding of gp120 to CD4 HIV-RT	[16, 73, 74] [75, 76]
Gallic acid derivatives: Methylgallate (**113**) 3,4,5-Tri-*O*-galloylquinic acid	*Sabium sebiferum* *Guiera senegalensis*	HSV HIV	Virucidal Binding of gp120 to CD4 HIV-RT	[12] [75, 76]
Dehydrogenation polymers of cinnamic derivatives (MW 800-150,000)	Synthesis in presence of peroxidase & H_2O_2	HIV	Unknown	[12]
Catechinic derivatives: Alkaline auto-oxidised catechinic acid Comps. (AOCA)	*Combretum micranthum*	HIV	Viral penetration	[12]
Catechols: Peltatols A (**114**), B, C	*Potomorpha peltata*	HIV	Unknown	[77]
Phloroglucinol derivatives: Sessiliflorene (**115**), Sessiliflorol (**116**), Methoxyresorcinol analogs, Butyrylmallotochromanol (**117**), Isomallotochroman, Euglobal G3 (**118**) Syzygiol (**119**), Chinesin II (**120**). Mallotochromene (**121**), Mallotojaponin (**122**) Macrocarpal A (**123**), B, C, D, E	*Mallotus japonicus* *Melicope sessiliflora* *Eucalyptus grandis* *Syzygium polycephaloides*, *Hypericum chinese* *Mallotus japonicus* *Eucalyptus grandis*	HSV HSV HIV HIV	Cytotoxicity Cytotoxic HIV-RT HIV-RT	[78, 79] [80, 81] [12] [82]
Oligostilbenes: Dibalanocarpol (**124**), Balanocarpol (**125**)	*Hopea malibato*	HIV	Unknown	[83]
Quinones/Xanthones: Anthraquinones/ xanthones: Aloe-emodin (**126**), Mangiferin (**127**)	Many sp.	HSV	Topically used	[84]

(Table 6). contd.....

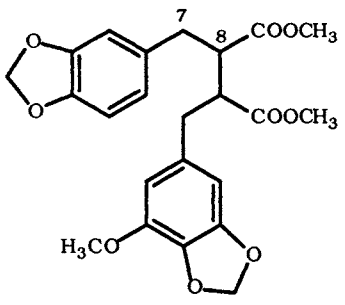
Lignan/: Type & Name Phenolic/quinone/Xan-thone	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Naphthodianthrones: Hypericin (**128**), Pseudohy-pericin (**129**)	*Hypericum triquetrifolium*, *H. perforatum* *Hypericin* sp.	HSV HIV	Non-specific union with viral & cellular Memberanes, Photosensitizers Viral & virion assembly	[12] [85] [86]
Naphthoquinones: Juglone (**130**), Plumbagin (**131**), β-lapachone (**132**) Conocurvone (**133**) Isoeleutherol (**134**), Isoeleutherin	*Juglans regia* *Drosera sp.* *Conospermum* sp. *Eleutherin americana*	HSV HIV HIV	Non-specific at subtoxic doses No virucidal effects Unknown Uknown	[16] [87] [88]
Phenylpropanoids: Luteosides A (**135**), B (**136**), C (**137**), Verbascoside (**138**), Isoverbascoside (**139**)	*Markhamia lutea*	RSV	Intracellular mechanism	[89]

lignans are diverse and complex despite they are essentially dimers of phenylpropanoid units (C_6-C_3) linked by the central carbons of their side chains [11]. Presently, there are six lignan subgroups: butane derivatives, lignanolides (butanolides), monoepoxylignans (tetrahydrofuran derivatives), bisepoxylignans (3,7-dioxabicyclo(3.3.0)-octane derivatives), cyclolignans (tetrahydronaphthalenes) and cyclolignans based on naphthalene [11]. Phenolics, benzoquinones, naphthoquinones, anthraquinones and phenylpropanoids are abundant secondary metabolites in plants. Table 6 illustrates the reported antiviral activities of these plant secondary metabolites.

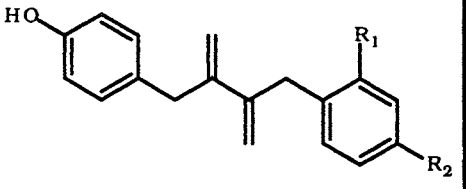


	R_1	R_2	R_3
α-Peltatin (**98**)	H	OH	H
Podophyllotoxin (**99**)	OH	H	CH_3

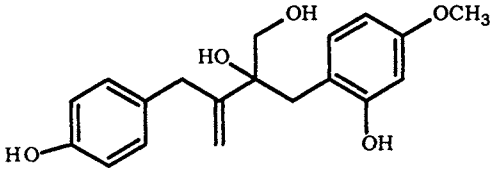
	R
(-)-Arctigenin (**100**)	H
(-)-Trachelogenin (**101**)	OH



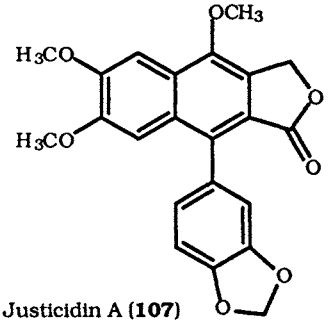
Rhinacanthin-F (**102**)
Rhinacanthin-E (**103**),$\Delta^{7,8}$ *E*



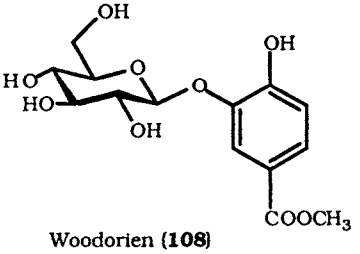
	R_1	R_2
Termilignan (**104**)	OH	OCH_3
Anolignan B (**105**)	H	OH



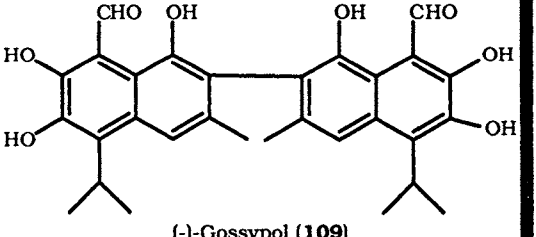
Thannilignan (**106**)



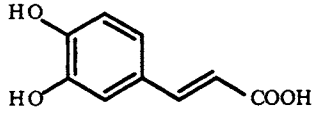
Justicidin A (**107**)



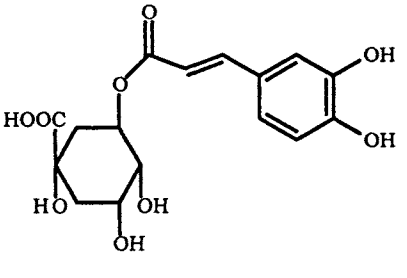
Woodorien (**108**)



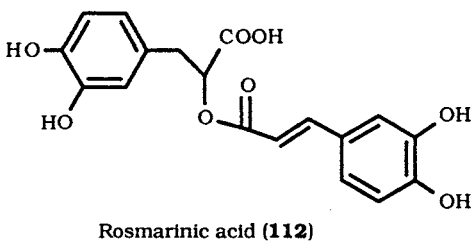
(-)-Gossypol (**109**)



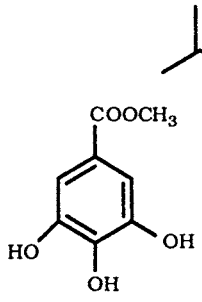
Caffeic acid (**110**)



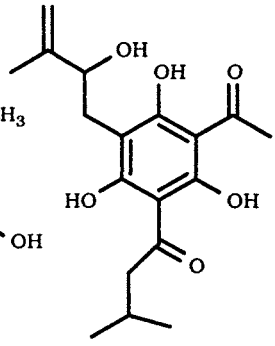
Chlorogenic acid (**111**)



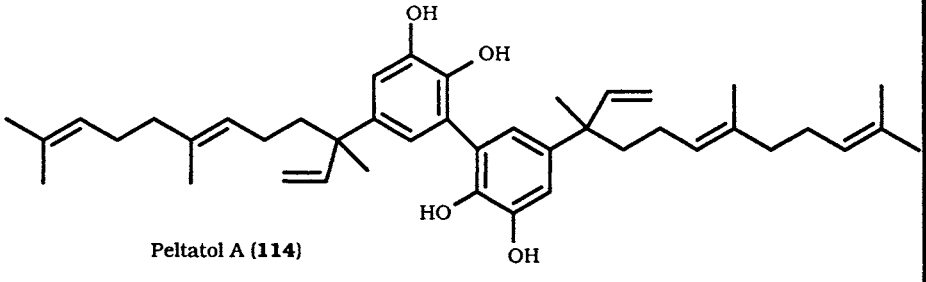
Rosmarinic acid (**112**)



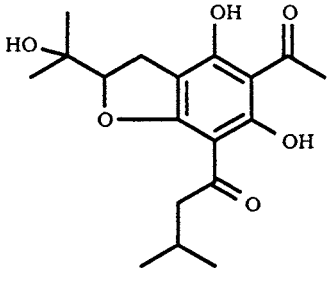
Methylgallate (**113**)



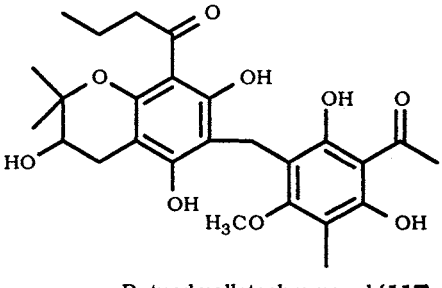
Sessiliflorene (**115**)



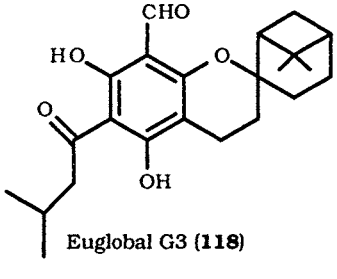
Peltatol A (**114**)



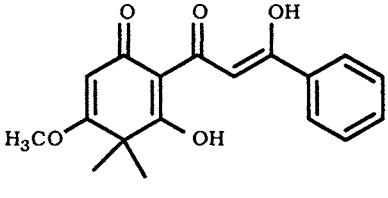
Sessiliflorol (**116**)



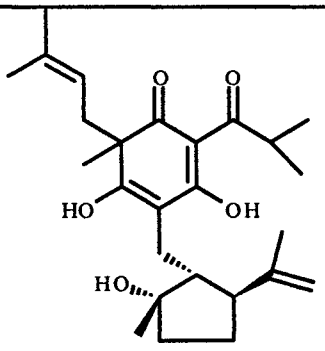
Butyrylmallotochromanol (**117**)



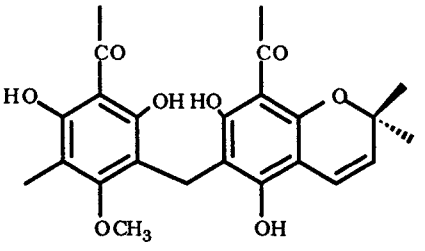
Euglobal G3 (**118**)



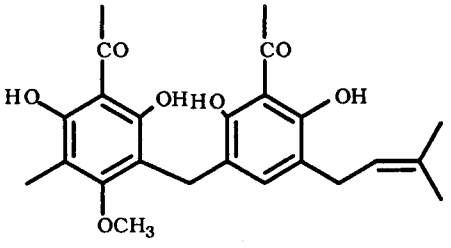
Syzygiol (**119**)



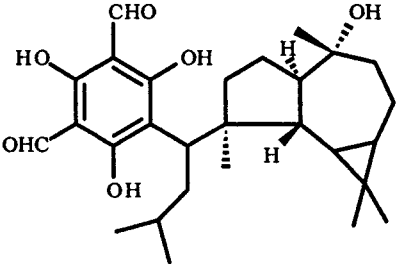
Chinesin II (**120**)



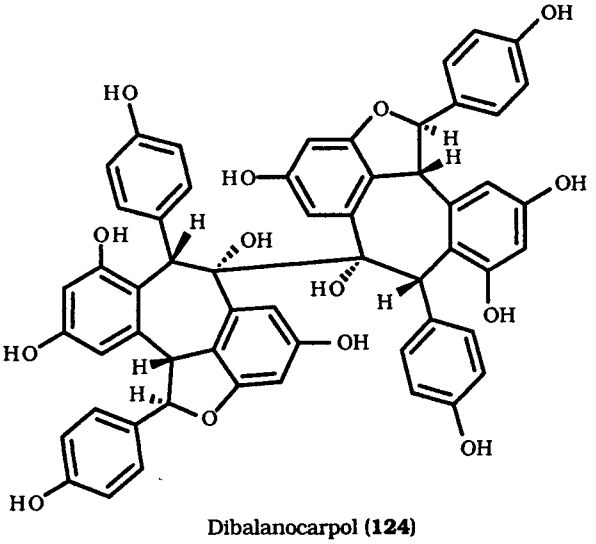
Mallotochromene (**121**)



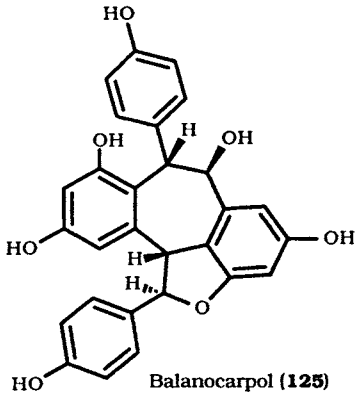
Mallotojaponin (**122**)



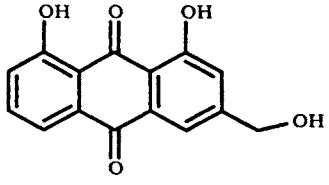
Macrocarpal (**123**)



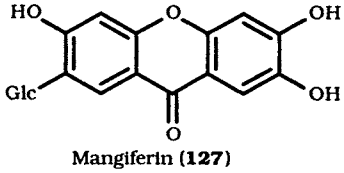
Dibalanocarpol (**124**)



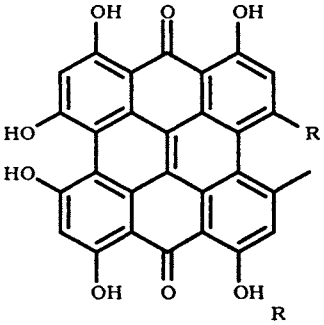
Balanocarpol (**125**)



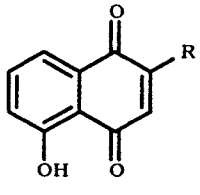
Aloe-emodin (**126**)



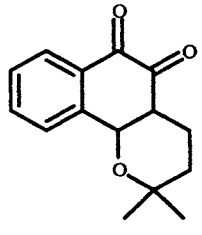
Mangiferin (**127**)



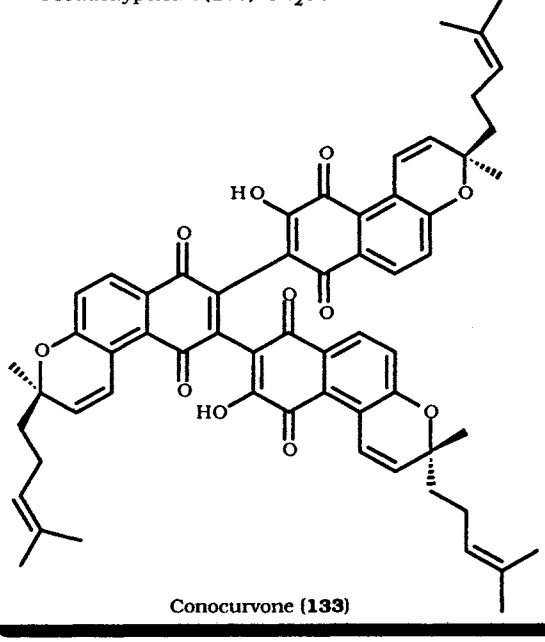
Hypericin (**128**) R = CH_3
Pseudohypericin (**129**) R = CH_2OH



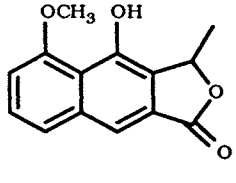
Juglone (**130**) R = H
Plumbagin (**131**) R = CH_3



β-lapachone (**132**)



Conocurvone (**133**)



Isoeleutherol (**134**)

Tannins, Terpenes, Steroids and Iridoids

Tannins are phenolic compounds that are abundant in plant kingdom. Basically, there are two types of tannins. Hydrolysable type which usually consists of simple phenolic acids, e.g., gallic acid, which is linked to sugar. The condensed type is similar to flavonoids. The known medicinal tannin-containing plant lemon balm (*Melissa officinalis*, Labiatae) is extensively studied as antiviral agent [11]. Leaves of this plant contain about 5%, dry weight of tannins which are mainly constructed from caffeic acid. A cream containing 1% of a specially prepared dried extract from lemon balm leaves has been introduced to the German market for local therapy of herpes infection of the skin [90]. The effect of this cream in the topical treatment is statistically significant as proven by clinical studies [90]. This is a decisive indication that constituents and /or extracts of plants could serve as useful leads for developing the antiviral drugs for the future. Terpenoids are also abundant secondary metabolites

Table 7. Antiviral Plant-Derived Tannins, Terpenes, Steroids and Iridoids

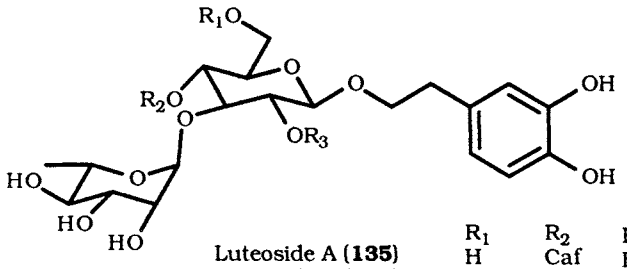
Tannin/: Type & Name Terpene	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Tannins: Hydrolysable tannins: Chebulagic acid (**140**), Eugeniin (**141**), Agrimoniin, Cas-uaractin, Coriariin, Geraniin (**142**), Galloylgeraniin, pentagalloylglucose, Oenothein B (**143**), Sanguin. **140**, Punicallin (**144**), Punicallagin (**145**), Gemin D (**146**), Nobotanin B (**147**), Camellin B (**148**), Trapanin B (**149**) Gallitannins & Ellagitannins: **143**, Agrimoniin (**150**), Coriarin A (**151**), Hepta & Octagalloylglucoses Ellagic acid (**152**), Digallic acid (**153**), 1,3,4-Tri-*O*-galloylquinic acid (**154**), 3,5-Di-*O* - galloylshikimic acid (**155**)	Many sp. *Terminalia chebula* *Geum japonicum* *Tibouchina semidecandra*, *Camellia japonica* *Trapa japonica* Many sp.	HSV HIV HIV-RT	Virucidal Attachment to CD4 rece-ptor, Poly (ADP-ribose), Glycohydrolase (gene transcriptase) HIV-RT	[91] [92] [93, 94] [95] [12] [17] [96] [97] [98] [99] [100]
Condensed tannins: Catechinic acid (**156**) condensed tannins, Pavetannins, Cinnamtannins. Galloyl catechin and epicatechin, Procyanidin B2 (**157**), Galloylated epicatechin oligomers, e.g., galoylated (-)-epicatechin 4,8-trimer (**158**)	*Comberetum micranthum*, *Pavetta owarien-sis*, *Cinnamomum* sp. Many sp. *Punica granatum*	HSV HIV-RT HSV-2	Virucidal Penteration in the cell HIV-RT Virucidal	[91] [101] [102] [103] [104] [105]

(Table 7). contd.....

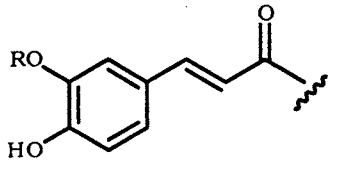
Tannin/: Type & Name Terpene	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Sulphated tannins:	Semi-synthetic	HIV	Attachment to CD4 receptor	[106]
Terpenes: Mono & Diterpenes: Δ^9-Tetrahydrocannabinol (**159**), Calcium elenolate, Scopadulcic acid B (**160**), Scopadulin	*Cannabis sativa* *Olea europaea* *Scoparia dulcis*	HSV	Virucidal membrane effect, Topical treatment	[107] [108, 109] [110]
Triterpene saponins: Aescin, Dammarenediol II (**161**), Glycyrrhizin (**162**), Saikosaponin G (**163**), Ursonic acid (**164**), Protopri-mulagenin (**165**) & its glycosides, Eichlerianic acid (**166**) Shoreic acid (**167**), Isofouquierol (**168**), 22-Hydroxyhopanone (**169**), Ponasterone A (**170**), Pterosterone (**171**), Ecdysterone (**172**), Oleanane glycosides. **162**, its sulphate & analogs Soya saponin B1, Gleditsia saponin C (**173**), Gymnocla-dus saponin G (**174**), 2α,19α-dihydroxy-3-oxo-12-ursen-28-oic acid (**175**), Ursolic acid (**176**), Maslinic acid (**177**), Betulinic acid (**178**) & its analogs, Platanic acid (**179**). Chikusetsusaponin III (**180**) Oleanolic acid (**181**), Pomolic acid (**182**) & other related triterpenoids	*Anagallis arvensis* Dipterocarpaceae *Gierocarpus intricatus* *Glycyrrhiza glabra* *Bupleurum falcatum* *Woodwardia orientalis* *Maesa lanceolata* *Myrsine* sp. *Glycyrrhiza glabra* *Glycine max.* *Gleditsia japonica* *Gymnocladus chinensis, Geum japonicum* *Syzygium claviflorum* *Panax ginseng* *Rosa woodsii & Hyptis capitata*	HSV HIV HSV-1 HIV	Viral DNA synthesis Viral capsidation Virus absorption Protein kinase C Virucidal, late proteins synthesis Unknown	[12] [111] [16] [112, 113] [114] [115] [116, 59] [117] [118] [43] [12] [116] [119] [120] [121, 122] [123] [124] [125]
Triterpene steroids: Digitoxin, Digitoxigenin (**183**) 1-β-Hydroxyaleuritolic acid 3-*p*-hydroxybenzoate (**184**), Nigranoic acid (**185**), Buxamine E (**186**), Cyclobuxamine H (**187**)	*Digitalis purpurea* *Maprounea africana* *Shisandra sphaerandra,* *Buxus semperv-irens*	HSV HIV-RT	Uknown HIV-RT	[16] [50] [126]
Iridoids: Fulvoplumerien (**188**)	*Plumeria rubra*	HIV-RT	HIV-RT	[29]

in plant world. Terpenoids are essentially derived from the basic 5-carbons isoprene unit. These are classified into: monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes, sterols, saponins,

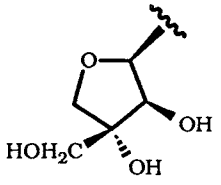
cardiac glycosides (basically all are C30) and carotenoids (C40). Iridoids are also common plant secondary metabolites. The antiviral activities of tannins, terpenes and iridoids are reported in table 7.



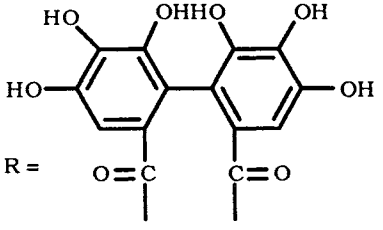
	R_1	R_2	R_3
Luteoside A (**135**)	H	Caf	H
Luteoside B (**136**)	Caf	H	H
Luteoside C (**137**)	Ac	Caf	Api
Verbascoside (**138**)	Caf	H	Api
Isoverbascoside (**139**)	Fer	H	Api

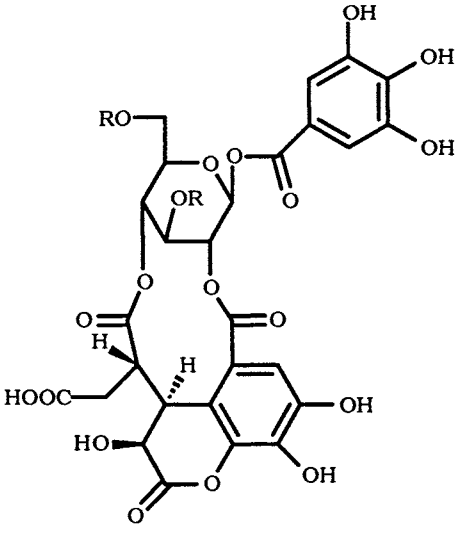


Caf = Caffeoly, R: H
Fer = Feruloyl, R: CH_3

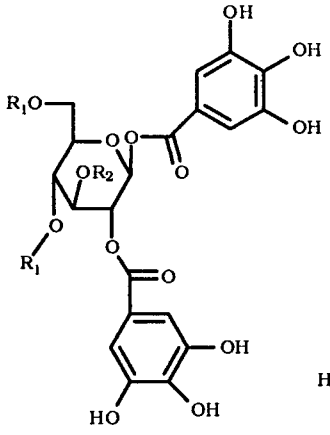


Api = Apiosyl

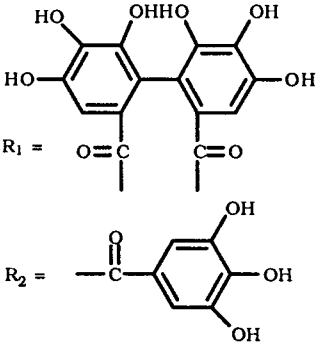


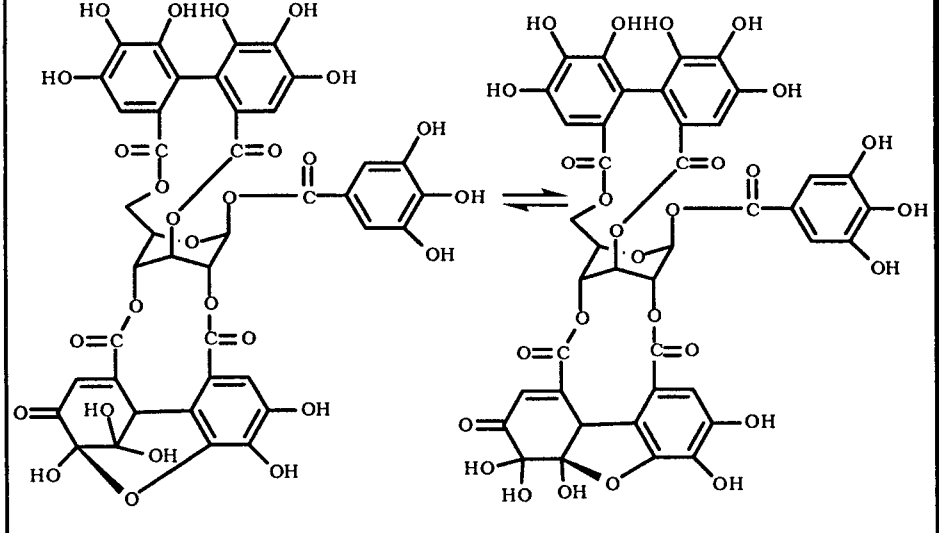


Chebulagic acid (**140**)

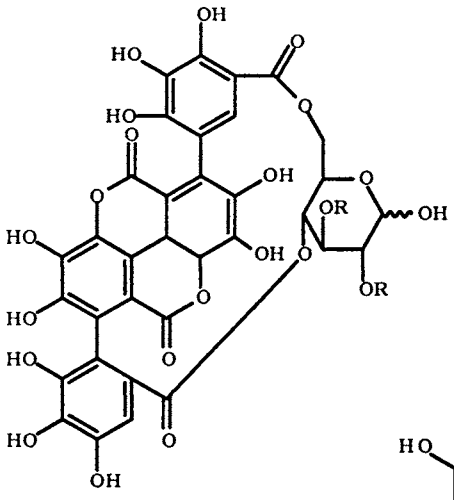


Eugeniin (**141**)

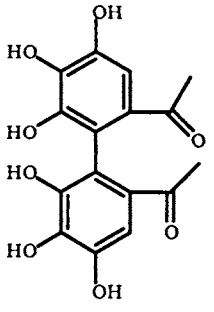




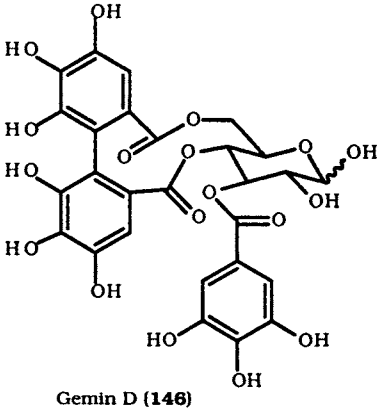
Geraniin (**142**)



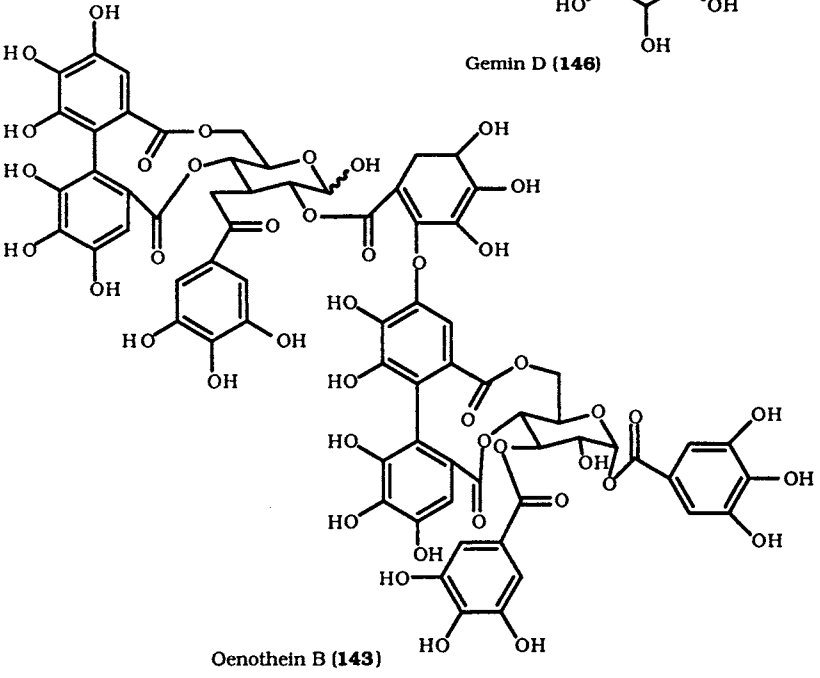
Punicallin (**144**)



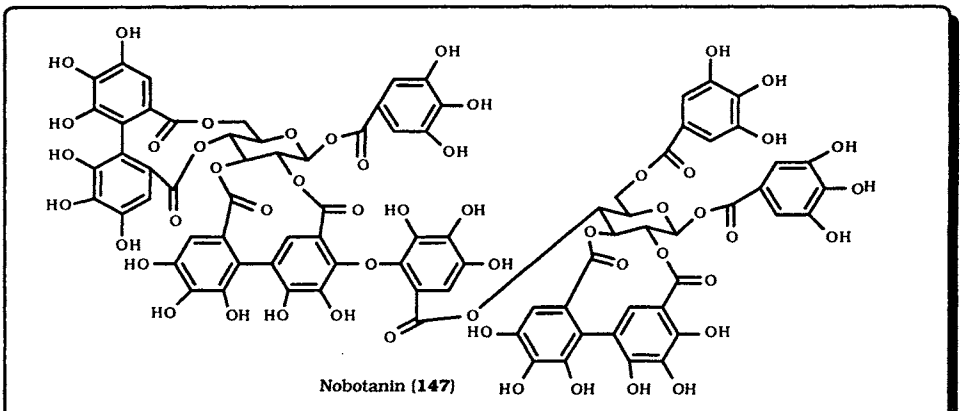
Punicallagin (**145**)



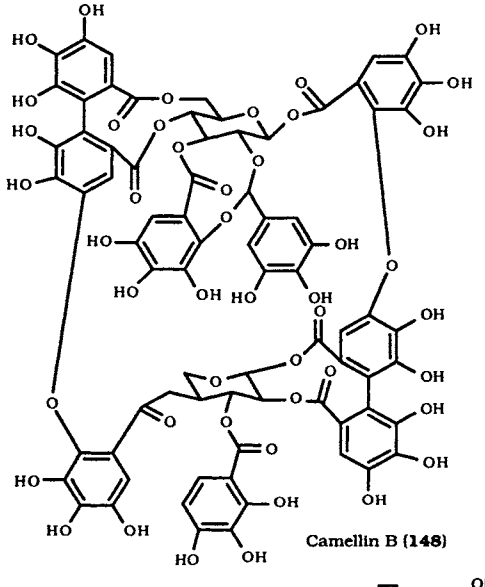
Gemin D (**146**)



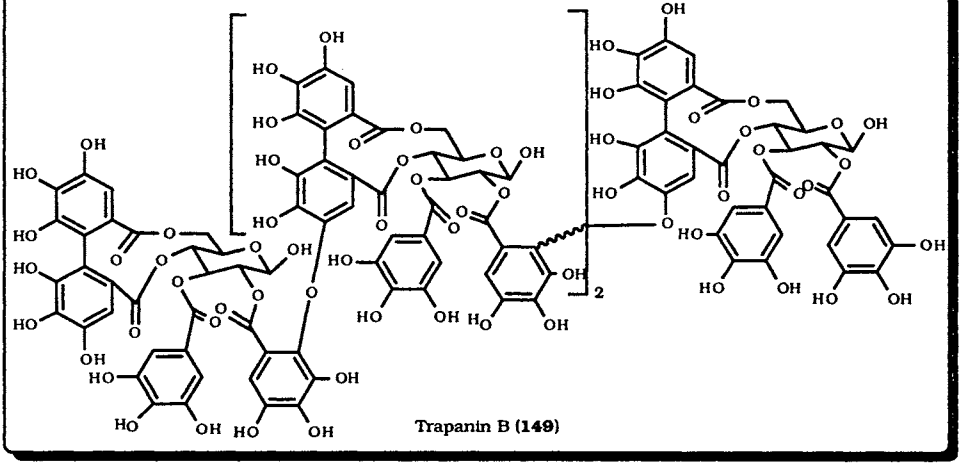
Oenothein B (**143**)



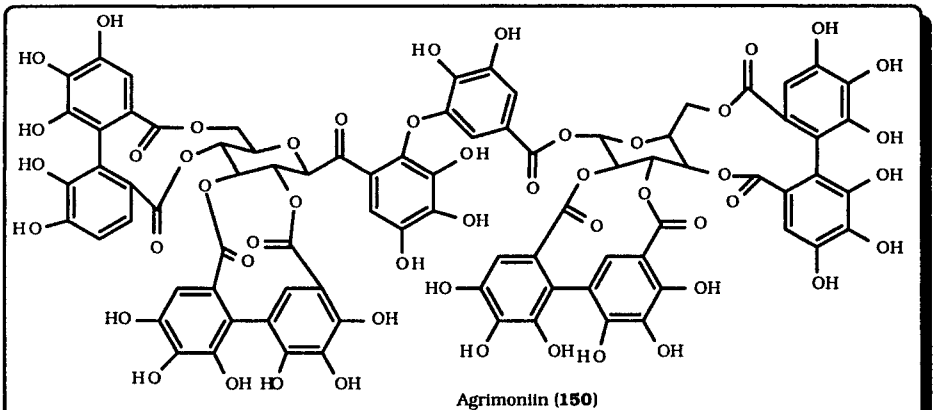
Nobotanin (**147**)



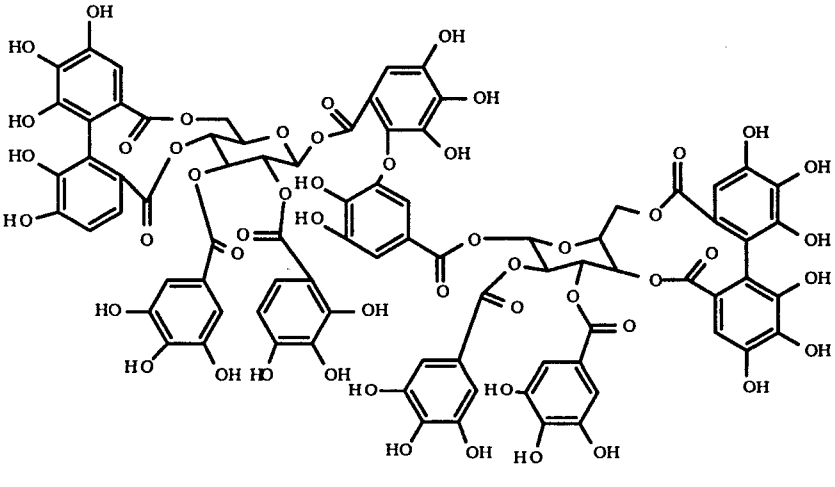
Camellin B (**148**)



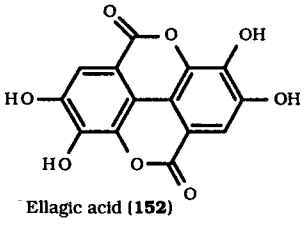
Trapanin B (**149**)



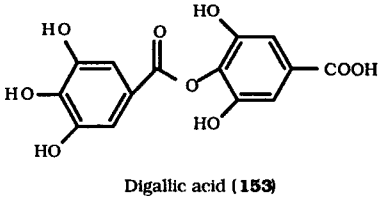
Agrimoniin (**150**)



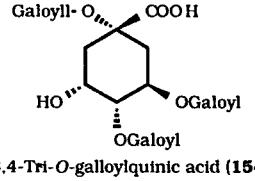
Coriarin A (**151**)



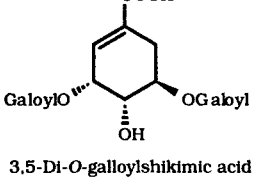
Ellagic acid (**152**)



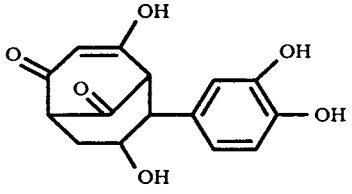
Digallic acid (**153**)



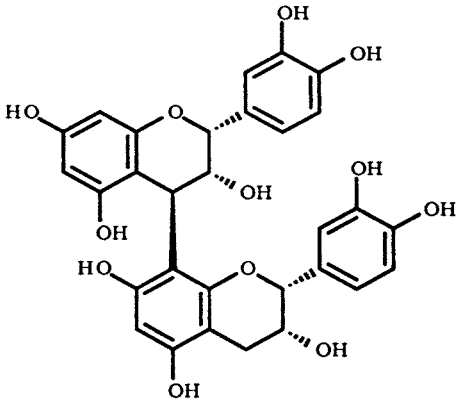
1,3,4-Tri-*O*-galloylquinic acid (**154**)



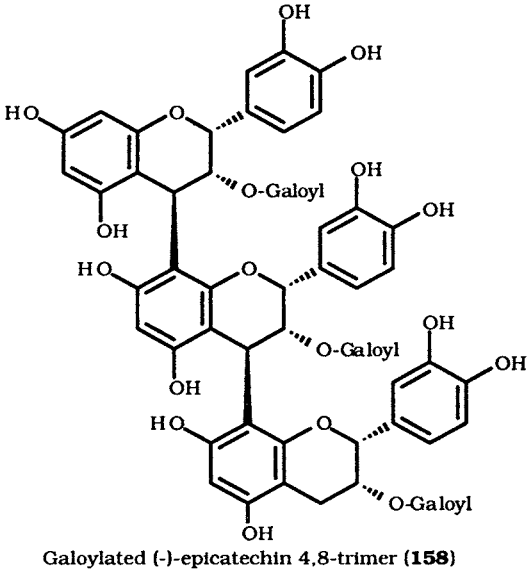
3,5-Di-*O*-galloylshikimic acid (**155**)



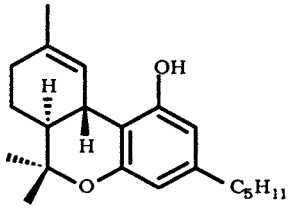
Catechinic acid (**156**)



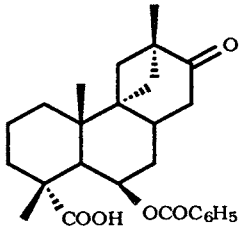
Procyanidin B2 (**157**)



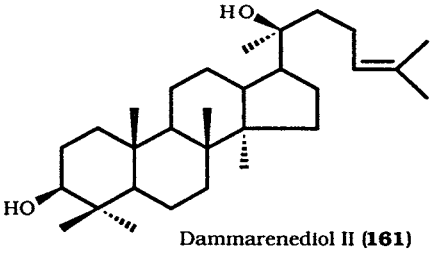
Galoylated (-)-epicatechin 4,8-trimer (**158**)



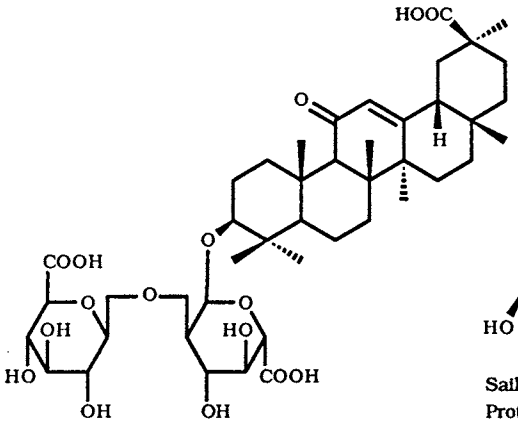
Δ^9-Tetrahydrocannabinol (**159**)



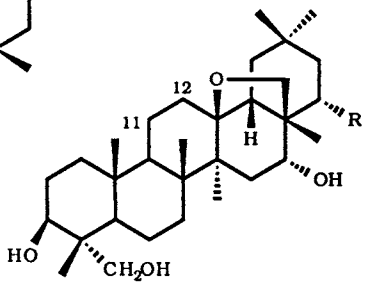
Scopadulcic acid B (**160**)



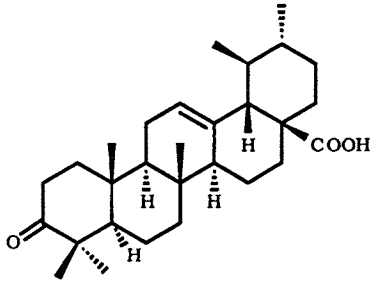
Dammarenediol II (**161**)



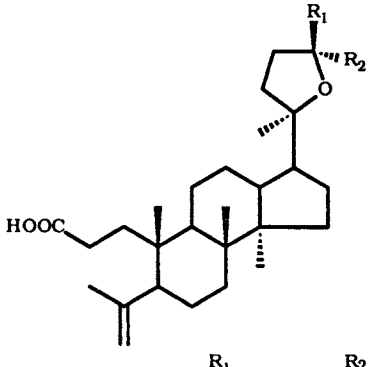
Glycyrrhizin (**162**)



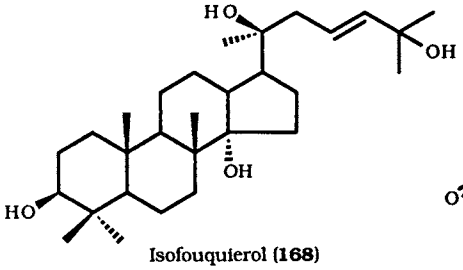
Saikosaponin G (**163**) R = H, $\Delta^{11,12}$
Protoprimulagenin (**164**) R = OH



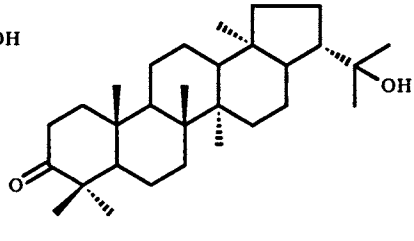
Ursonic acid (**165**)



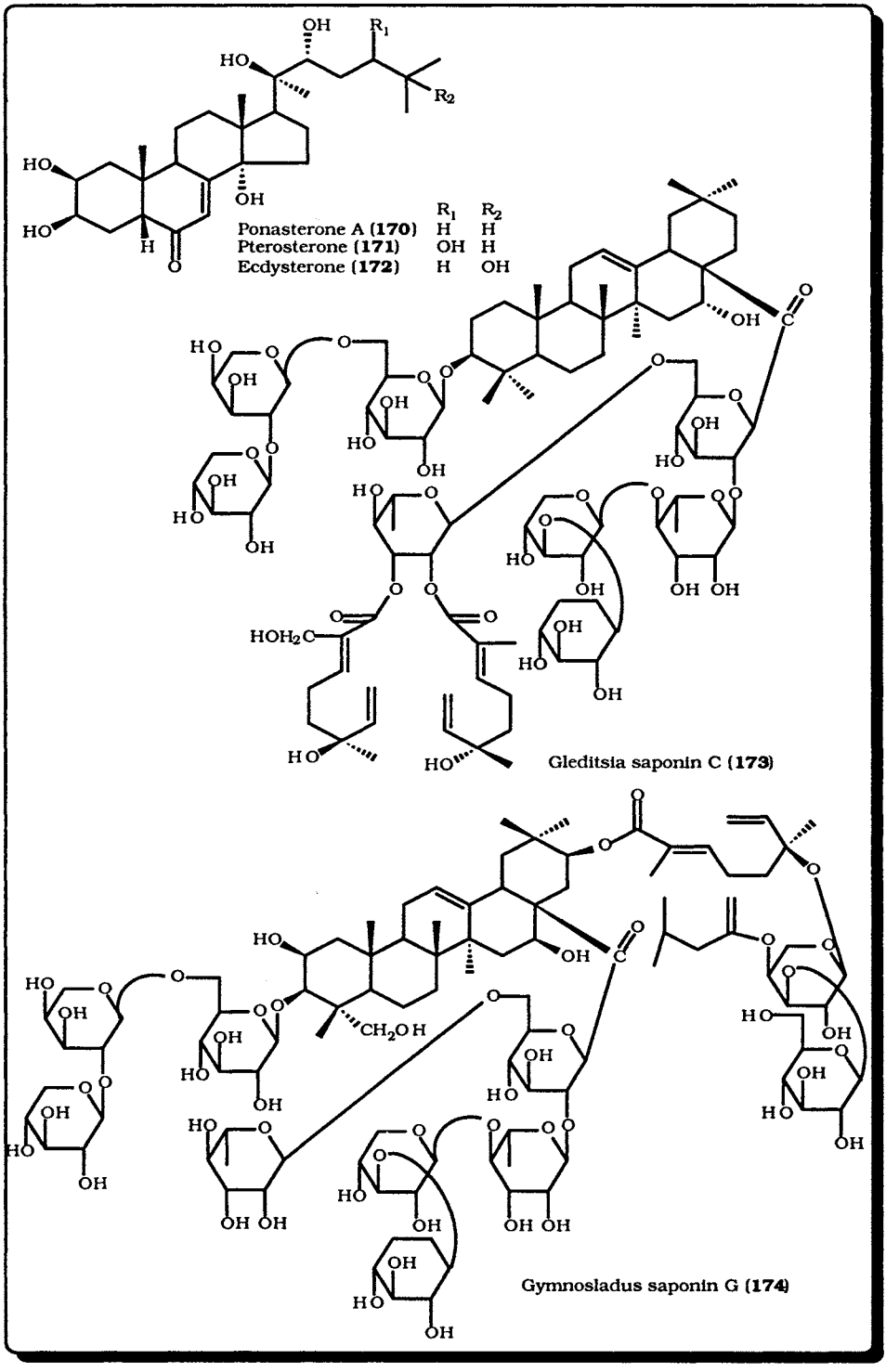
	R_1	R_2
Eichlerianic acid (**166**)	$-C(CH_3)_2OH$	H
Shoreic acid (**167**)	H	$-C(CH_3)_2OH$

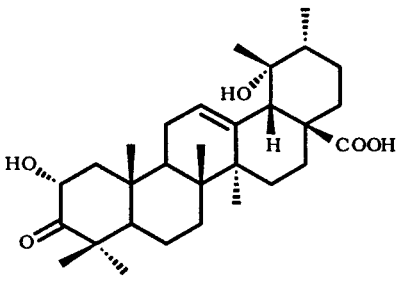


Isofouquierol (**168**)

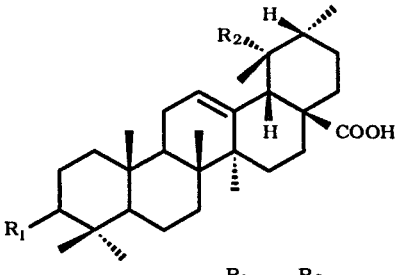


22-Hydroxyhopanone (**169**)

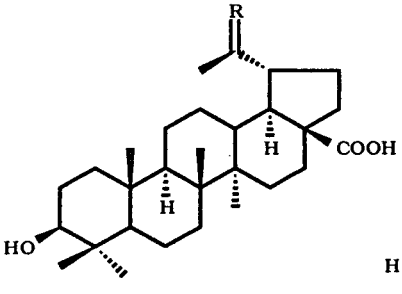

R1 R2
Ponasterone A (170) H H
Pterosterone (171) OH H
Ecdysterone (172) H OH
Gleditsia saponin C (173)
Gymnosladus saponin G (174)



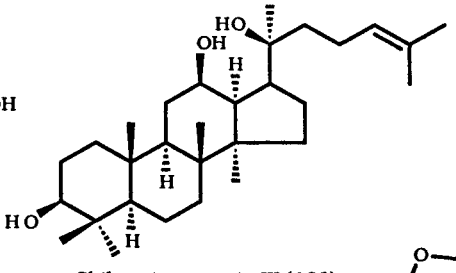
2α, 19α-dihydroxy-3-oxo-12-ursen-28-oic acid (**175**)



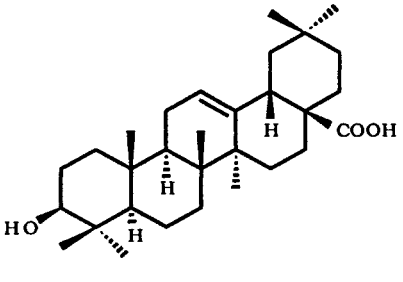
	R_1	R_2
Ursolic acid (**176**)	β-OH	H
Maslinic acid (**177**)	α-OH	OH
Pomolic acid (**182**)	β-OH	OH



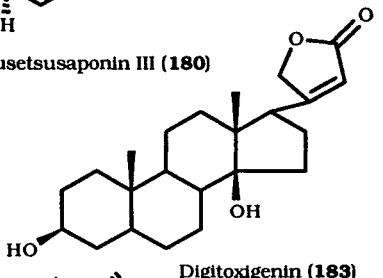
Betulinic acid (**178**) R = H_2
latanic acid (**179**) R = O



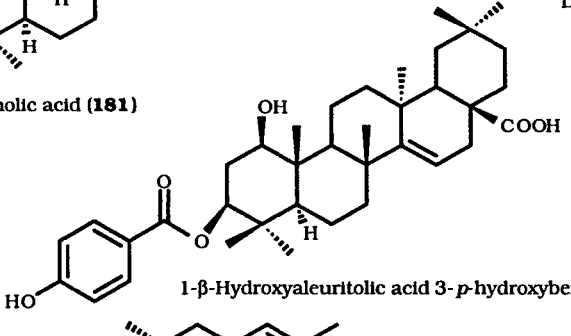
Chikusetsusaponin III (**180**)



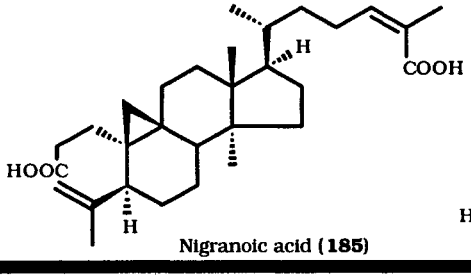
Oleanolic acid (**181**)



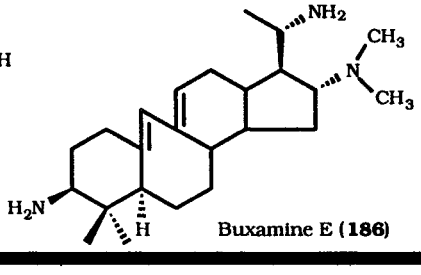
Digitoxigenin (**183**)



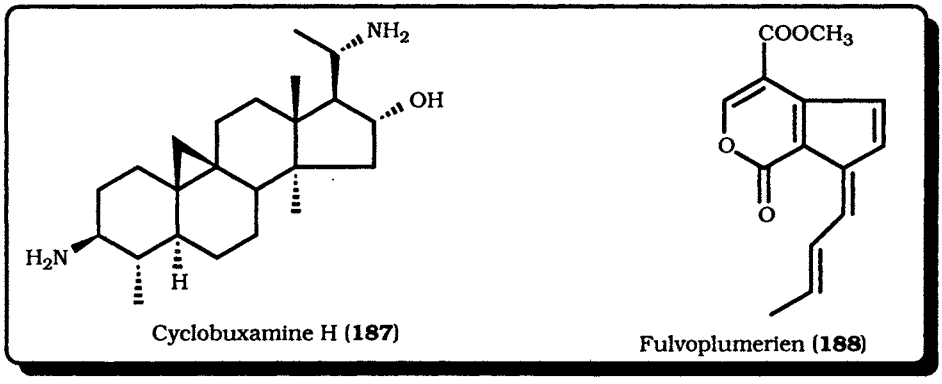
1-β-Hydroxyaleuritolic acid 3-*p*-hydroxybenzoate (**184**)



Nigranoic acid (**185**)



Buxamine E (**186**)



Cyclobuxamine H (**187**)

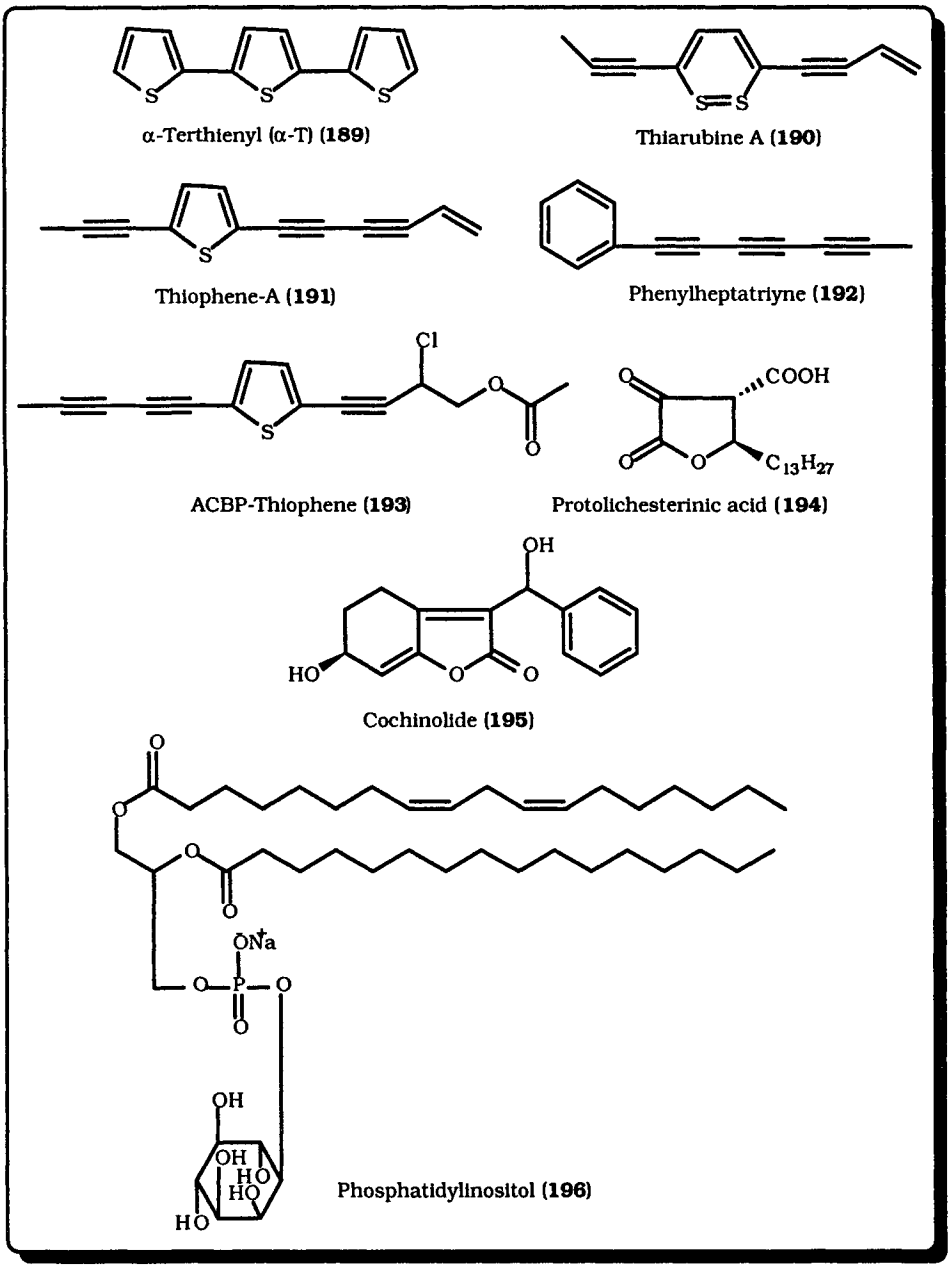
Fulvoplumerien (**188**)

Thiophenes, Polyacetylenes, Lactones, Butenolides and Phospholipids

About seven hundred polyacetylenes have been isolated so far mainly from plants belonging to the family of Asteraceae, Umbelliferae and Campanulaceae [11]. Polyacetylenes occur principally as straight chain polyines, allenes, phenyl, thiophenyl, thioether and spiroketal-enoether derivatives in a quite high yield. Thiophenes and related sulfur compounds are usually grouped together with the polyacetylenes because of their common biosynthetic pathways [11]. Few plant-derived lactones, butenolides and phospholipids show antiviral activity. The antiviral activities of thiophenes, polyacetylenes, lactones, butenolides and phospholipids from plant origin are reported in table 8.

Table 8. Antiviral Plant-Derived Thiophenes, Polyacetylenes, Lactones, Butenolides and Phospholipids

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Thiophenes & Polyacetylene: α-Terthienyl (α-T) (**189**) Thiarubrine A (**190**) Thiophene-A (**191**) Phenylheptatriyne (**192**) ACBP-Thiophene (**193**)	*Chenactis douglasii* *Tagetes* sp. *Bidens* spp.	HIV CMV HSV	Photo-oxidative damage (UVA, 320-400 nm)of viral unsaturated membranelipids and associated proteins	[11]
Lactones: Protolichesterinic acid (**194**)	*Citraria islandicus*	HIV-RT	HIV-RT	[50]
Butenolides: Cochinolide (**195**)	*Homalium cochinchinensis*	HSV-1 & 2	Unknown	[127]
Phosphlipids: Phosphatidylcholine, Phosphatidylethanolamine, Phosphatidylinositol (**196**)	Many sp.	HIV	Accumulation of toxic metabolic products into the HIV memberanes	[12] [128]



Proteins and Peptides

Plants are endowed with a multitude range of proteins and peptides. Several groups of plant proteins exhibit fairly non-specific antiviral activity. These constitute:

Single-chain (Homologous) Ribosome-Inactivating Proteins (RIPs)

Since 1925, extracts of the pokeweed plant (*Phytolacca americana*) were shown to selectively reduce the infectivity of tobacco mosaic virus (TMV) without demonstrable effect on the host cell. A protein of molecular weight 29,000 daltons designated poekeweed antiviral protein (PAP) was purified from the leaf extract [11]. Additional proteins (PAP-II and PAP-s) were found in relative smaller amounts. Subsequently, other RIPs were found in other plants and exhibit similar antiviral activity, e.g., tritin from *Triticum aestivum* seed, gelonin from *Gelonium multiflorum* seed, momordin from *Momordica charantia* seed, saporin from *Saponaria officinalis* seed, *dianthin* from *Dianthus caryophyllus* leaf, tricosanthin from *Trichosanthes kirilowii* [11], bryodin 2 from *Bryonia dioica* [129] and *Bougainvillea* antiviral protein I (BAP I) from *Bougainvillea spectabilis* root [130]. The possible mechanism of RIPs by which they inhibit viral growth is through inactivating the large subunit of eukaryotic ribosomes (except for the donor plant ribosomes). The antiviral spectrum of PAP includes: TMV, southern bean mosaic virus and cucumber mosaic virus in plants. On the other hand, PAP also shows activity against the mammalian viruses HSV and poliovirus. PAP was found to bind irreversibly to poliovirus, enters its cell cultures and inactivate its ribosomes [11]. PAP also was found to have anti-HIV activity through the inhibition of translation topisomerase [131-133].

Dimeric Ribosome-inactivating Proteins

These cytotoxic glycosylated proteins consist of two distinct polypeptide groups, the A and B chains, each constitutes about 30,000 dalton molecular weight. Both chains are attached to each other by a disulfide bond. The B chain is responsible for initiating the cytotoxicity. Chain A, which seems to be homologous to the single chain RIPs, inactivates ribosome function. Unlike the single chain RIPs, this dimeric type is equally toxic to uninfected and virus-infected cells. Ricin (from *Ricinus communis* seed), abrin (from *Abrus precatorius* seed) and modeccin (from *Adenia digitata* root) are examples of these toxins. These three toxins inhibit the TMV in a similar manner to PAP-related RIPs [11]. Ricin was shown to decrease the latent HSV-1 infection in trigeminal ganglia of HSV-immune mice [11].

Lectins

These cell-agglutinating proteins have been reported active against certain membrane-containing viruses. Concanavalin A (con A, from *Canavalia ensiformis*) was found to inactivate HSV, vesicular stomatitis virus (VSV), influenza virus and CMV infectivity and also found to interfere with the viral replication [11]. Other examples for these toxins are: lentil lectin

(from *Lens culinaris*), phytothemagglutinin (from *Phaseolus vulgaris*) and wheat germ agglutinin (from *Triticum vulgaris*), which all shown to abolish HIV-1 infectivity [11].

Antiviral Factor (AVF)

Some varieties of *Nicotiana glutinosa* produce a protein called AVF which afford some protection against TMV by restricting its lesions in an analogy manner to interferons [11]. AVF Is a glycoprotein which is terminally phosphorylated with 22,000 daltons molecular weight. The mechanism of action of AVF is not yet established.

Meliacin

Meliacin is an antiviral glycopeptide of molecular weight 5000-6000 daltons, isolated from the leaves of *Melia azedarach* (Meliacea) [11,134]. Its mechanism of action was proposed recently through the prevention of uncoating process of virus and not through the virucidal or inhibition of viral penetration [135]. The activity of this glycopeptide is displayed against VSV, HSV-1, poliovirus, SV and foot and mouth disease virus (FMDV).

Aprotinine

Aprotinine is another plant-derived antiviral polypeptide which specifically inhibit myxoviruses especially influenza A. Aportinine is known to be a protease inhibitor. It acts by interfering with the essential step of cleavage of the precursor Hao into subunit polypeptides and hence prevents the viral infection [11].

Oligopeptides

Many plant-derived di- and tri-peptides were proved to be active against HSV and measles virus (MV). These peptides consist mainly of carbobenzoxy derivatives of phenylalanine [11]. Cationic peptides are used as nature's antibiotics, being produced in response to an infection in virtually most organisms including plants and insects. Cationic peptides and proteins are now proceeding through clinical trials as topical antibiotics and antiendotoxins [136].

Plant Extracts

Several thousand plant extracts have been shown to possess *in vitro* antiviral activity with little overlap in species between studies. In most cases, the assay methods are designed to detect virucidal, prophylactic

Table 9. Antiviral Plant Extracts

Plant Name	Activity Against	Mechanism/ Inhibition	Reference
Agalia roxburghiana	Newcastle disease virus (NDV)	Preinfection treatment	[11]
Cassia fistula	NDV & VV	Preinfection treatment	
Hemidesmus indicus	NDV, VV	Preinfection treatment	
Zingiber capitatum	NDV, VV	Preinfection treatment	
Melia azedarach Neem seed oil	SV, VSV, Potato virus Y	Preinfection treatment Inhibits transmission	[11] [137]
Cedrela tubiflora	SV, VSV, HSV, Poliovirus-1	Postinfection treatment	[11]
Trichilia glabra	SV, VSV, HSV, Poliovirus-1	Postinfection treatment	[11]
Baccharis crispa, B. notosergila	VSV	Postinfection treatment	[11]
Geranium sanguineum	Influenza, HSV, VV, HIV-1	Postinfection treatmen	[138, 139]
Phyllanthus amarus, P. orbiculatus, P. Pseudoconami, P. urinari	HBV MCMV, SV	mRNA transcription	[140-142] [11]
Larrea tridentata	HSV	Protein synthesis	[143]
Persea americana	HSV	Virucidal	[144]
Acanthospermum hispidum	HSV	Virucidal	[145]
Callicarpa japonica	HIV	gp-120-CD4	[146]
Sedum sarmentosum	HIV	gp-120-CD4	[146]
Caraganae Radix	HSV-1, HSV-2	Virucidal	[147]
Veratrum patulum	HSV-1, HSV-2	Virucidal	[147]
Osmundae japonica	HSV-1, HSV-2	Virucidal	[147]
Veratrum viride	HSV-1	Unknown	[148]
Rooibos tea leaves	HIV	Unknown	[149]
Croton cuneatus, C. lechleri, C. palanostigma, C. trinitatis	SV, MCMV	Virucidal	[11]
Hevea brasiliensis	SV, MCV	Virucidal	[11]
Jatropha curcas, J. gossypiifolia, J. Weberbaueri	SV, MCMV	Virucidal	[11]
Apocynum sp., *A. cannabinum*	VV, Polio, Pseudorabies virus (PRV). VV	Postinfection treatment	[11]
Nerium oleander	VV, Polio	Postinfection treatment	[11]
Thevetia nerifolia	VV, Polio	Postinfection treatment	[11]
Asarium canadense	HSV, PRV	Postinfection treatment	[11]
Asclepias incarnata	Polio	Postinfection treatment	[11]
Campanula trachelium	HSV	Postinfection treatment	[11]

(Table 9). contd.....

Plant Name	Activity Against	Mechanism/ Inhibition	Refe-rence
Tradescantai virginiana	VV, PRV	Postinfection treatment	[11]
Artemisia sp.	Polio	Postinfection treatment	[11]
Xanthium sp.	Polio	Postinfection treatment	[11]
Aster patens	Measles	Postinfection treatment	[11]
Coreoptis tripteris	Polio	Postinfection treatment	[11]
Eupatorium purpureum	HSV	Postinfection treatment	[11]
Hieraceum aurantiacum	Polio	Postinfection treatment	[11]
Solidago sempervirens	HSV	Postinfection treatment	[11]
Satureja vulgaris	VV	Postinfection treatment	[11]
Scilla campanulata	PRV, HSV	Postinfection treatment	[11]
Lycopodium obscurum	HSV	Postinfection treatment	[11]
Nuphar advena	VV	Postinfection treatment	[11]
Chelidonium majus	Measles	Postinfection treatment	[11]
Piper methysticum	Polio	Postinfection treatment	[11]
Lysimachia quadrifolia	VV	Postinfection treatment	[11]
Gerardia pedicularia	Polio, Coxsackie	Postinfection treatment	[11]
Sium suave	PRV	Postinfection treatment	[11]

activities and to define extracts that interfere with viral replication in cultured cells. Aqueous and organic extracts have generally been proved equally fruitful and hence it is not feasible to assert that any one method of extraction is preferable. Further characterization of the active constituents in these active extracts should reveal some useful compounds. Many of active extracts may turn out to be identical or related to the previously described structure classes. Yet, there also may be a possibility for some novel phytochemicals. Table 9 summarizes some of the most active extracts in the literature.

Marine-Derived Antiviral Compounds

With marine species comprising approximately one half of total global biodiversity for which estimates range between 3-500 x 10^6 species of prokaryote and eukaryote organisms. The marine macrofauna represents a broader range of taxonomic diversity than found in terrestrial evironment [150]. With a typical eukaryote possessing 50,000 genes, the global marine macrofauna are the source of 2.5 x 10^{10} -1.5 x 10^{12} primary products and an associated extensive range of secondary metabolites [150]. Presently,

Only few thousand novel compounds from marine origin have been identified. These compounds have been revealed unique in chemical and pharmacological terms. However, only few promising therapeutic leads

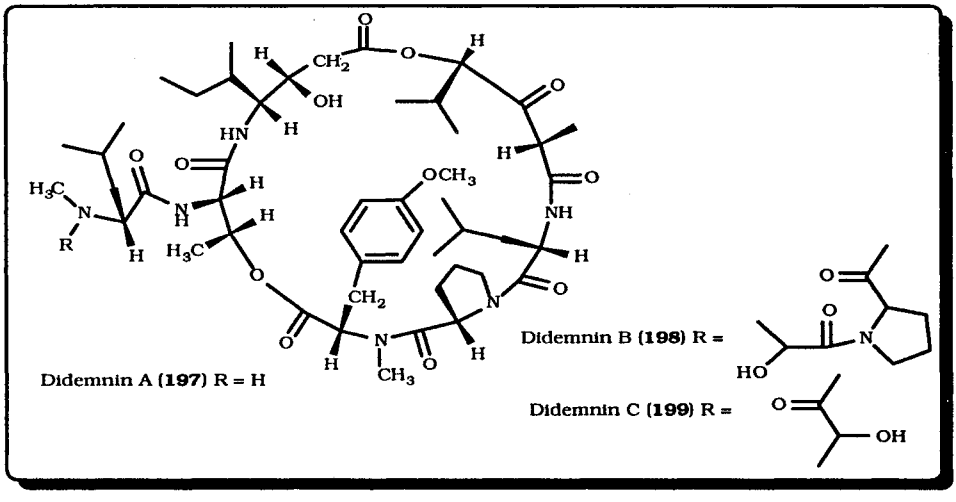
Table 10. Antiviral Marine-Derived Peptides, Alkaloids, Proteins, Nucleosides and Other *N*-Containing Compounds

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Peptides:				
Didemnin A (197), B (198), C (199) and other didemnins	Tunicate, *Tridemnum* sp.	HSV-1 & 2 & other RNA viruses	DNA, RNA synthesis Protein synthesis	[156, 157, 158]
Kahalalide E (202)	Mollusk, *Elysia rufescens*	HSV-2	Unknown	[159]
Callipeltin A (203)	Sponge, *Callipelta* sp.	HIV-1	Protective	[160]
Alkaloids & *N*-Containing Compounds:				
Eudistomin C (204), E (205)	Tunicate, *Eudistoma olivaceum, E. glaucus, E. album.*	HSV-1, HSV-2	Cytotoxicity Cytotoxicity	[161]
K (206), L (207)		HSV-1, VSV & Coronavirus	Cytotoxicity	[162]
Topsentin (208)	Sponges, *Topsentia genitrix & Spongosorites* sp.	CMV	Unknown	
Bromotopsentin (209)		HIV	Unknown	
4,5-dihydroxy-6''-deoxybromotopsentin (210)	Sponge, *Dercitus* sp.	HSV-1, VSV	Unknown	
Dercitin (211)	Softcoral, *Tubastrea aurea*	HSV-1	Cytotoxicity	[163]
Tubastrine (212)		HSV-1		
Acarnidine A (213), B (214), C (215)	Sponge, *Acaranus erithacus*	HSV-1	Protein synthesis	[164]
Polyandrocarpidine A (216), B (217), C (218), D (219)	Tunicate, *Polyandrocarpa* sp.	HSV-1, Poliovirus	Protein synthesis	[165]
Sceptrin (220), Debromosceptrin (221), Dibromosceptrin (222), Oxysceptrin (223), Ageliferin (224)	Sponge, *Agelas coniferin* & A. cf. *mauritiana*	HSV-1, VSV, Coronavirus A59	Viral replication Viral replication	[166]
Mycalamide A (225), B (226)	Sponge, *Mycale* sp.	HSV-1	Unknown	[167, 168, 169]
Onnamide A (227)	Sponge, *Theonella* sp.	HSV-1	Cytotoxicity Unknown	
Ptilomycalin A (228)	Sponges, *Ptilocaulis spiculifer & Hemimycale* sp.	HSV-1	Binding of gp120 to CD4	[170, 171]
Crambesscidins 816 (229), 830 (230), 844 (231) & 800 (232)	Sponge, *Crambe crambe*	HSV-2	Unknown	[172]
Hennoxazole A (233)	Sponge, *Polyfibrospongia* sp.	HSV-1	Unknown	
6-Cyano-5-methoxy-12-methylindolo[2, 3A]carbazole (234) & its 12-Demethyl deiv.	Blue-green alga, *Nostoc sphaericum*	HIV	Unknown	[173]
Aplidiasphingosine (235)	Tunicate, *Aplidium* sp.	HSV-2 HSV HIV-1		[174] [175] [176]
Batzelladine A (236), B (237)	Sponge, *Batzella* sp.			[177]
Bauerine A (238), B (239), C (240)	Blue-green alga, *Dichothrix baueriana*			[178]
Variolin B (241)	Sponge, *Kirkpatrickia varialosa*			[179] [180]
Trikendiol (242)	Sponge, *Trikentrion loeve*			[181]

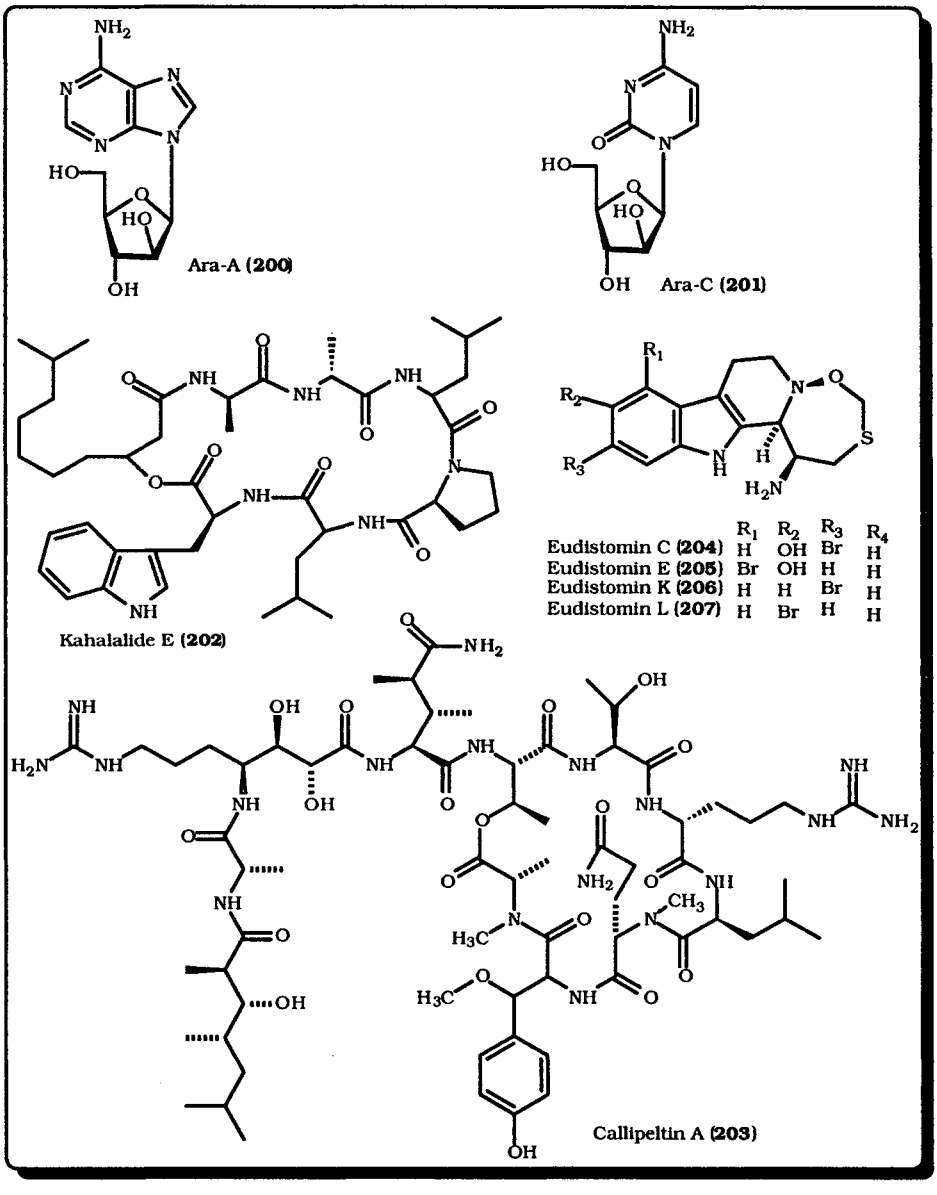
(Table 10). contd.....

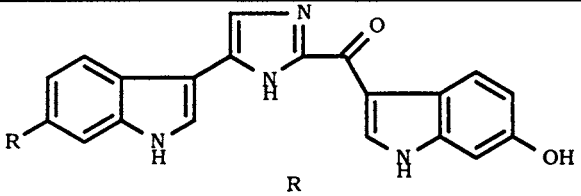
Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
Nucleosides:				
Spongothymidine (ara-T, **243**), Spongouridine (**244**)	Sponge, *Cryptotethia crypta*	HSV-1 & -2,	Cytotoxicity	[182, 183]
Ara-A (**200**), 3'-O-Acetylara-A	Gorgonian,*Eunicella cavolini*	HSV-1 & -2, vaccinia, rhinovirus 9	Cytotoxicity	[184]
Proteins:				
BDS-1	Anemone, *Anemonia sulcata*	mouse hepatitis virus MSV-A59	Unknown	[185]
Niphatevirin	Sponge, *Nephates erecta*	HIV	Bind to CD4, preventing gp120 binding	[186]
Cyanovirin-N	Blue-green alga, *Nostoc ellipsosporum*	HIV	Viral replication, gp120 binding	[187]

have been reported to display antiviral activity. Didemnins A (**197**), B (**198**) and C (**199**) are a group of cyclic depsipeptides isolated from the Caribbean marine tunicate *Tridemnum solidum*, which has been extensively studied for its antitumor and antiviral activities. Didemnin B (**198**) was found to inhibit cell cycle progression at G1 and binds to elongation factor 1α in the presence of GTP [151]. It is clinically evaluated in the early 1980s in a large phase I/II and was proved interesting antitumor activities [152]. Both compounds **197** and **198** inhibited the replication of HSV-1 and HSV-2 with $ID_{50} < 1.5$ μg/mL [153]. Similar efficacy was shown against coxsackie virus A21, equine rhinovirus, parainfluenza virus 3, Rift Valley fever virus, Venezuelan equine encephalovirus and yellow fever virus [154,155]. Despite their significant antiviral activities, didemnins are cytotoxic and inhibit cellular

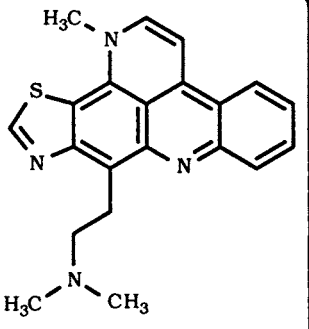


DNA, RNA and protein synthesis at concentrations close to those at which viral growth was inhibited and hence they have both low antiviral selectivity and therapeutic index. Some improvements in the therapeutic index have been achieved through structural modifications [156]. Two synthetic antiviral agents are currently under clinical use; ara-A (9β-D-arabinofuranosyladenin, **200**) and ara-C (1-β-D-arabinosyl-cytosine, **201**) are related to the arabinosides isolated in the early 1950s from the marine sponge *Cryptotethia crypta*, (Table 10) [155].

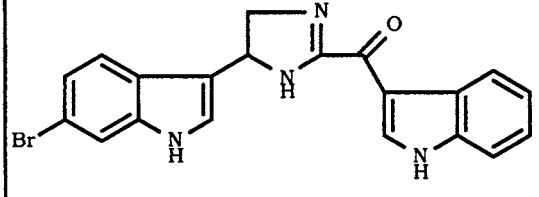




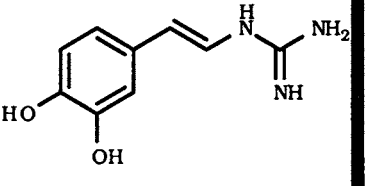
	R
Topsentin (**208**)	H
Bromotopsentin (**209**)	Br



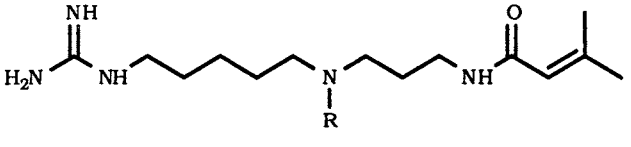
Dercitin (**211**)



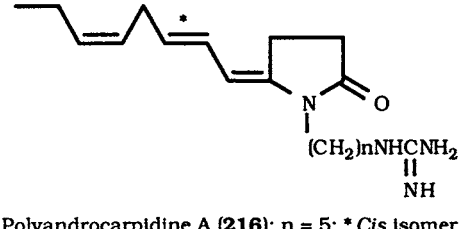
4,5-dihyroxy-6"-deoxybromotopsentin (**210**)



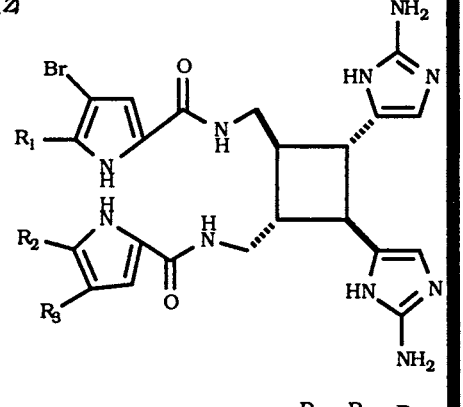
Tubastrine (**212**)



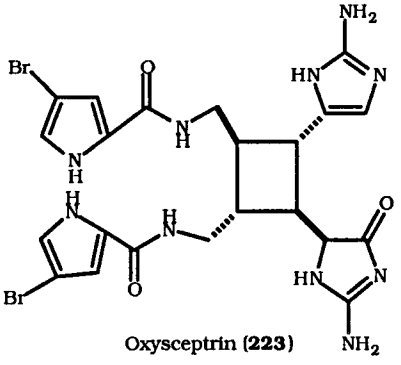
	R
Acarnidine A (**213**)	$CO(CH_2)_{10}CH_3$
Acarnidine B (**214**)	$CO(CH_2)_3CH{=}CH(CH_2)_5CH_3$(*Z*)
Acarnidine C (**215**)	$COC_{13}H_{21}$



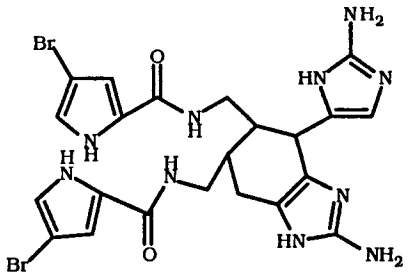
Polyandrocarpidine A (**216**): n = 5; * *Cis* isomer
Polyandrocarpidine B (**217**): n = 5; * *trans* isomer
Polyandrocarpidine C (**218**): n = 4; * *Cis* isomer
Polyandrocarpidine D (**219**): n = 4; * *trans* isomer



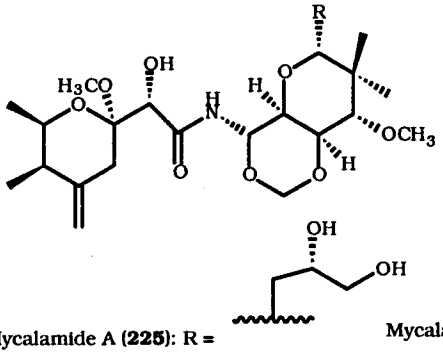
	R_1	R_2	R_3
Sceptrin (**220**)	H	Br	H
Debromosceptrin (**221**)	H	H	H
Dibromosceptrin (**222**)	Br	Br	Br



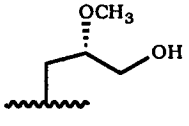
Oxysceptrin (**223**)



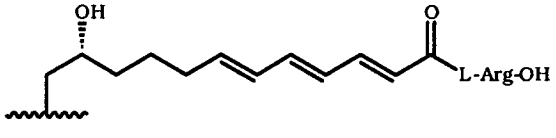
Ageliferin (**224**)



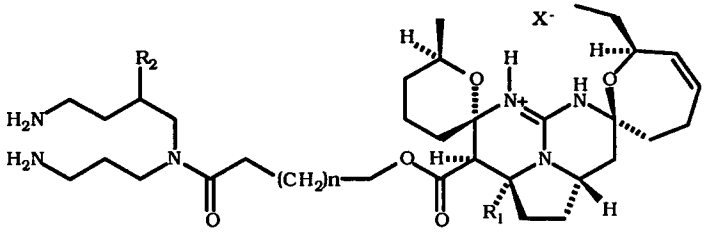
Mycalamide A (**225**): R =



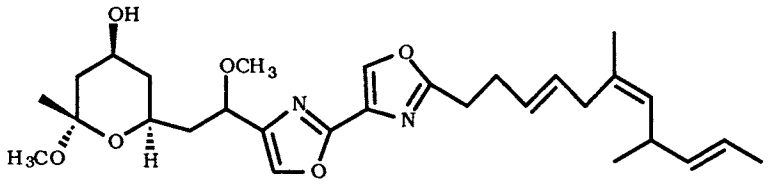
Mycalamide B (**226**): R =



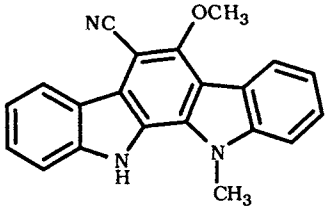
Onnamide A (**227**): R =



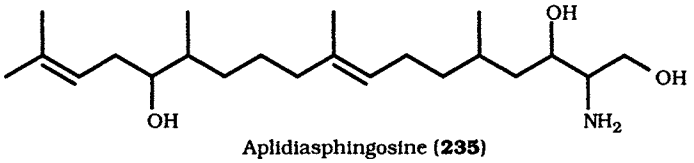
	R_1	R_2	n
Ptilomycalin A (**228**)	H	H	13
Crambesscidin 816 (**229**)	OH	OH	13
Crambesscidin 830 (**230**)	OH	OH	14
Crambesscidin 844 (**231**)	OH	OH	15
Crambesscidin 800 (**232**)	H	OH	13



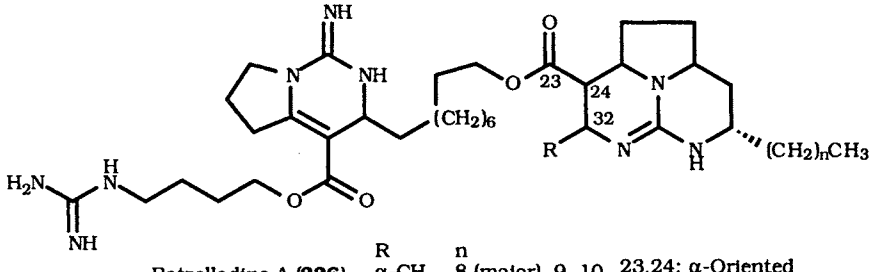
Hennoxazole A (**233**)



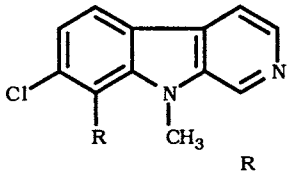
6-Cyano-5-methoxy-12-methylindolo[2, 3A]carbazole (**234**)



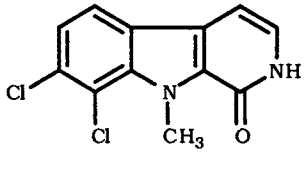
Aplidiasphingosine (**235**)



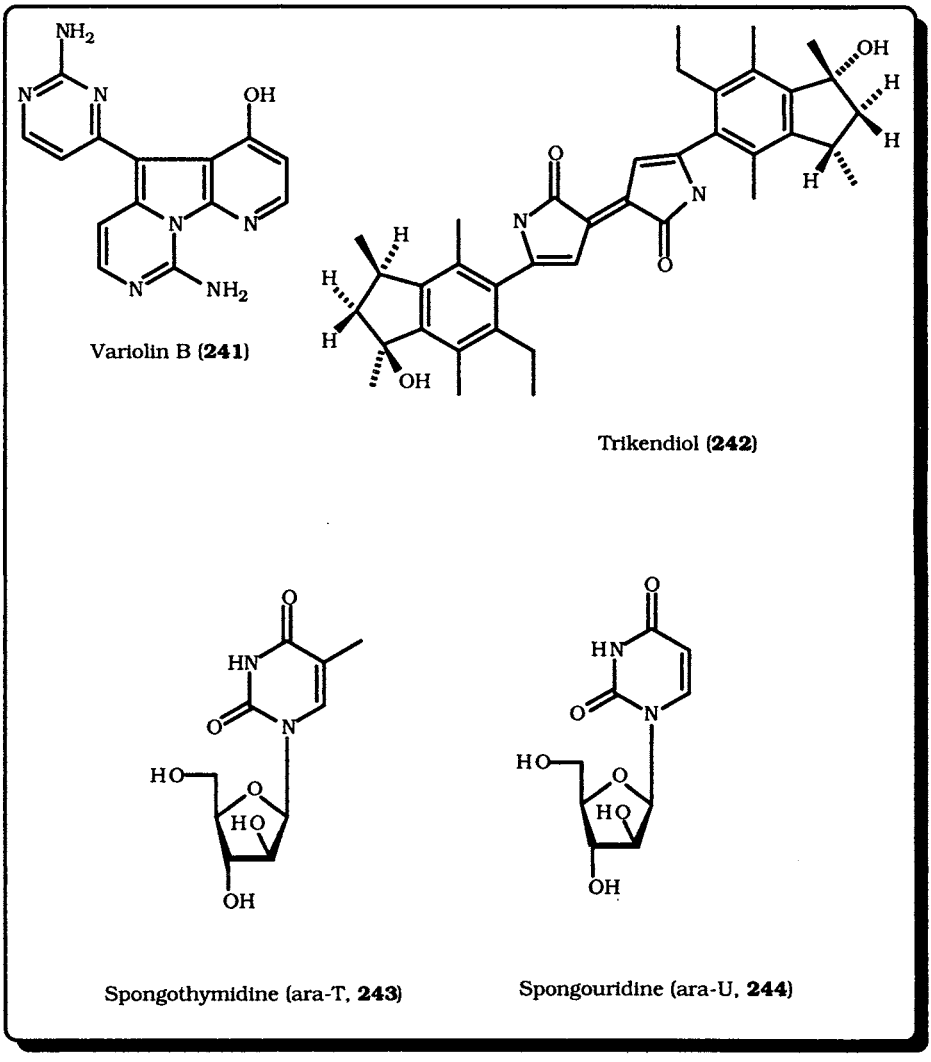
	R	n	
Batzelladine A (**236**)	α-CH_3	8 (major), 9, 10	23,24: α-Oriented
Batzelladine B (**237**)	CH_3	6 (major), 7, 8	$\Delta^{32,24}$



	R
Bauerine A (**238**)	H
Bauerine B (**239**)	Cl



Bauerine C (**240**)



Marine-Derived Antiviral Peptides, Alkaloids, Proteins, Nucleosides and Other* N-*Containing Compounds

Many marine-derived peptides, alkaloids, proteins, nucleosides and other *N*-containing compounds were shown to be active against several viral species. Table 10 illustrates these activities.

Marine-Derived Antiviral Terpenoids, Steroids and Carotenoids

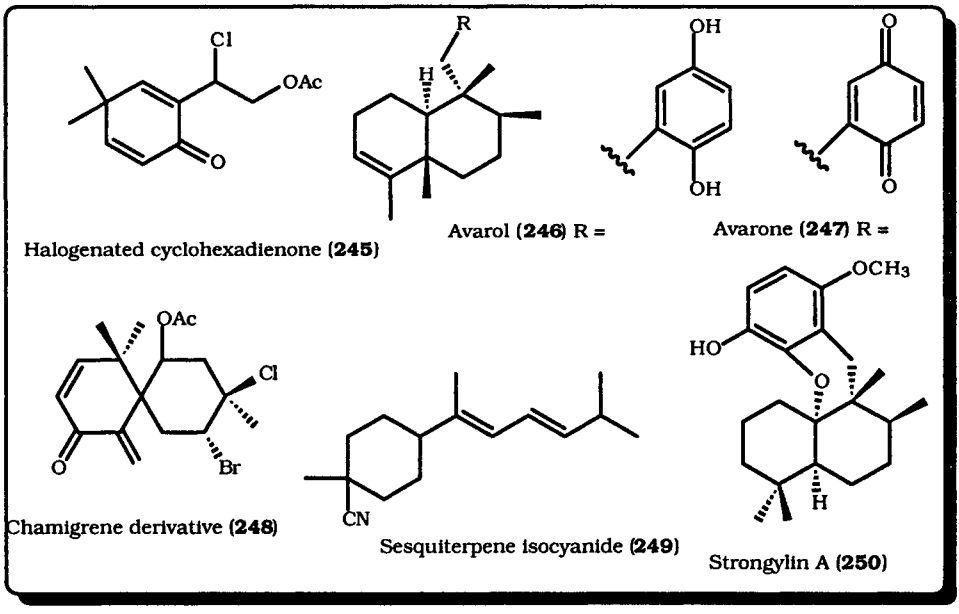
The antiviral activities of various marine-derived terpenoids, steroids and carotenoids are summarized in Table 11.

Table 11. Marine-Derived Antiviral Terpenoids, Steroids and Carotenoids

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Monoterpene:				
Halogenated cyclohexadienone (**245**)	Red alga, *Desmia hornemanni*	HSV-1, VSV HIV	Unknown Viral replication	[188]
Sesquiterpenes:			Uknown	
Avarol (**246**), Avarone (**247**)	Sponge, *Dysidea avara*	HSV, VSV Coronavirus A59	Virucidal	[189]
Chamigrene derivative (**248**)	Gland of the sea hare, *Aplysia dactylomela*			[190]
Sesquiterpene isocyanide (**249**)	Sponge, *Bubaris* sp.			[191]
Strongylin A (**250**)	Sponge, *Strongylophora hartmani*	Influenza PR-8	Unknown	[192]
15-Cyanopuupehenol (**251**)	Verongida sponge	HSV-2	Unknown	[193]
Peyssonol A (**252**), B (**253**), Hyatellaquinone (**254**)	Alga, *Peyssonnelia* sp. Sponge, *Hyatella intestinalis*	HIV	HIV-RT	[194]
(-)-Frondosin A (**255**), D (**256**)	Sponge, *Euryspongia* sp.	HIV	Unknown	[195]
Diterpenes:				
Spongiadiol (**257**), Epispongiadiol (**258**), Isospongiadiol (**259**)	Sponge, *Spongia* sp.	HSV-1	Cytotoxicity	[196]
Solenolide A (**260**), D (**261**), E (**262**)	Gorgonian, *Solenopodium* sp.	Rhinovirus, HSV, Polio III, Ann Arbor, Maryland, Semliki Forest Coronavirus A59, HSV-1	Unknown	[197]
Brianthein V (**263**), Y (**264**), Z (**265**)	Gorgonian, *Briareum asbestinum, B. polyanthes*		Unknown	[198]
Halitunal (**266**)	Alga, *Halimeda tuna*	Coronavirus A59	Unknown	[199]
Reiswigin A (**267**), B (**268**)	Sponge, *Epipolasis reiswigi*	HSV-1, VSV, Rhinovirus A59	Unknown	[200]
Norsesterterpenes:				
Mycaperoxide A (**269**), B (**270**)	Sponge, *Mycale* sp.	HSV	Unknown	[201]
Sesterterpenes: Variabilin (**271**)	Sponge, *Ircinia* sp. & *Sarcotragus* sp.	HSV	Cytotoxicity	[202]
Triterpenes:				
Thyrsiferol (**272**), Thyrsiferol Acetate (**273**), Venustatriol (**274**)	Red alga, *Laurencia venusta*	VSV, Coronavirus A59, HSV-1	Cytotoxicity	[203]
Holothurinoside A (**275**), Desholothurin A (**276**)	Sea Cucumber, *Holothuria forskalii*	HSV	Unknown	[204]

(Table 11). contd.....

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Crossasteroids B (277), D (278)	Starfishes	Suid herpes virus	Cytotoxicity	[205]
Steroids: Secosteroids: Calciferol D (279)	Gorgonian, *Muricella* sp.	HSV-1, HSV-2, Poliovirus	Uknown	[206]
Sulfated sterols: Ibisterol trisodium sulfate (280), Halistanol trisodium sulfate (281),26-Methylhalistanol trisodium sulfate (282), 25-Demethylhalistanol trisodium sulfate (283)	Sponge Spp., *Topsentia, Halichondria cf. moorei, Pseudaxinyssa digitata*	HIV-1, HIV-2	Cytotoxicity, HIV-RT	[207]
Weinbersterols disodium sulfate A (284), B (285)	Sponge, *Petrosia weinbergi*	Feline leukemia virus, HIV-1	Uknown	[208]
Orthosterol disodium sulfates A (286), B (287), C (288)	Sponge, *Petrosia weinbergi*	Feline leukemia, Influenza PR8, coronaviruse A59	Uknown	[209]
Meroterpenes: Usneoidols Z (289), E (290)	Brown seaweed, *Cystoseira usneoides*	HSV	Uknown	[210]
Carotenoids: Cucumariaxanthin C (291)	Sea Cucumber, *Cucumaria japonica*	Epstein-Barr virus	Uknown	[211]



Halogenated cyclohexadienone (245)

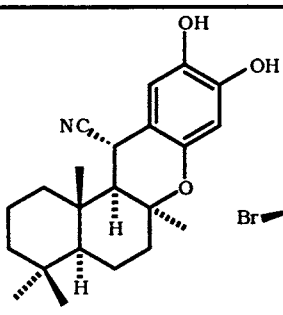
Avarol (246) R =

Avarone (247) R =

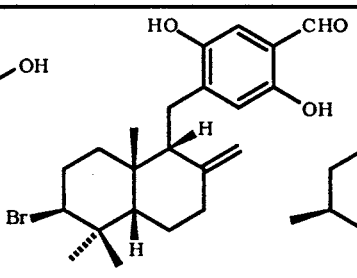
Chamigrene derivative (248)

Sesquiterpene isocyanide (249)

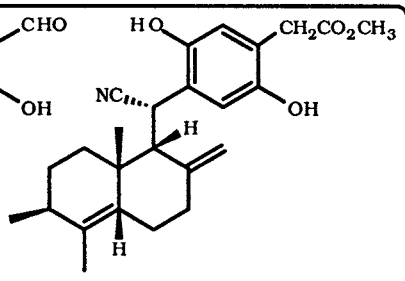
Strongylin A (250)



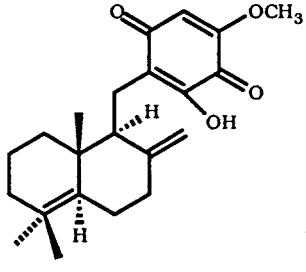
15-Cyanopuupehenol (**251**)



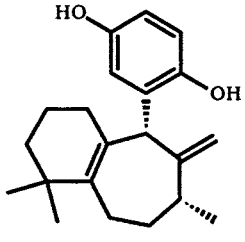
Peyssonol A (**252**)



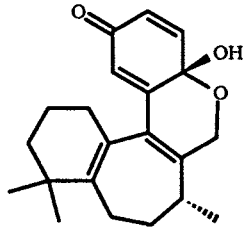
Peyssonol B (**253**)



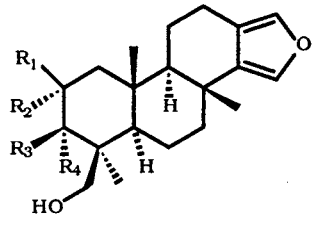
Hyatellaquinone (**254**)



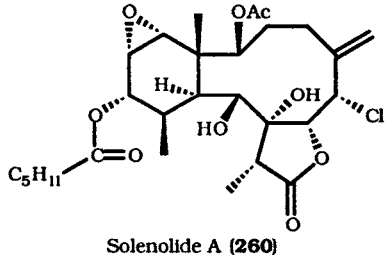
(-)-Frondosin A (**255**)



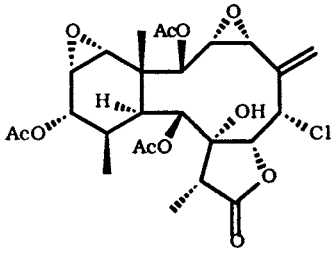
(-)-Frondosin D (**256**)



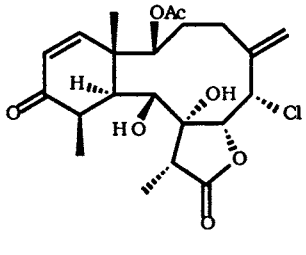
	R_1	R_2	R_3	R_4
Spongiadiol (**257**)	=O		H	OH
Epispongiadiol (**258**)	=O		OH	H
Isospongiadiol (**259**)	H	OH	=O	



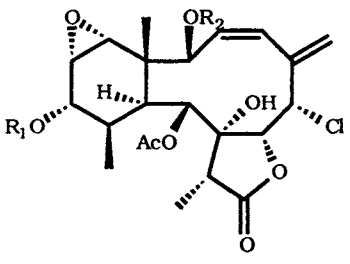
Solenolide A (**260**)



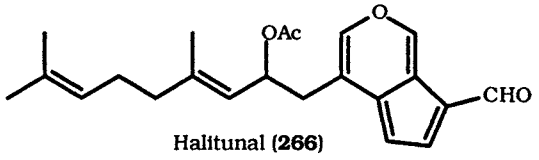
Solenolide D (**261**)



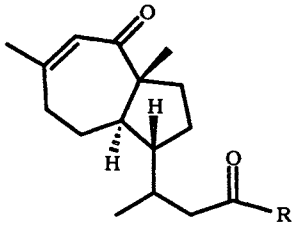
Solenolide E (**262**)



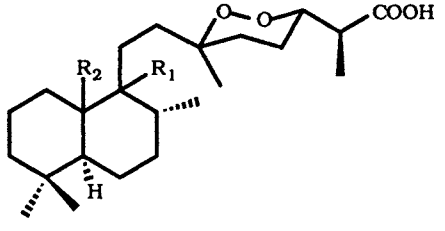
	R_1	R_2
Brianthein V (**263**)	Butyroyl	Butyroyl
Brianthein Y (**264**)	Ac	Butyroyl
Brianthein Z (**265**)	Ac	Ac



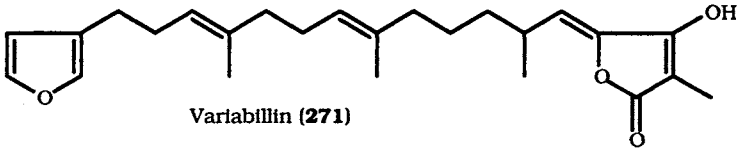
Halitunal (**266**)



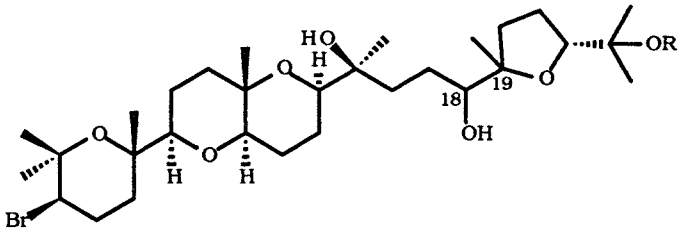
	R
Reiswigin A (**267**)	$CH_2CH(CH_3)_2$
Reiswigin B (**268**)	$CH{=}C(CH_3)_2$



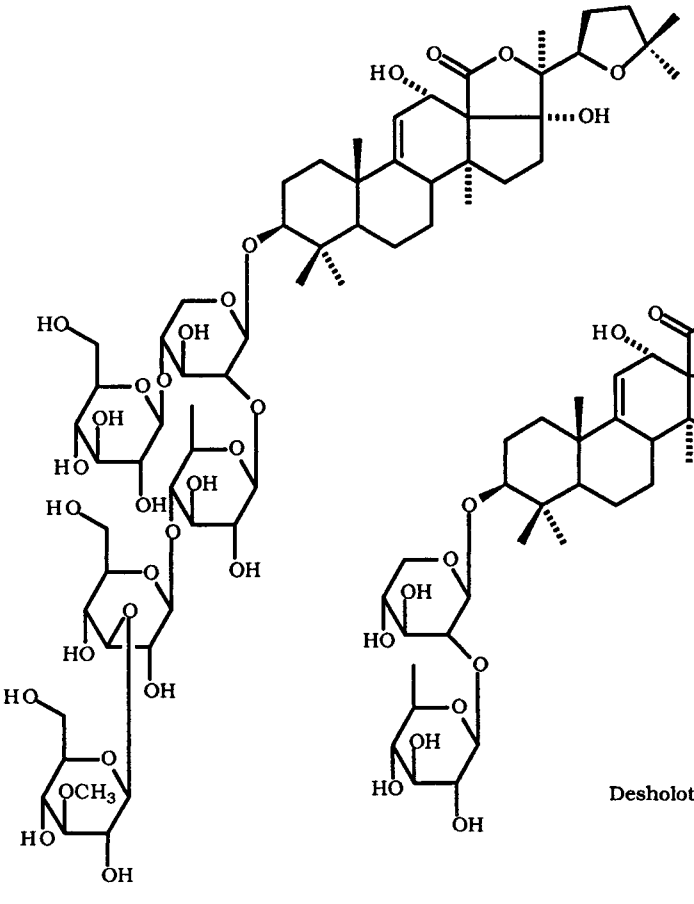
	R_1	R_2
Mycaperoxide A (**269**)	β-CH_3	α-OH
Mycaperoxide B (**270**)	α-OH	β-CH_3



Variabilin (**271**)

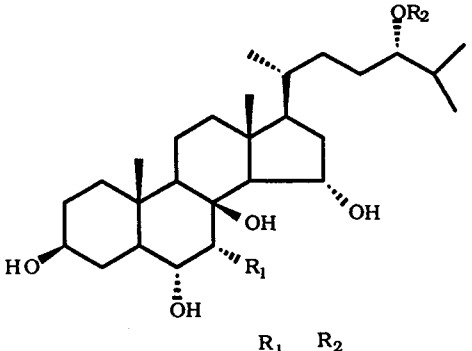


	R	
Thyrsiferol (**272**)	H	18*S*, 19*R*
Thyrsiferol Acetate (**273**)	Ac	18*S*, 19*R*
Venustatriol (**274**)	H	18*R*, 19*S*

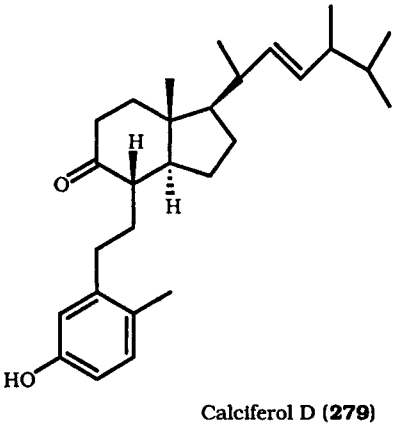


Holothurinoside A (**275**)

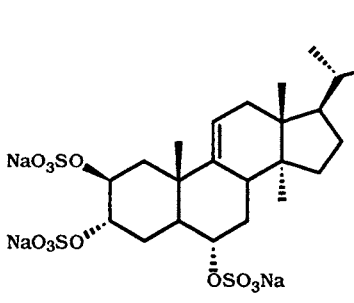
Desholothurin A (**276**)



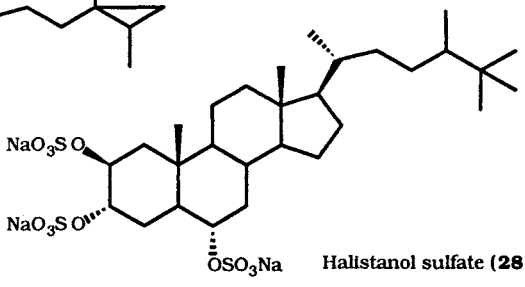
	R_1	R_2
Crossasteroids B (**277**)	H	4-O-Me-Xyl-(1-2)-3-O-Me-Xyl
Crossasteroids D (**278**)	OH	Xyl-(1-2)-3-O-Me-Xyl



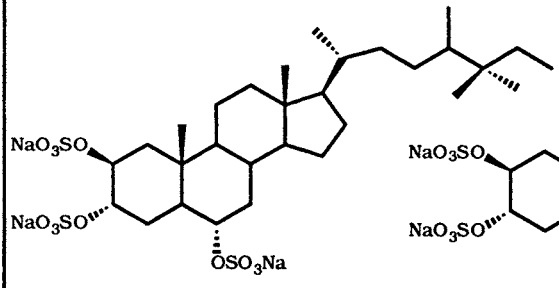
Calciferol D (**279**)



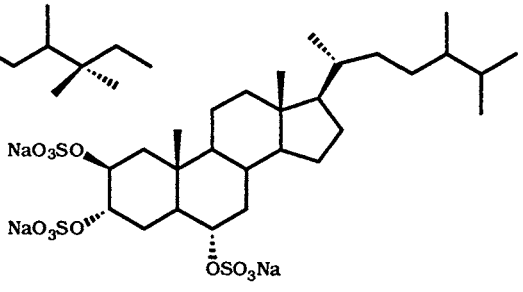
Ibisterol sulfate (**280**)



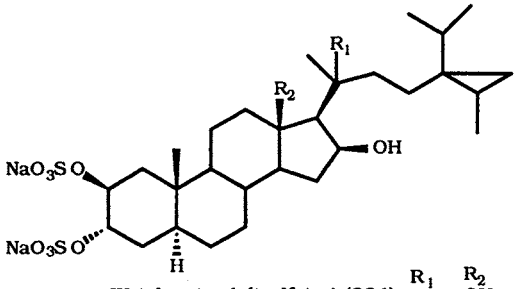
Halistanol sulfate (**281**)



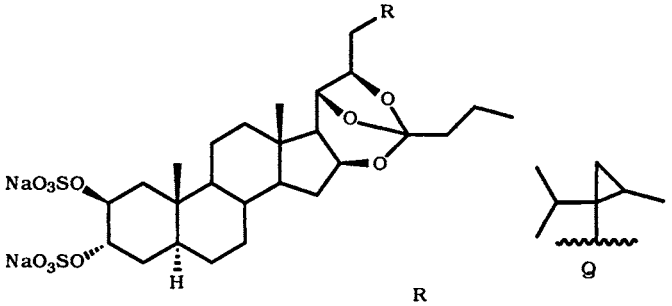
26-Methylallistanol sulfate (**282**)



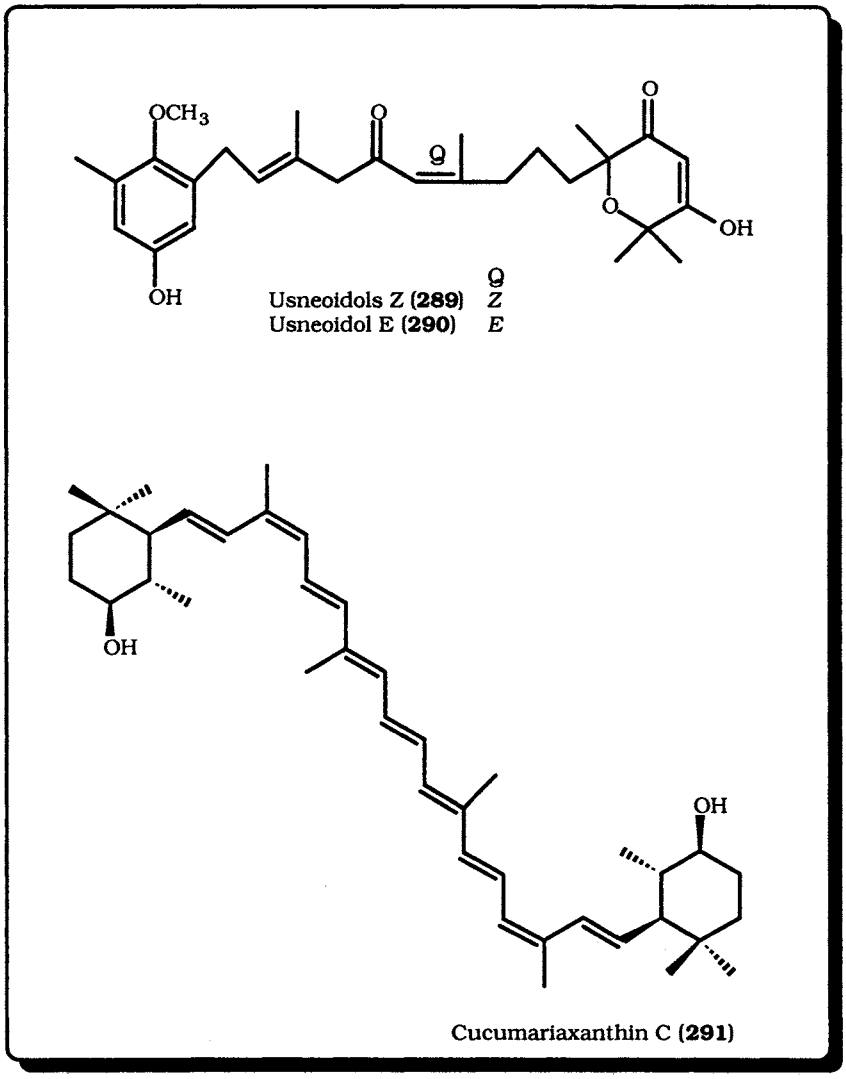
25-Demethylallistanol sulfate (**283**)



	R_1	R_2
Weinbersterol disulfate A (**284**)	H	OH
Weinbersterol disulfate B (**285**)	OH	H



	R
Orthosterol disulfate A (**286**)	C $(CHMe_2)$=CHMe
Orthosterol disulfate B (**287**)	Q
Orthosterol disulfate C (**288**)	$CHEtCHMe_2$



Marine-Derived Antiviral Polysaccharides

The cell wall polysaccharide carrageenan, isolated from the red algae (Rhodophyta) is constructed from galactose with varying amounts of sulfate substituents. Samples collected in Senegal include: *Hypnea musciformis*, *Anatheca montagnei*, *Agardhiella tenera* and *Euchema cottonii* inhibited the activity of yellow fever virus by up to 25.8% [212]. A commercial sample of carrageenan (Sigma Co.) inhibited HSV-1 cell growth in Hela cells without becoming cytotoxic when concentrations were up to 200 μg/mL [213]. The activity against HIV of water soluble

compounds extracted from *Schizymenia californa* was also observed and carrageenan was reported to be one of the constituents which inhibits HIV-RT [214,215].

Sulfated derivatives of a polysaccharide prepared by chlorosulfonic acid treatment of a fucosamine-containing polysaccharide from a marine *Pseudomonas* sp. showed strong anti-HSV-1. This sulfated polysaccharide inhibited the CPE of HSV-1 at 0.72 μg/mL. No cytotoxic effects on Vero cells were detected up to 1000 μg/mL [216]. Another study indicated the inhibition of HIV-1 replication in MT-4 cells by a sulfated derivative of fucosamine-containing polysaccharide obtained from a marine *Pseudomonas* strain HA-318 and also showed no cytotoxicity [217].

A polysaccharide from the green marine alga *Ulva lactuca* inhibited the reproduction of many human and avian influenza viruses. Acid hydrolysis of this polysaccharide revealed the presence of arabinose, xylose, rhamnose, galactose, mannose and glucose in ratio of 1:1:9:5:2:5:16, respectively along with an unidentified sugar [218].

Treatment of laminarin isolated from the marine alga *Laminaria cichorioides* by endo-β-1,3-glucanase from marine invertebrates transformed β-1,3:1,6-glucan into a highly efficient preparation against tobacco mosaic virus named antivir [219]. Polysaccharides, composed of mannose, galactose, glucose, uronic acid and sulfate groups (7-8% wt/wt) was obtained from the marine microalga *Cochlodinium polykrikoides* show potent inhibitory activities against: influenza viruses type A and B, respiratory syncytial viruses type A and B, HIV-1, HSV-1 and parainfluenza viruses type 2 and 3. No cytotoxicity nor inhibition to the blood coagulation were observed up to 100 μg/mL [220].

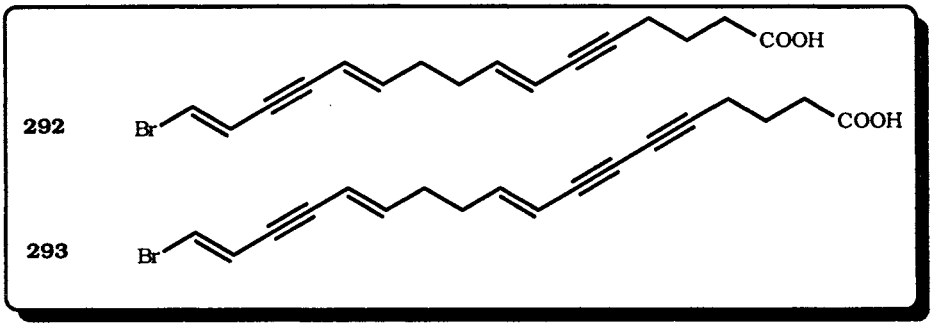
An unusual sulfated mannose homopolysaccharide, isolated from the Pacific tunicate *Didemnum molle* shows *in vitro* anti-HIV activity. The NMR data of this polysaccharide reveals that it consists of a sequence of 2,3-disulfated mannose units joined through β (1,6) glycosidic linkages [221]. A natural sulfated mucopolysaccharide (OKU40), extracted from a marine plant *Dinoflagellata* and an artificial sulfated polysaccharide (OKU41), was prepared from a marine *Pseudomonas*, displayed antiviral activities against HIV-1 and -2, zidovudine-resistant HIV-1, HSV-1, influenza viruses A and B, respiratory syncytial virus and measles virus without displaying cytotoxicity or inhibition of blood coagulation of host cells [222].

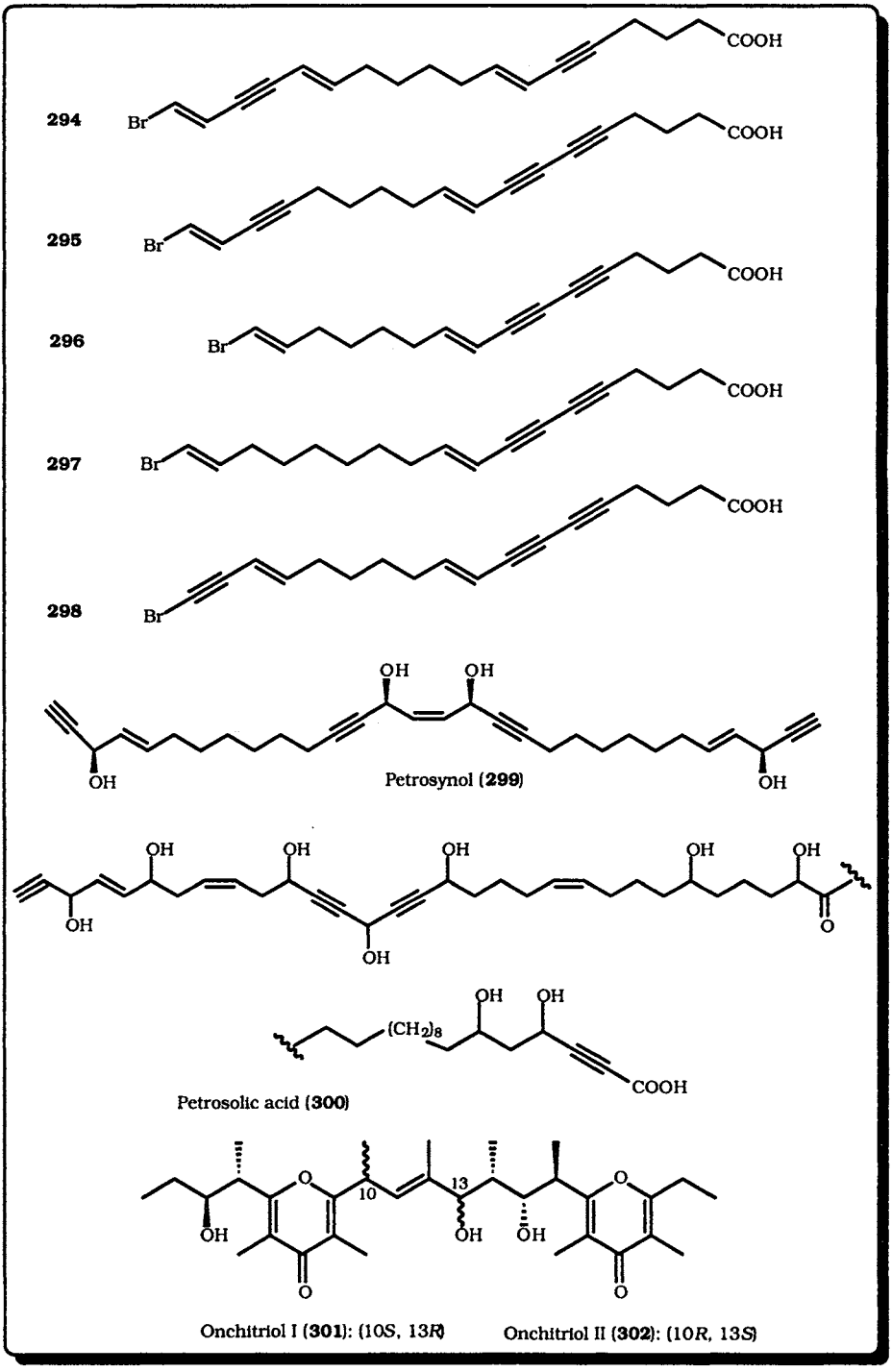
Marine-Derived Antiviral Polyacetylenes, Quinones/Pyrones, Macrolides and Prostaglandins

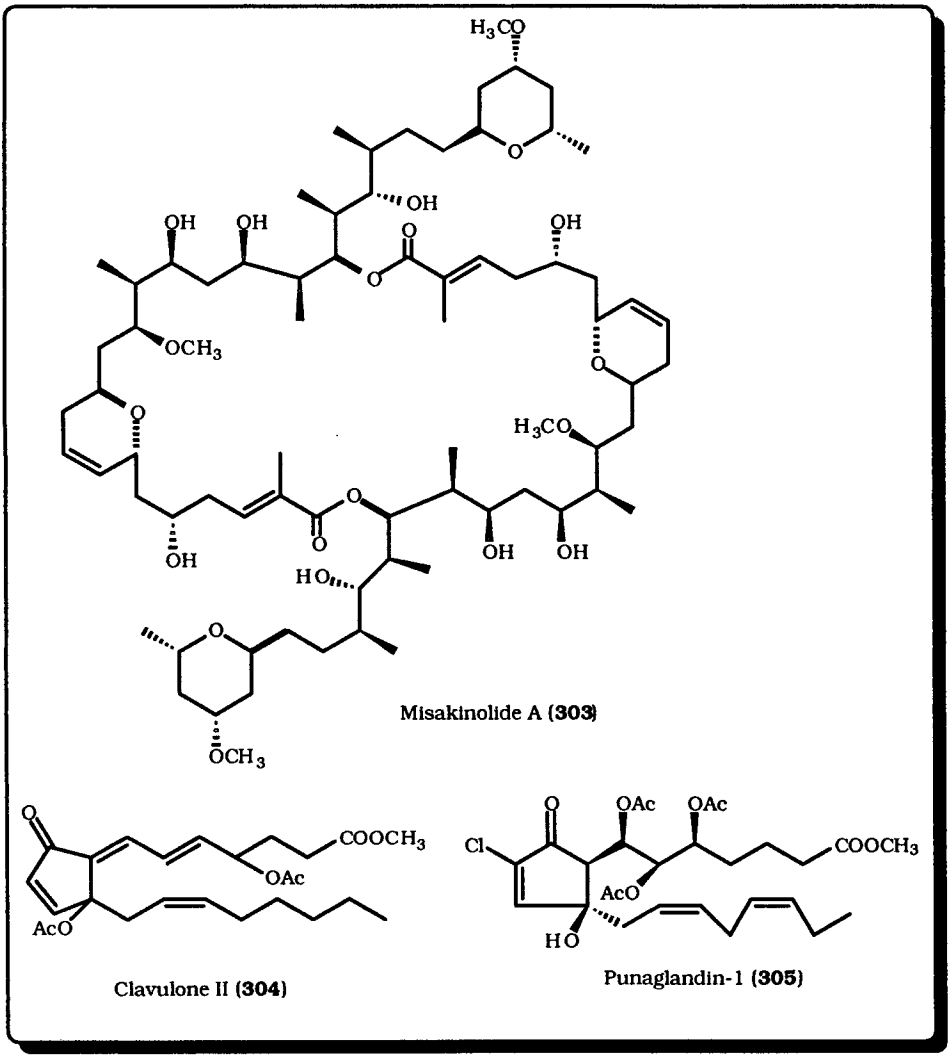
Table 12 illustrates the reported antiviral activities of the common marine secondary metabolites polyacetylenes, quinones/pyrones, macrolides and prostaglandins.

Table 12. Marine-Derived Antiviral Polyacetylenes, Quinones/Pyrones, Macrolides and Prostaglandins

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
Polyacetylenes:				
16-Bromo-(7*E*, 11*E*, 15*E*)-hexadeca-7,11, 15-triene-5,13-diynoic acid (**292**)	Sponge, *Xestospongia muta*	HIV HIV-1	HIV protease HIV-RT	[223]
18-Bromo-(9*E*, 13*E*, 17*E*)-octadeca-9,13, 17-triene-5,7,15-triynoic acid (**293**)	Sponge, *Petrosia* sp.			
18-Bromo-(7*E*, 13*E*, 17*E*)-octadeca-7,13, 17-triene-5,15-diynoic acid (**294**)				
18-Bromo-(9*E*, 17*E*)-octadeca-9,17-diene-5,7,15-triynoic acid (**295**)				
16-Bromo-(9*E*,15*E*)-hexadeca-9, 15-diene-5,13-diynoic acid (**296**)				
18-Bromo-(9*E*, 17*E*)-octadeca-9,17-diene-5,7 -diynoic acid (**297**)				
18-Bromo-(9*E*, 15*E*)-octadeca-9,15-diene-5,7,15-triynoic acid (**298**)				
Petrosynol (**299**)				[224]
Petrosolic acid (**300**)				
Quinones/Pyrones:				
Onchitriol I(**301**), II (**302**)	Mollusc, *Onchidium* sp.	HSV HIV-1, -2, murine leukemia virus	Cytotoxicity HIV-RT	[225] [226]
2-Hexaprenylhydroquinone	Sponge, *Ircinia* sp.			
Macrolides:				
Misakinolide A (**303**)	Sponge, *Theonella* sp.	HSV-1, VSV	Cytotoxicity	[227]
Prostaglandins:				
Clavulone II (**304**)	Soft coral, *Clavularia viridis*	VCV, EMC	Uknown	[155]
Punaglandin-1 (**305**)	Octacoral, *Telesto riisei*	HSV		[155]




294
Br
COOH
295
Br
COOH
296
Br
COOH
297
Br
COOH
298
Br
COOH
OH
OH
OH
OH
Petrosynol (299)
OH
OH
OH
OH
OH
OH
OH
O
OH
(CH2)8
OH
OH
COOH
Petrosolic acid (300)
O
10
13
OH
OH
OH
O
O
Onchitriol I (301): (10S, 13R)
Onchitriol II (302): (10R, 13S)



Microbial-Derived Antiviral Compounds

The human dream of finding an antiviral antibiotic from microbial origin which selectively affects the viral but not the host cell in a similar manner to the regular antibiotics has not become a reality. However, several microbial-derived metabolites show promising activity. The use of microbes to modify synthetic compounds or to accomplish specific desired reaction is common in pharmaceutical industry. Adenine arabinoside (Ara A, **200**), which is approved for clinical investigation, is also produced by a *Streptomyces* sp [19]. Examples of secondary

metabolites from microbial origin that show antiviral activities are presented below.

Rifamycins

Rifamycins are microbial-derived macrolides that were isolated in 1957 from the actinomycete *Streptomyces mediterranei*, obtained from the soil of the pine forests of southern France [18]. Of these, rifamycin B (**306**) is the least toxic. Addition of diethylbarbituric acid to the fermentation medium results in the production of **306** only. Rifampicin is the C3-hydazone semisynthetic derivative of rifamycins. Rifamycins show *in vitro* and *in vivo* anti-poxyviruses, e.g., VV activities [18]. These activities are apparently due to inhibition of the early step of viral morphogenesis which affects the assembly of immature viral particles. The inhibitory activity of rifamycins on retroviruses is also reported [18]. Many natural and semisynthetic rifamycins inhibit the virion RNA-dependent DNA polymerase (RT) [18]. Rifamycin B (**306**) was reported active against murine sarcoma virus (MSV) due to its RT, focus formation and cell transformation inhibitory activities [18]. Rifamycin antibiotics also inhibit the RT of Rauuscher leukemia virus, preventing its leukomogenic activity [18].

The Ansamycin Antibiotics

Streptovaricin B (**307**), tolypomycin and geldanamycin are examples of ansamycins which are chemically related to rifamycins. The streptovaricins and tolypomycins resemble rifamycins in RT-inhibitory activity [18]. Streptovaricin B inhibits the replication of poxviruses by inhibiting early stages of mRNA synthesis [18]. Inhibition of focus formation of MSV by streptovaricins is also reported [18].

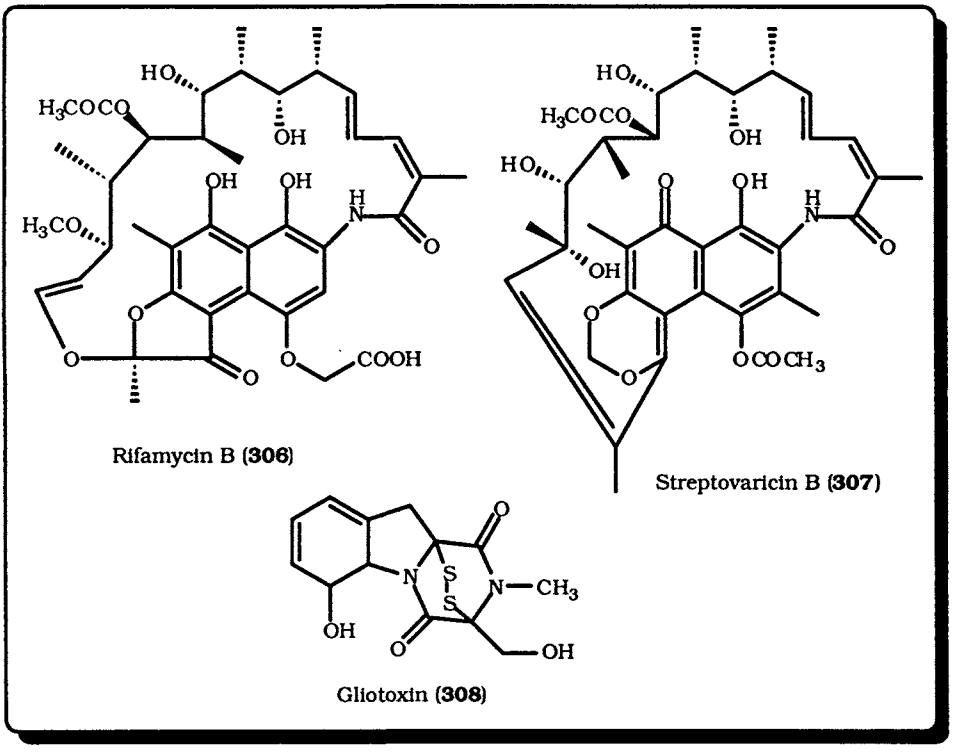
Gliotoxin and Related Compounds

Gliotoxin (**308**) is a fungal metabolite, isolated from *Aspergillus terreus* and found to have antibacterial, antitumor and antifungal effects [18]. Gliotoxin acetate inhibited the CPE of poliovirus in monkey kidney cell cultures due to the early stage inhibition of RNA viral replication [18]. Gliotoxin also inhibits influenza virus-induced RNA polymerase.

Arantonins are related compounds, isolated from *Arachniotus aureus* and *Aspergillus terreus* and show RT inhibitory activity [19]. The activity is attributed to the epidithiapiperazinedione moiety, as the case of **308**.

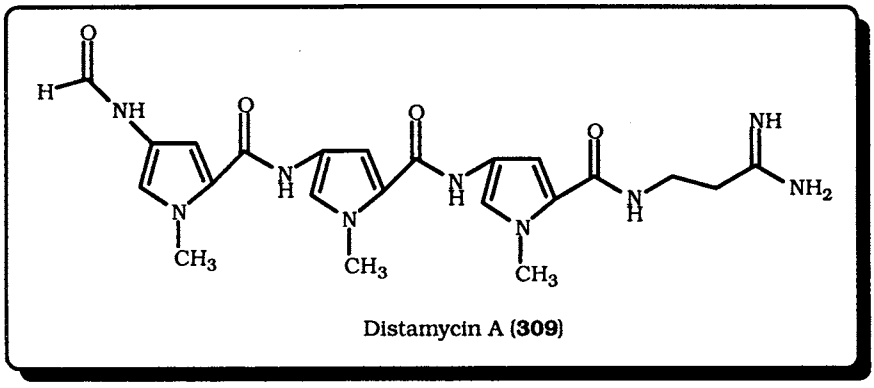
Sporidesmin and its metabolites were isolated from *Chaetomium cochliodes* and show structural similarity to **308**. They also inhibit the

RNA-containing viruses but with remarkable toxicity which prohibited their therapeutic applicability.



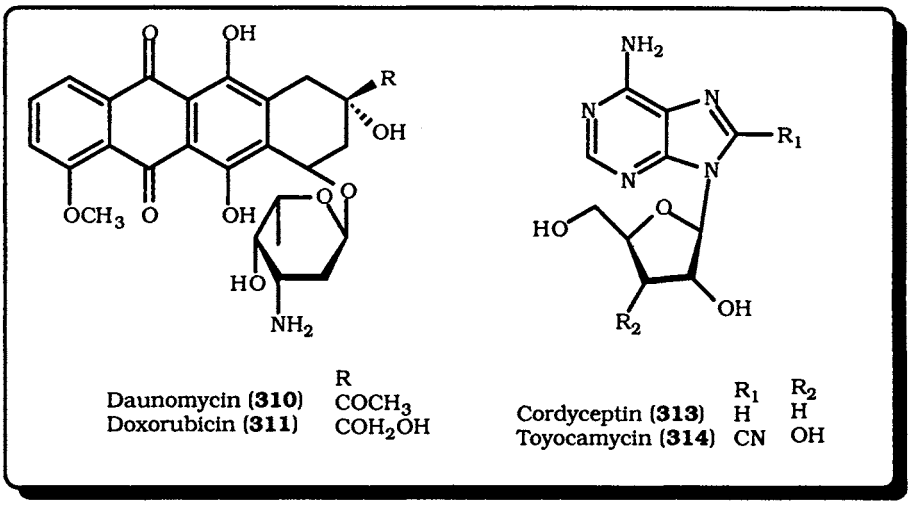
Distamycins (Pyrrole Amidines)

Distamycin A (**309**) is an oligopeptide, isolated from *Streptomyces distallicus* that inhibits transcription and replication of DNA viruses along with its other related semisynthetic analogs [18]. Example of DNA viruses inhibited by this group are vaccinia virus and HSV-1. Distamycin A also shows inhibitory activity for RT of retroviruses [18].



Daunomycin and Doxorubicin

Daunomycin (**310**) and doxorubicin (**311**) are anthracycline glycosides, isolated from *Streptomyces peucetius* [18]. These compounds are used in cancer chemotherapy due to their ability to bind DNA. Both compounds inhibit RT and production of murine leukemia virus [18].



	R
Daunomycin (**310**)	$COCH_3$
Doxorubicin (**311**)	COH_2OH

	R_1	R_2
Cordyceptin (**313**)	H	H
Toyocamycin (**314**)	CN	OH

Bleomycins

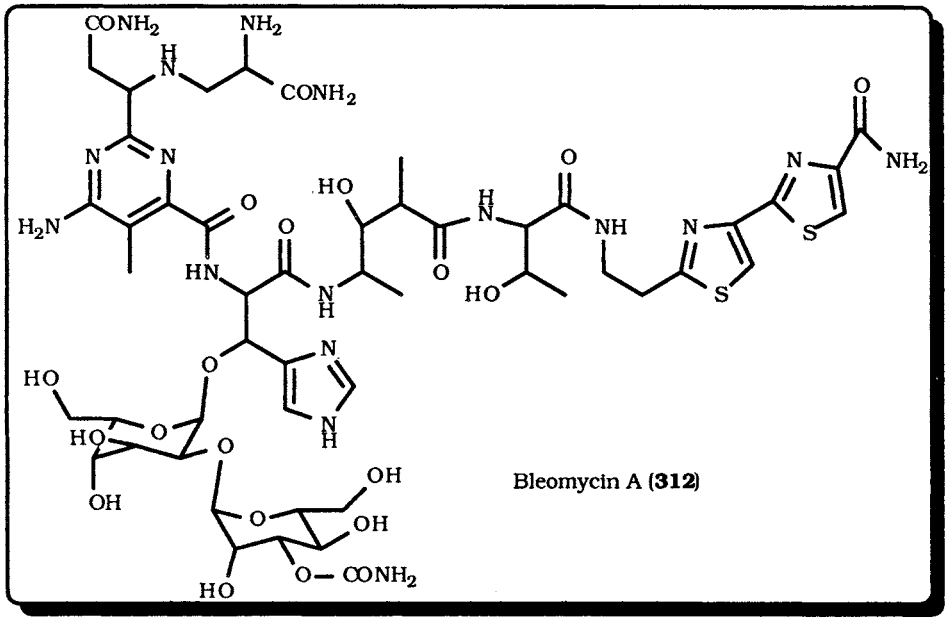
Bleomycins are glycopeptide antibiotics, isolated from *Streptomyces verticillus*. Bleomycins interact with DNA and induce breakage of DNA with a concomitant release of free bases. Bleomycin A (**312**) inhibits the replication of VV [18].

Actinomycin D and Mithramycin

Actinomycin D is a peptide antibiotic, produced by *Streptomyces parvulu.* It interacts with cellular DNA and inhibits the replication of mammalian viruses that depend on cellular functions, e.g., rabies virus [18]. Mithramycin is a related compound that inhibits influenza and pseudorabies viruses probably due to inhibition of host cell RNA polymerase II [18].

Cordyceptin (3'-Deoxyadenosine), Toyocamycin and Sinefungin

Cordyceptin (**313**) is a fermentation product of the fungi *Aspergillus nidulans* and *Cordyceps militaris*. Cordyceptin inhibits the synthesis of mRNA and hence the replication of both RNA and DNA viruses [18].



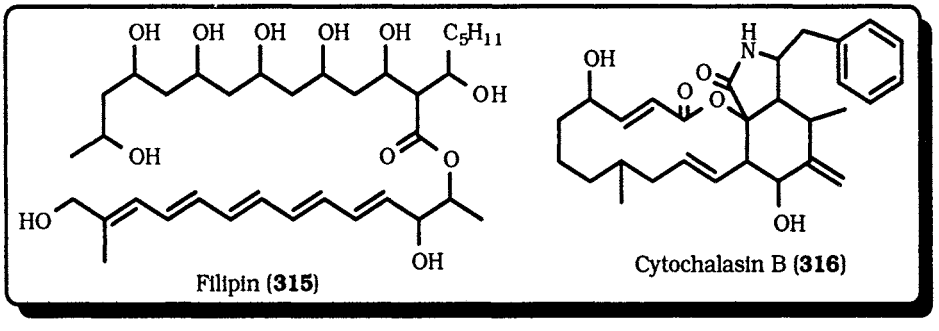
This effect displayed by activity of **313** against VV, HSV, adenovirus, rhinovirus, poliovirus and MSV [18].

Toyocamycin (**314**) is another adenosine derivative produced by *Streptomyces toyocaensis* [18]. This compound selectively inhibits the ribosomal RNA synthesis in fibroblasts. The synthesis of adenovirus-specific mRNA is also inhibited by **314** [18].

Sinefungin is an adenine derivative, isolated from *Streptomyces griseolus* and it effectively inhibits VV mRNA (guanine-7-)methyltransferase and hence inhibits methylation of its mRNA [18].

Filipin and Amphotericin B

Filipin (**315**) is a polyene antibiotic that is capable of interaction with sterols in liposomes and biological membranes, leading to alteration of



bilayer structure. Filipin shows activity against VSV and to less degree against influenza and Rauscher leukemia virions [18].

Amphotericin B is another related antifungal antibiotic. Its methyl ester is active against HSV-1 and -2, VV, SV and VSV with less cytotoxicity and improved water solubility [18].

Aphidicolin

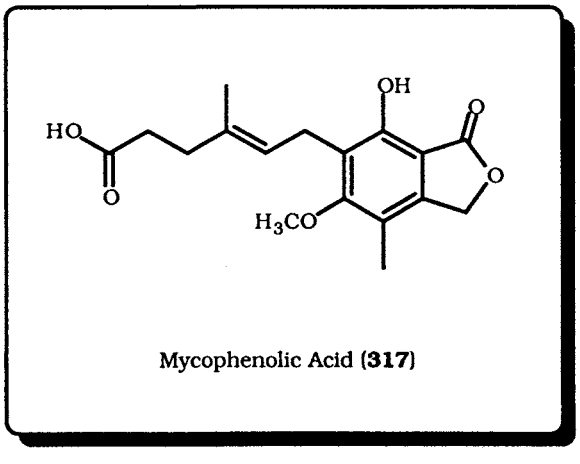
Aphidicolin is a tetracyclic diterpenoid, produced by the fungus *Cephalosporium aphilicola*. It has the ability to inhibit HSV-1, -2, VV and herpetic keratitis of rabbit [19]. The mechanism of this compound is not yet established.

Cytochalasins

Cytochalasin B (**316**) is a metabolite of the mold *Helminthosporium dermatoideum* [19]. It inhibits hexose transport in cells and hence it is used for the study of virus-specific glycoprotein synthesis. It shows potent inhibitory activity against HSV-1 and -2 apparently due to the inhibition of viral glycosylation [19]. Cytochalasin D is a closely related compound that shows activity against adenovirus but it enhances the infectivity of poliovirus and parainfluenza [19].

Mycophenolic Acid (317)

It is a phenolic acid, isolated from a *Penicillium* sp. and shows inhibitory activity against HSV-1 and -2, VV, Semliki forest, influenza A viruses and coxsackievirus. Its effect is probably due to cytotoxicity [19].



Mycophenolic Acid (**317**)

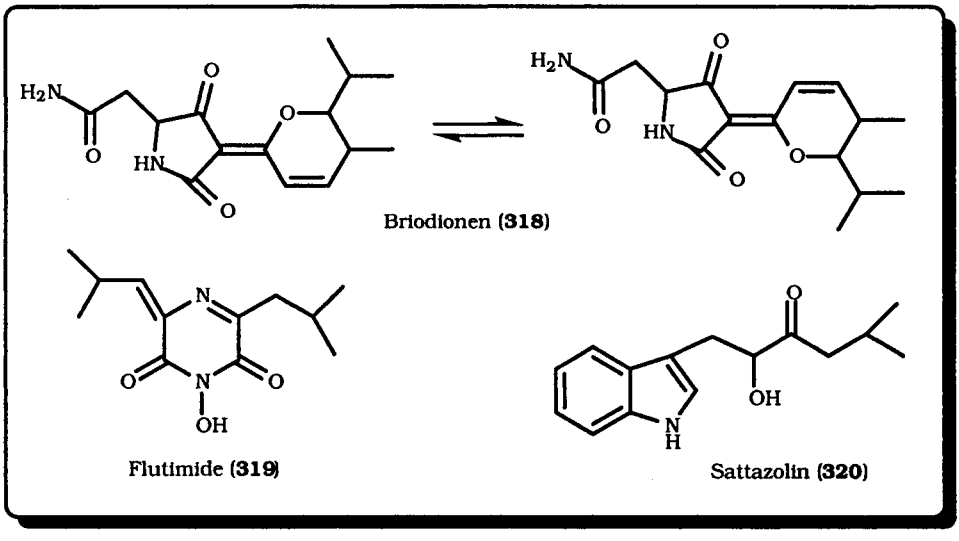
Additional antiviral microbial-derived metabolites are summarized in Table 13.

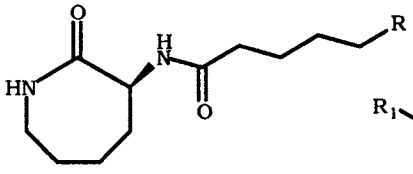
Table 13. Microbial-Derived Antiviral Compounds

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Reference
N-Containing, Protein and Peptide Compounds: Briodionen (**318**)	*Streptomyces* sp. WC76599	Human CMV	HCMV Protease	[228]
Flutimide (**319**)	*Delitschia confertaspora*	Influenza virus	Endonuclease	[229]
4-Hydroxysattabacin, Sattazolin (**320**), 2'-Methylsattazolin	*Bacillus* sp.	HSV-1, HSV-2	Protein synthesis	[230]
Kistamicin A and B	*Microtetraspora parvossata* ATCC 55076	Influenza A	Uknown	[231]
Caprolactin A (**321**) and B (**322**)	Unidentified gm+ve marine bacterium	HSV-2	Cytotoxicity	[232]
Lycogarubin A (**323**), B (**324**), C (**325**)	*Lycogala epidendrum*	HSV-1	Uknown	[233]
Fenalamide I (**326**)	*Myxococcus stipitatus*	HIV-1	Replication	[234]
Thiangazole (**327**)	Gliding bacteria	HIV-1	Cytotoxicity	[235]
Fluvirucins A1, A2, B1, B2, B3, B4, B5	Unidentified actinomycetes	Influenza A	Unknown	[236]
MM46115 (**328**)	*Actinomadura pelletieri*	Parainfluenza-1 and 2	Unknown	[237]
Phenoxan (**329**)	*Polygonium* PI VO19	HIV-1	Cytotoxicity	[238]
Pumilacidin A, B, C, D, E, F, G	*Bacillus pumilus*	HSV-1	Unknown	[239]
Lanthiopeptin	*Streptoverticillium cinnamoneum*	HSV-1	Unknown	[240]
Bu-2231	*Streptoalloteichus hindustanus*	HSV-1	Unknown	[241]
Oxetanocin A (**330**)	*Bacillus megaterium*	HSV-2	Protein synthesis	[242]
Adechlorin (**331**)	*Actinomadura* OMR-37	HSV, VV Ara-A Synergistic	Adenosine deaminase	[243]
Chromostin	Unidentified actinomycete	Avian myeloblastosis virus	RT II	[244]
Virantmycin (**332**)	*Streptomyces nitrosporeus*	HSV	Unknown	[245]

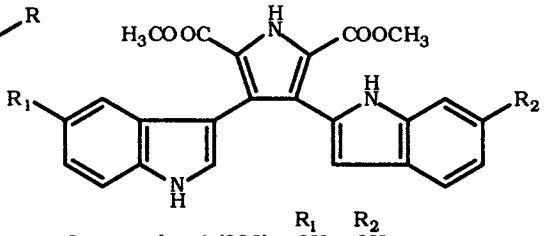
(Table 13). contd.....

Compound: Type & Name	Source	Activity Against	Mechanism/ Inhibition	Refe-rence
SF-1836C (**333**)	*Streptomyces zaomuceticus*	Influenza	Replication	[246]
Aromatics and Phenolics				
Sattabacin (**334**)	*Bacillus* sp.	HSV-1, HSV-2	Protein synthesis	[230]
AH-1763	*Streptomyces cyaneus*	HSV-1, HSV-2	Unknown	[247]
Sch 68631 (**335**)	*Streptomyces* sp.	HCV	Proteinase	[248]
Pradimicins	*Actinomadura* AA085	HIV	Unknown	[249]
Mutactimycin A (**336**)	Mutated *Streptomyces*	HSV-1, HSV-2, Influenza A3, Coxsackie B6	Protein synthesis	[250]
Macrolides:				
Cycloviracins B1 (**337**), B2	*Kibdelosporangium albatum*	HSV-1	Unknown	[251]
Quatromicins A1 (**338**), A2 (**339**), A3 (**340**)	*Amycolatopsis orientalis*	HSV-1	Cytotoxicity	[252]
Acyclic acids:				
Podoscyphic acid	*Podoscypha* sp.	Avian myeloblastosis, Moloney murine leukemia	Protein synthesis	[253]

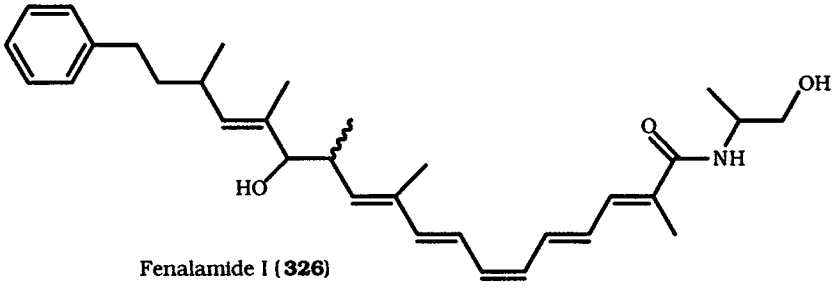




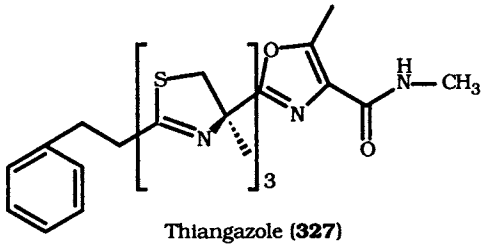
	R
Caprolactin A (**321**)	CH_2CHMe_2
Caprolactin B (**322**)	$CHMe_2$



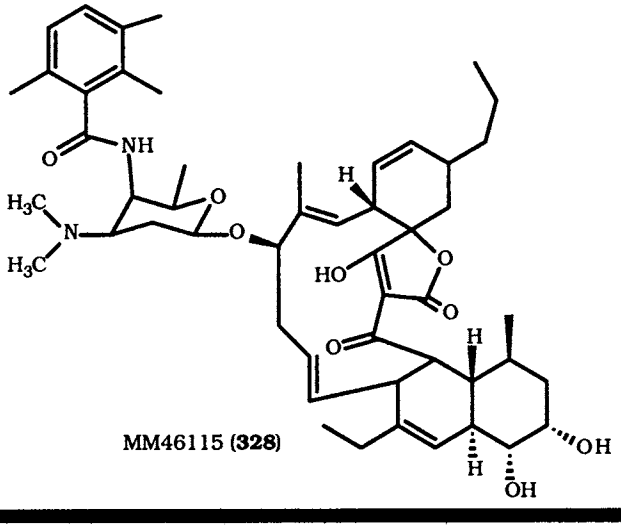
	R_1	R_2
Lycogarubin A (**323**)	OH	OH
Lycogarubin B (**324**)	OH	H
Lycogarubin C (**325**)	H	H



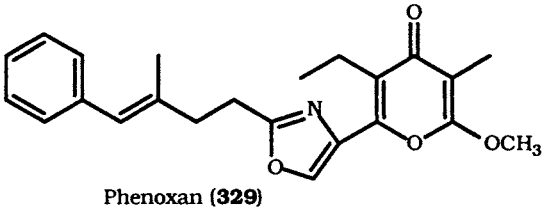
Fenalamide I (**326**)



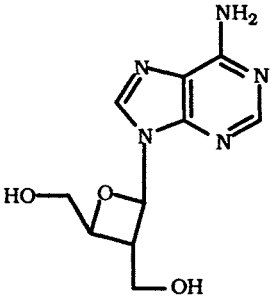
Thiangazole (**327**)



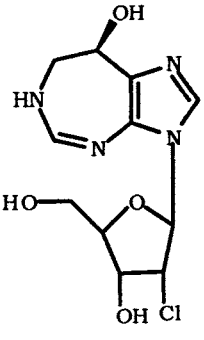
MM46115 (**328**)



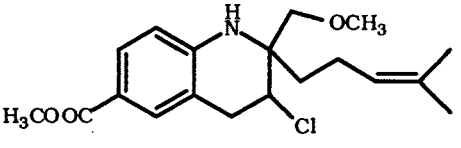
Phenoxan (**329**)



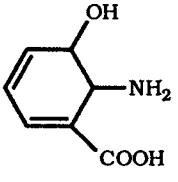
Oxetanocin A (**330**)



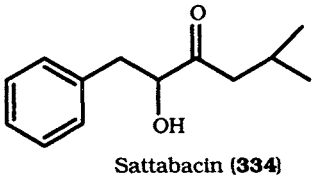
Adechlorin (**331**)



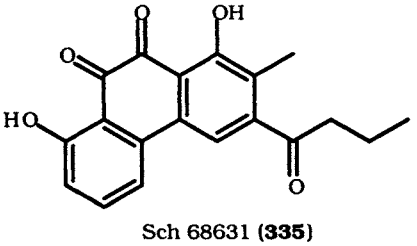
Virantmycin (**332**)



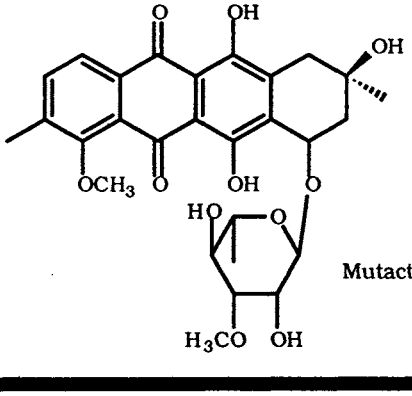
SF-1836C (**333**)



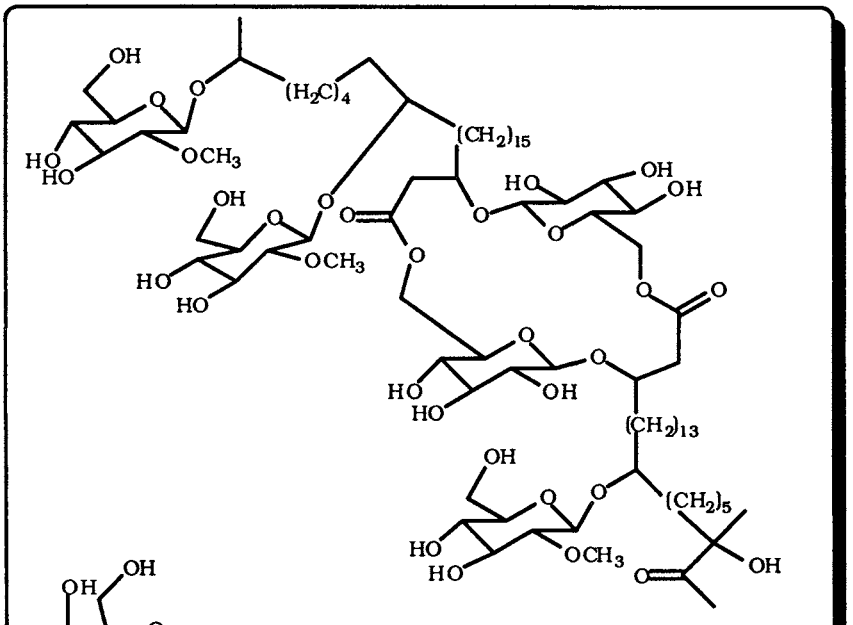
Sattabacin (**334**)



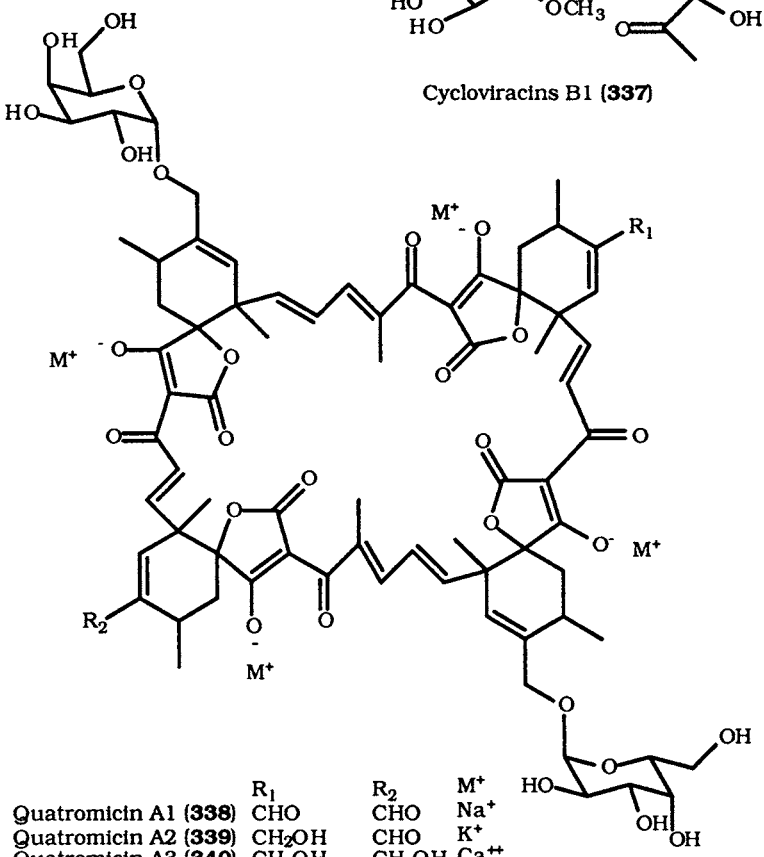
Sch 68631 (**335**)



Mutactimycin A (**336**)



Cycloviracins B1 (**337**)



	R_1	R_2	M^+
Quatromicin A1 (**338**)	CHO	CHO	Na^+
Quatromicin A2 (**339**)	CH_2OH	CHO	K^+
Quatromicin A3 (**340**)	CH_2OH	CH_2OH	Ca^{++}

CONCLUSIONS

There is an urgent need to identify novel active chemotypes as lead for effective antiviral chemotherapy. Recent years have witnessed great advances in this area. The enormity of natural products as antiviral agents started to be expressed in the area of antiviral chemotherapy. This is represented by the FDA's approval for clinical investigation of two plant-derived compounds, in addition to one compound of marine origin and one microbial-derived compound. Out of ten synthetic approved drugs between 1983-1994, seven were modeled on a natural product paren [4]. The development of recent techniques to dereplicate, accurately detect, isolate, structurally define and automated assay the bioactive natural products will result in more lead of antiviral agents. It has been estimated that only 5-15% of the approximately 250, 000 species of higher plants have been systematically investigated for the presence of bioactive compounds while the potential of the marine environment has barely been tapped [4]. Consequently, natural products represent potential antiviral leading resources for imaginative discoverers.

ACKNOWLEDGMENTS

I am grateful to Dr. Ahmed F. Halim, Mansoura University, for his continuous support and introducing me to Pharmacognosy science; Dr. James D. McChesney, Napro Biotherapeutics, for his continuous support and encouragement; Dr. Farouk S. El-Feraly, King Saud University, for his valuable editorial guidance; Dr. Mark Hamann, University of Mississippi, for offering me the opportunity to explore the fascinating world of marine natural products; Ms. Nadia E. Hashish, University of Minnesota, for informative literature and valuable discussions. Mr. Muhammad A. Yaqoob, H.E.J. Research Institute of Chemistry, is acknowledged for his valuable editorial assistance.

I am indebted to The Department of Pharmacognosy, School of Pharmacy, University of Mississippi, for the data base search facilities.

LIST OF ABBREVIATIONS

AVF	=	Antiviral Factor
BAP	=	*Bougainvilla* Antiviral Protein
CMV	=	Cytomegalovirus
CPE	=	Cytopathic Effect
EBV	=	Ebstein-Barr Virus
FMDV	=	Foot and Mouth Disease Virus
HBV	=	Hepatitis B Virus

HCMV	=	Human Cytomegalovirus
HCV	=	Hepatitis C Virus
HDV	=	Hepatitis Delta Virus
HHV-6	=	Human Herpes Virus-6
HIV	=	Human Immunodeficiency Virus
HSV	=	Herpes Simplex Virus
INFs	=	Interferons
MCMC	=	Mice Cytomegalovirus
MSV	=	Murine Sarcoma Virus
MV	=	Measles Virus
NDV	=	Newcastle Disease Virus
PAP	=	Pokeweed Antiviral Proteins
PRV	=	Pseudorabies Virus
RIPs	=	Ribosome-Inactivating Proteins
RSV	=	Respiratory Syncytial Virus
RT	=	Reverse Transcriptase
SV	=	Sindbis Virus
TMV	=	Tobacco Mosaic Virus
VSV	=	Vesicular Stomatitis Virus
VV	=	Vaccinia Virus
VZV	=	Varicella Zoster Virus

REFERENCES

[1] Clark, A.M. Natural Products as a Resource for New Drugs. *Pharmaceutical Research*, **1996**, *13*, 1133-1141.

[2] Shu, Y-Z. Recent Natural Products Based Drug Development: A Pharamaceutical Industry Perspective. *J. Nat. Prod.* **1998**, *61*, 1053-1071.

[3] Vanden Berghe, D.A.; Vlietinck, A.J.;, Van Hoof, L. Plant Products as Potential Antiviral Agents. *Bull. Instit. Pasteur*, **1986**, *84*, 101-147.

[4] Cragg, G.M.; Newman, D.J.; Sander, K.M. Natural Products in Drug Discovery and Development. *J. Nat. Prod.* **1997**, *60*, 52-60.

[5] Hughes, S.S. In "The Virus A History of the Concept", Heineman Educational Books, London, Science History Publications, New York, **1977**, p 109-113.

[6] Starr, C.; Taggart, R. In "Biology, the Unity and Diversity of Life", Wadsworth Publishing Company, Belmont, California, **1991**, p 347-350.

[7] Joklik, W.K. In "Virology", 3rd edition, Appleton & Lange, Norwalk, Connecticut, San Mateo, **1988**, p 1-38.

[8] Razvi, E.S.; Welsh, R.M. Apoptosis in Viral Infections. In "Advances in Virus Research", Maramorosch, K.; Murphy, F.A.; Shatkin, A.J. Eds. Academic Press, San Diego, London, **1995**, *45*, p 1-60.

[9] Lockshin, R.A.; Zakeri, Z. In "Apoptosis: The Molecular Basis of Cell Death" Tomei, L.D.; Cope, F.O., eds, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, **1991**, p 47-60.

[10] Feldmann, H.; Klenk, H-D. Marburg and Ebola Viruses. In "Advances in Virus Research", Maramorosch, K.; Murphy, F.A.; Shatkin, A.J. Eds. Academic Press, San Diego, London, **1996**, *47*, p 1-52.
[11] Hudson, J.D. In "Antiviral Compounds from Plants", CRC Press, Inc., Boca Raton, Florida, **1990**, p 43-57.
[12] Vlietinck, A.J.; De Bruyne, T.; Vanden Berghe, D.A. Plant Substances as Antiviral Agents. *Current Organic Chemistry*, **1997**, *1*, 307-344.
[13] Safrin, S.; Chambers, H.F. In "Basic & Clinical Pharmacology" 7th edition, Katzung, B.G., ed. Appleton & Lang, Stamford, Connecticut, **1998**, p 788-802.
[14] De Clercq, E. Antiviral Agents: Characteristic Activity Spectrum Depending on the Molecular Target With Which They Interact. In "Advances in Virus Research", Maramorosch, K.; Murphy, F.A.; Shatkin, A.J. Eds. Academic Press, San Diego, London, **1993**, *42*, p 1- 54.
[15] Sen, G.C.; Ransohoff, R.M. Interferon-Induced Antiviral Actions and Their Regulation. In "Advances in Virus Research", Maramorosch, K.; Murphy, F.A.; Shatkin, A.J. Eds. Academic Press, San Diego, London, **1993**, *42*, p 57-102.
[16] Vanden Berghe, D.A., Vlietinck, A.J.; Van Hoof, L. Plant Substances as Antiviral Agents. *Bull. Inst. Pasteur*, **1986**, *84*, 101-147.
[17] Munro, M.H.G; Luibrand, R.T.; Blunt, J.W. In "Biorganic Marine Chemistry", Springe Verlag, Berlin, **1987**, *1*, p 93-112.
[18] Becker, Y. Antiviral Agents from Natural Sources. *Pharmac. Ther.*, **1980**, *10*, 119-159.
[19] Came, P.E.; Steinberg, B.A. Chemotherapy of Viral Infection. Natural Products. In "Handbook of Experimental Pharmacology", Springe Verlag, Berlin, **1982**, *61*, p 479-518.
[20] Chu, C.K.; Culter, H.G. In "Natural Products as Antiviral Agents", Plenium Press, New York, **1992**.
[21] Ng, T.B.; Huang,B; Fong, W.P.; Yeung, H.W. Anti-Human Immunodeficiency Virus (Anti-HIV) Natural Products with Special Emphasis on HIV Reverse Transcriptase Inhibitors. *Life Sciences*, **1997**, *61*, 933-949.
[22] Che, C-T. Marine Products as a Source of Antiviral Leads. *Drug Development Research*, **1991**, *23*, 201-218.
[23] Rinehart, K.L.; Shield, L.S.; Cohen-Parson, M. Antiviral Substances. In "Marine Biotechnology, Pharmaceutical and Bioactive Natural Products", Attaway, D.H.; Zaborsky, O.R. Eds. Plenium Press, New York, London, **1993**, *1*, p 309-342.
[24] Vanden Berghe, D.A.; Ieven, M.; Mertens, F.; Vlietinck, A.J.; Lammens, E. Screening of Higher Plants for Biological Activities. II. Antiviral Activity. *Lloydia*. **1978**, *41*, 463-471.
[25] Ieven, M; Vlietinck, A.J.; Vanden Berghe, D.A.; Totte, J.; Dommisse, R.; Esmans, E.; Alderweireldt, F. Plant Antiviral Agents. III. Isolation of Alkaloids from *Clivia miniata* Regel (Amaryllidaceae). *J. Nat. Prod.* **1982**, *45*, 564-573.
[26] Montanha, J.A.; Amoros, M.; Bastic, J.; Girre, L. Antiherpes Virus Activity of Aporphine Alkaloids. *Planta Medica*, **1995**, *61*, 419-424.
[27] Kim, H.K.; Farnsworth, N.R.; Blomster, R.N; Fong, H.H.S. Biological and Phytochemical Evaluation of Plants. V. Isolation of Two Cytotoxic Alkaloids from *Chelidonium majus*. *J. Parm. Sci.* **1969**, *58*, 372-374.
[28] Kakiuchi, N.; Hattori, M.; Ishii, H.; Namba, T. Effect of Benzo[*c*]phenanthidine Alkaloids on Reverse Transcriptase and Their Binding Property to Nucleic Acids. *Planta Medica*, **1987**, *53*, 22-27.

[29] Tan, G.T.; Pezzuto, J.M.; Kinghorn, A.D. Evaluation of Natural Products as Inhibitors of Human Immunodeficiency Virus Type-1 (HIV-1) Reverse Transcriptase. *J. Nat. Prod.* **1991**, *54*, 143-154.

[30] Beutler, J.A.; Cardellina II, J.H.; McMahon, J.B.; Boyd, M.R. Anti-HIV and Cytotoxic Alkaloids from *Buchenavia capitata*. *J. Nat. Prod.* **1992**, *55*, 207-213.

[31] Tafur, S.; Nelson, J.D.; Delong, D.C.; Svoboda, G.R. Antiviral Components *of Ophiorrhiza mungo*. Isolation of Camptothecin and 10-Methoxycamptothecin. *Lloydia*. **1976**, *39*, 261-262.

[32] Hohenschutz, L.D.; Bell, E.A.; Jewens, P.J.; Leworthy, D.P.; Pryce, R.J.; Arnold, E.; Clardy, J. Castanospermine, A 1,6,7,8-Tetrahydroxyoctahydroindolizidine Alkaloid, from Seeds of *Castanospermum Australe*. *Phytochemistry*, **1981**, *20*, 811-814.

[33] Nash, R.J.; Fellows, I.E.; Dring, J.V.; Stirton, C.H.; Carter, D.; Hegarty, M.P.; Bell, E.A. Castanospermine in *Alexia* species. *Phytochemistry*, **1988**, *27*, 1403-1404.

[34] Scofield, A.M.; Fellows, L.E.; Nash, R.J.; Fleet, G.W.H. Inhibition of Mammalian Digestive Disaccharides by Polyhydroxy Alkaloids. *Life Sci.* **1986**, *39*, 645-650.

[35] Boyd, M.R.; Hallech, Y.F.; Cardellina II, J.H.; Manfredi, K.P.; Blunt, J.W.; McMahon, J.B.; Buckheit Jr, R.W.; Bringman, S.; Schaffer, M.; Cragg, G.M.; Thomas, D.W.; Jato, J.C. Anti-HIV Michellamines from *Ancistrocladus korupensis*. *J. Med. Chem.* **1994**, *37*, 1740- 1745.

[36] McMahon, J.B.M.; Currem, M.J.; Gulakowski, R.J.; Buckheit Jr. R.W.; Lachmen-Smith, C.; Hallock, Y.F.; Boyd, M.R. Michellamine B, A Novel Plant Alkaloid, Inhibits Human Immunodeficiency Virus-Induced Cell Killing by at Least Two Distinct Mechanisms. *Antimicrob. Ag. Chemther.* **1995**, *39*, 484-488.

[37] Kmpotic, E.; Farnsworth, N.R.; Messner, W.M. Cryptopleurine, An Active Antiviral Alkaloid from *Boehmeria cylinderica* (L.) SW. (Urticaceae) *J. Pharm. Sci.* **1972**, *61*, 1508-1509.

[38] Kite, G.C.; Fellows, L.E.; Fleet, G.W.J.; Liu, P.S.; Scofield, A.M.; Smith, N.G. α-Homono- jirimycin [2,6-Dideoxy-2,6-imino-Dglycerol-L-heptitol] from *Omphalea diandra* L.: Isolation and Glucosidase Inhibition. *Tetrahedron Lett.* **1988**, *29*, 6483-6486.

[39] Sethi, M.L. Enzyme Inhibition. VIII: Mode of Inhibition of Reverse TranscriptaseActivity by Analogues, Isomers and Related Alkaloids of *Coralyne*. *J. Pharm. Sci.* **1985**, *74*, 889- 891.

[40] McCommick, J.L.; McKee, T.C.; Cardellina, J.R.; Boyd, M.R. HIV Inhibitory Natural Products. 26. Quinoline Alkaloids from *Euodia oxburghiana*. *J. Nat. Prod.* **1996**, *59*, 469-471.

[41] Alarcon, B.; Gonzales, M.E.; Carrasco, L. Antiherpes virus Action of Atropine. *Antimcrob. Agents. Chemother.* **1984**, *26*, 702-706.

[42] Ghoneum, M. Anti-HIV Activity in Vitro of MGN-3, an Activated Arabinoxylan from Rice Bran. *Biochem. Biophys. Res. Commun.* **1998**, *243*, 25-29.

[43] Nakashima, H.; Kudo, Y.; Kobyashi, N.; Motoki, Y.; Neushul, M.; Yamamoto, N. Purification and Characterization of an Avian Myeloblastosis and Human Immunodeficiency Virus Reverse Transcriptase Inhibitors, Sulfated Polysaccharides Extracted from Sea Algae *Antimicrob. Agents Chemother.* **1987**, *31*, 1524-1528.

[44] Batinic, D.; Robey, F.A. J. Biol. Chem. The V3 Region of The Envelope Glycoprotein of Human Immunodeficiency Type 1 Binds Sulfated Polysaccharides and CD4-Derived Synthetic Peptides. 1992, 267, 6664-6671.

[45] Patel, A.D.; Freyer, A.J.; Egglerton, D.S.; Hultiwonger, R.C.; Bean, M.F.; Taylor, P.B.; Caranfa, M.J.; Breen, A.L.; Barton, H.M.; Johnson, R.K.; Herteberg, R.P.; Westley, D.W. The Inophyllums, Novel Inhibitors of HIV-1 Reverse Transcriptase Isolated from The Malaysian Tree, *Callophyllum inophyllum* Linn. *J. Med. Chem.* **1993**, *36*, 4131.

[46] Balzarini, J.; Schols, D.; Neyts, J.; Van Damme, E.; Peumans, W.; De Clercq, E. α-(1-3)-D- Mannose-Specific Plant Lectins Are Markedly Inhibitory to Human Immunodeficiency Virus and Cytomegalovirus Infections *In Vitro*. *Antimicrob. Agents Chemother.* **1991**, *35*, 410-416.

[47] Hatano, T.; Yasuhara, T.; Miyamoto, K.; Okuda, T. Anti-Human Immunodeficiency Virus Phenolics from Licorice. *Chem. Pharm. Bull.* **1988**, *36*, 2286-2288.

[48] Kashman, Y.; Gustatson, K.R.; Fuller, R.W.; Cardellina II, J.H.; McMahon, J.B.; Curren, M.J.; Buckheit Jr. R.W.; Hughes, S.K.; Cragg, G.M.; Boyd, M.R. The Calanolides, A Novel HIV-Inhibitory Class of Coumarin Derivatives from The Tropical Rainforest Tree *Callophyllum langigerum*. *J. Med Chem.* **1992**, *35*, 2735-2743.

[49] Hizi, A.; Tal, R.; Shaharabary, M.; Currens, M.J.; Boyd, M.R.; Hughes, S.H.; McMahon, J.B. Specific Inhibition of The Reverse Transcriptase of Human Immunodeficiency Virus Type 1 and The Chimeric Enzymes of Human Immunodeficiency Virus Type 1 and 2 by Non- nucleoside Inhibitors. *Antimicrob. Agents Chemother.* **1993**, *37*, 1037-1042.

[50] Pengsuparp, F.; Sirit, M.; Hughes, S.H.; Soejarto, D.D.; Pezutto, J.M. Specific Inhibition of Human Immunodeficiency Virus Type 1 Reverse Transcriptase Mediated by Soulattrolide, A Coumarin Isolated from The Latex of *Calophyllum teysmannii*. *J. Nat. Prod.* **1996**, *59*, 839-842.

[51] Nishibe, S.; Ono, K.; Nakane, H.; Kawamura, T.; Noro, Y.; Tanaka, T. Studies of the Plantaginis herba. 9. Inhibitory Effects of Flavonoids from *Plantago* Species on HIV Reverese Transcriptase Activity. *Nat. Med.* **1997**, *51*, 547-549.

[52] Raghavan, K.; Boulamwini, J.K.; Fesen, M.R.; Pommier, Y.; Kohn, J.W.; Weinstein, J.N. Three Dimensional Quantitative Structure-Activity Relationship (QSAR) of HIV Integrase Inhibitors: A Comparative Molecular Field Analysis (CoMFA) Study. *J. Med. Chem.* **1995**, *38*, 890-897.

[53] Beladi, I.; Pusztai, R.; Mucsi, I.; Bakay, M.; Gabor, M. Activity of Some Flavonoids Against Viruses, *Ann. N. Y. Acad. Sci.* **1977**, *284*, 358-364.

[54] Selway, J.W.T. Antiviral Activity of Flavones and Flavans, In "Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological and Structure-Activity Relationships" Cody, V.;Middleton, E.; Harborne, J.B. Eds, Alan R. Liss, Inc., London, 1986, p 521-536.

[55] Vlietinck, A.J.; Vanden Berghe, D.A.; Van Hoof, L.M.; Vrijsen, R.; Boeye, A. Antiviral Activity of 3-Methoxyflavones, In "Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological and Structure-Activity Relationships" Cody, V.; Middleton,E.; Harborne, J.B. Eds., Alan R. Liss, Inc., London, 1986, p 537-540.

[56] Streissle, G.; Paessens, A.; Oedigert, H. New Antiviral Compounds In "Advances in Virus Research", Maramorosch, K.; Murphy, F.A.; Shatkin, A.J. Eds. Academic Press, San Diego, London, **1985**, *30*, p 83-138.

[57] Hayashi, K.; Hayashi, T.; Otsuka, H.; Takeda, Y. Antiviral Avtivity of 5,6,7-. *Chemother.* Trimethoxyflavone and Its Potentiation of the Antiherpes Activity of Acyclovir. *J. Antimicrob* **1997**, *39*, 821-824.

[58] Ono, K.; Nakane, H.; Meng, Z.H.; Ose, Y.; Sakai, Y.; Mizuno, M. Differential Inhibitory Effects of Various Herb Extracts on The Activities of Reverse Transcriptase and Various Deoxyribonucleic Acid (DNA) Polymerase. Chem. Pharm. Bull. **1989**, *37*, 1810-1812.

[59] Xu, H.X.; Kadota, S.; Kurokawa, M.; Shiraki, K.; Matsumoto, T.; Namba, T. Isolation and Structure of Woodorien, A New Glucoside Having Antiviral Activity from *Woodwardia orientalis. Chem. Pharm. Bull.* **1993**, *41*, 1803-1806.

[60] Pengsuparp, F.; Cai, L.; Constant, H.; Fong, H.H.; Lin, L.Z.; Kinghorn, A.D.; Pezutto, J.M.; Cordell, G.A. Mechanistic Evaluation of New Plant-Derived Compounds That Inhibit HIV- Reverse Transcriptase. *J. Nat. Prod.* **1995**, *58*, 1024-1031.

[61] MacRae, W.D. and Towers, G.H.N. Biological Activities of Lignans, *Phytochemistry*, **1984**, *23*, 1207-1220.

[62] Eich, E. Secondary Metabolites from Plants as Antiretroviral Agents: Promising Lead Structures for Anti-HIV Drugs of The Future. *ACS Symp. Ser.* **1998**, *691* (Phytomedicines of Europe), 83-96.

[63] Bedows, E.; Hatfield, G.M. An Investigation of The Antiviral Activity of *Podophyllum peltatum. J. Nat. Prod.* **1982**, *45*, 725-729.

[64] McRae, W.D.; Hudson, J.B.; Towers, G.N.R. Studies on The Pharmacological Activities of Amazonian Euphorbaceae. *J. Ethnopharmacol.* **1988**, *22*, 143-172.

[65] Eberhardt, F.L.; Young, R.A. Assesment of The Anti-HIV Activity of a Pine Cone Isolate. *Planta Medica* **1996**, *62*, 63-65.

[66] Eich, E.; Schulz, J.; Truman, S.; Sarin, J.S.; Maidhof, A.; Menz, H.; Schroeder, H.C.; Muller, W.E.G. Lignanolides: Novel In Vitro Anti-HIV Active Agents. *Planta Medica.* **1990**, *56*, 506.

[67] Eich, E.; Partz, H.; Kaloga, M.; Schulte, J.; Fesen, M.R.; Mazondu, A.; Pommier, Y.J. (-)- Arctigenin as A Lead Structure for Inhibitors of Human Immunodeficiency Virus Type-1 Integrase. *J. Med. Chem.* **1996**, *39*, 86-95.

[68] Kernan, M.R.; Sendl, A.; Chen, J.L.; Jolad, S.D.; Blanc, P.; Murphy, J.T.; Stoddart, C.A.; Nanakorn, W.; Balick, M.J.; Rozhon, E.J. Two New Lignans with Activity Against Infuenza Virus from the Medicinal Plant *Rhinacanthus nasutus. J. Nat. Prod.* **1997**, *60*, 635-637.

[69] Valsaraj, R.; Pushpangadan, P.; Smitt, U.W.; Adsersen, A.; Christensen, S.B.; Sittie, A.; Nyman, U.; Nielsen, C.; Olsen, C.E. New Anti-HIV, Antimalarial and Antifungal Compounds from *Terminalia bellerica. J. Nat. Prod.* **1997**, *60*, 739-742.

[70] Asano, J.; Chiba, K.; Tada, M.; Yoshi, T. Antiviral activity of Lignans and Their Glycosides from *Justicia procumbens. Phytochemistry.* **1996**, *42*, 713-717.

[71] Lin, T.S.; Shinazi, R.; Griffith, B.; August, E.M.; Eriksson, B.F.H.; Zhang, D.K.; Huang, L.; Prusoff, W.H. Selective Inhibition of Human Immunodeficiency Virus Type-1 Replication by The (-)-But Not The (+)- Enantiomer of Gossypol. *Antimicrob. Agents Chemother.* **1989**, *33*, 2149-2151.

[72] Royer, R.E.; Deck, L.M.; Van der Jagt, D.C. Synthesis and Anti-HIV Activity of 1,1'-Dideoxy- gossypol and Related Compounds. *J. Med. Chem.* **1995**, *38*, 2427-2432.

[73] Helbig, B.; Thiel, K.D. Vergleich Der Antiviralen Aktivitat Von Oxidierter Kaffusaure und Hydrokaffeesaure Gegen Herpesvirus Hominis Typ 1 und typ 2 *In Vitro.Pharmazie.* **1982**, *37*, 603-604.

[74] Corthout, J.; Pieters, L.; Claeys, M.; Vanden Berghe, D.; Vlietinck, A.J. Antiviral Caffeoyl Esters from *Spondias mombin. Phytochemistry.* **1992**, *31*, 1979-1981.

[75] Nishizawa, M.; Yamagishi, T.; Dutschman, G.E.; Parker, W.B.; Bodner, A.J.; Kilkhuskic, R.E.; Cheng, Y.C.; Lee, K.H. Anti-AIDS Agents, 1. Isolation and Characterization of Four New Tetragalloylquinic Acids as A New Class of HIV Reverse Transcriptase Inhibitors from Tannic Acid. *J. Nat. Prod.* **1989**, *52*, 762-768.

[76] Nonaka, G.I.; Nishioka, I.; Nishizawa, M.; Yamagishi, T.; Kashiwada, Y.; Dutschman, G.E.; Bodner, A.J.; Kilkushic, R.E.; Cheng, Y.C.; Lee, K.H. Anti-AIDS Agents, 2. Inhibitory Effects of Tannins on HIV Reverse Transcriptase and HIV Replication in H9 Lymphocyte Cells. *J. Nat. Prod.* **1990**, *53*, 587-595.

[77] Gustafson, K.R.; Cardellina II, J.H.; McMahon, J.B.; Pannel, L.K.; Cragg, G.M.; Boyd, M.R. The Peltatols, Novel HIV-Inhibitory Catechol Derivatives from *Pothomorphe peltata. J. Org. Chem.* **1992**, *57*, 2809-2811.

[78] Chan, J.A.; Schutis, E.A.; Carr, S.A.; De Brusse, C.W.; Eagleton, D.S.; Francis, T.A.; Hayland, L.J.; Johnson, W.P.; Killman, L.B.; Staiger, D.R.; Westley, J.W. Novel Phloroglucinols from The Plant *Melicope sessiliflora* (Rutaceae). *J. Org. Chem.* **1989**,*54*, 2098-2103.

[79] Arisawa, M.; Fujita, A.; Hayashi, T.; Ockiai, H.; Morita, N. Cytotoxic and Antiherpetic Activity of Phloroglucinol Derivatives from *Mallotus japonicus* (Euphorbiaceae). *Chem. Pharm. Bull.* **1990**, *38*, 1624-1626.

[80] Takasaki, M.; Konishima, T.; Shingu, T.; Tokuda, H.; Nishino, H.; Iwashima, A.; Kozuka, M. Structure of Euglobal-G1, -G2 and -G3 from *Eucalyptus gerandis*, Three New Inhibitors of Epstein-Barr Virus Activation. *Chem. Pharm. Bull.* **1990**, *38*, 1444-1446.

[81] Nishizawa, M.; Yamada, H.; Sano, J.; Ito, S.; Hayashi, Y.; Ikeda, H.; Chairul, S.M.; Tokuda, H. Structure of Syzygiol: A Skin-Tumor Promotion Inhibitor. *Tetrahedron Lett.* **1991**, *32*, 211-212.

[82] Nishizawa, M.; Emura, M.;Kan, Y.; Yamada, H.; Ogawa, K.; Hamanaka, N. Macrocarpals: HIV-Reverse Transcriptase Inhibitors of *Eucalyptus globulus*. *Tetrahedron Lett.* **1992**, *33*, 2983-2986.

[83] Dai, J-R.; Hallock, Y.F.; Cardellina II, J.H.; Boyd, M.R. HIV-Inhibitory and Cytotoxic Oligostilbenes from the Leaves of *Hopea malibato. J. Nat. Prod.* **1998**, *61*, 351-353.

[84] Sydiskis, R.J.; Owen, D.G.; Lohr, J.L.; Rosler, K.H.; Blomster, R.N. Inactivation of Enveloped Viruses by Anthraquinones Extracted from Plants. *Antimicrob. Agents Chemother.* **1991**, *35*, 2463-2466.

[85] Schinazi, R.F.; Chu, C.K.; Babu, J.R.; Oswald, B.J.; Saalmann, V.; Cannon D.L.; Eriksson, B.H.F.; Nasa, M. Anthraquinones as A New Class of Antiviral Agents Against Human Immunodeficiency Virus. *Antiviral Res.* **1990**, *13*, 265-272.

[86] Fehr, M.J.; McCloskey, M.A.; Petrick, J.W. J. Light-Induced Acidification by The Antiviral Agent Hypericin. *J. Am. Chem. Soc.* **1995**, *117*, 1833-1836.

[87] De Closterd, L.A.; Parsons, I.C.; Gustafson, K.R.; Cardellina II, J.H.; McMahon, J.B.; Cragg, G.M.; Murata, Y.; Pannell, L.K.; Steiner, J.R.; Clardy, J.; Boyd, M.R. Structure, Absolute Stereochemistry and Synthesis of

Concocurvone, A Potent Novel HIV-Inhibitory Naphthoquinone Trimer from a *Concospermum* sp. *J. Am. Chem. Soc.* **1993**, *115*, 6673-6679.

[88] Hara, H.; Maruyama, N.; Yamashita, S.; Hayashi, Y.; Lee, K.H.; Basto, K.; Chairful, F.; Marumoto, R.; Imakura, Y. Elecanacin, a Novel New Naphthoquinone from the Bulb of *Eleutherine americana*. *Chem. Pharm. Bull.* **1997**, *45*, 1714-1716.

[89] Kernan, M.R.; Amarquaye, A.; Chen, J.L.; Chan, J.; Sesin, D.F.; Parkinson, N.; Ye, Z-J.; Barrett, M.; Bales, C.; Stoddart, C.A.; Solan, B.; Blanc, P.; Limbach, C.; Mrisho, S.; Rozhon, E.J. Antiviral Phenylpropanoid Glycosides from the Medicinal Plant *Markhamia lutea*. *J. Nat. Prod.* **1998**, *61*, 564-570.

[90] Eich, E. Secondary Metabolites from Plants as Antiretroviral Agents: Promising Lead Structure for Anti-HIV Drugs of The Future. In ACS Synposium Series 691: Phytomedicines of Europe Chemistry and Biological Activity. Lawson, L.D.; Bauer, R. Eds. American Chemical Society, Washington DC, **1998**, p 83-95.

[91] Takechi, M.; Tanaka, Y. Purification and Characterization of Antiviral Substances from The Bud of *Syzygium aromatica*. *Planta Medica.* **1981**, *42*, 69-74.

[92] Takechi, M.; Tanaka, Y. Antiviral Substances from The Root of *Paeonia* species. *Planta Medica.* **1982**, *45*, 252-253.

[93] Okuda, T.; Yoshida, T.; Hatano, T. Ellagitannins as Active Constituents of Medicinal Plants. *Planata Medica.* **1989**, *55*,117-122.

[94] Takechi, M.; Tanaka, Y.; Takehara, M.; Nonaka, G.I.; Nishioka, I. Structure and Antiherpetic Activity Among The Tannins. *Phytochemistry.* **1985**, *24*, 2245-2250.

[95] Corthout, J.; Pieters, L.; Claeys, M.; Vanden Berghe, D.A.; Vlietinck, A.J. Antiviral Ellagitannins from *Spondias mombin Phytochemistry.* **1991**, *30*, 1129-1130.

[96] Kakiuchi, N.; Hattori, M.; Namba, T.; Nishizawa, M.; Yamagishi, T.; Okuda, T. Inhibitory Effects of Tannins on Reverse Transcriptase from RNA Tumor Virus. *J. Nat. Prod.* **1985**, *48*, 614-621.

[97] Asanaka, M.; Kurimura, T.; Kobayashi, R.; Okuda, T.; Mori, M.; Yokoi, H. Anti-HIV Activity of Ellagitannins. Fourth International Conference on Immuno Pharmacology, May, **1988**, Osaka, Japan. Abstract p.47.

[98] Take, Y.; Inoye, Y.; Nakamura, S.; Allaudeen, R.S.; Kubo, A. Comparative Studies of The Inhibitory Properties of Antibiotics on Human Immunodeficiency Virus and Avaian Myeloblastosis Virus Reverse Transcriptase and Cellular DNA Polymerase. *J. Antibiotics.* **1989**, *42*, 107-115.

[99] Gallo, R.C.; Stericher, H.Z.; Border, S. In "AIDS", Marcel Dekker, New York, **1987**, p 1.

[100] John, T.J.; Mukundan, P. Virus Inhibition by Tea, Caffeine and Tannic Acid. *Ind. J. Med. Res.* **1979**, *69*, 542-545.

[101] Balde, A.M.; Van Hoof, L.; Pieters, L.A.; Vanden Berghe, D.A.; Vlietinck, A.J. Plant Antiviral Agents. VII. Antiviral and Antibacterial Proanthocyanidins from The Bark of *Pavetta owariensis*. *Phytother. Res.* **1990**, *4*, 182-188.

[102] Balde, A.M.; Pieters, L.A.; Wray, V; Kolodziej, H.; Vanden Berghe, D.A.; Claeys, M.; Vlietinck, A.J. A-Type Proanthocyanidins from Stem Bark of *Pavetta owariensis*. *Phytochemistry*, **1991**, *30*, 337-342.

[103] Balde, A.M.; Pieters, L.A.; Wray, V; Kolodziej, H.; Vanden Berghe, D.A.; Claeys, M.; Vlietinck, A.J. Dimeric and Trimeric Proanthocyanidins Possessing A Doubly Linked Structure from *Pavetta owariensis*. *Phytochemistry*, **1991**, *30*, 4129-4135.

[104] Zhang, J.; Zhan, B.; Yao, X.; Song, J. Antiviral Activity of Tannin from The Pericarp of *Punica granatum* L. Against Genital Herpes Virus *In Vitro*. *Zhongguo Zhongyao Zazhi.* **1995**, *20*, 556-558. CAN 124:249811.

[105] Kakiuchi, N.; Kusumoto, I.T.; Hattori, M.; Namba, T.; Hatano, T.; Okuda, T. Effects of Condensed Tannins and Related Compounds on Reverse Transcriptase. *Phtotherapy Res.* **1991**, *5*, 270-272.

[106] Mizuno, T.; Uchino, K.; Toukairin, T.; Tanabe, A.; Nakashima, H.; Yamamato, N.; Ogawara, H. Inhibitory Effects of Tannic Acid Sulfate and Related Sulfates on Infectivity, Cytopathic Effect and Giant Cell Formation of Human Immunodeficiency Virus.*Planata Medica.* **1992**, *58*, 535-539.

[107] Renis, H.E. *In Vitro* Antiviral Activity of Calcium Elenolate. *Antimicrob. Agents Chemother.* **1969**, *0*, 167-172.

[108] Hayashi, T.; Hayashi, K.; Uchida, K.; Niwayama, S.; Morita, N. Antiviral Agents of Plant Origin. II. Antiviral Activity of Scopadulic Acid B Derivatives. *Chem. Pharm. Bull.* **1990**, *38*, 239-242.

[109] Blevins, R.D.; Dumic, M.P. The Effect of Δ^9-Tetrahydrocannabinol on *Hepes simplex* Virus Replication. *J. gen. Virol.* **1980**, *49*, 427-431.

[110] Hayashi, T.; Kawasaki, M.; Miwa, Y.; Taga, T.; Morita, N. Antiviral Agents of Plant Origin. III. Scopadulin, A Novel Tetracyclic Diterpene from *Scoparia dulcis*. *Chem. Pharm. Bull.* **1990**, *38*, 945-947.

[111] Ushio, Y.; Abe, H.; Inactivation of Measels Virus and *Herpes simplex* Virus by Saiko- saponins. *Planta Medica.* **1992**, *58*, 171-173.

[112] Amoros, M.; Girre, L. Structure of Two Antiviral Triterpene Saponins from *Anagallis arvensis*. *Phytochemistry.* **1987**, *26*, 787-791.

[113] Pochland, B.L.; Carte, B.K.; Francis, T.A.; Hyland, L.J.; Allaudeen, H.S.; Troupe, N. *In Vitro* Activity of *Dammar* Resin Triterpenoid. *J. Nat. Prod.* **1987**, *50*, 706.

[114] Amoros, M.; Fauconnier, B.; Girre, L. Effect of Saponins from *Anagallis arvensis* on Experimental *Herpes simplex* Keratitis in Rabbits. *Planta Medica.* **1988**, *54*, 128-131.

[115] Simos, C.M.O.; Amoros, M.; Schenkel, E.P.; Shinkim, J.S.; Rucker, G.; Girre, L. Preliminary Studies of Antiviral Activity of Triterpenoid Saponins: Relationships Between Their Chemical Structures and Antiviral Activity. *Planta Medica.* **1990**, *56*, 652-653.

[116] Hirabayashi, K.; Iwata, S.; Matsumoto, H.; Mori, T.; Shibata, S.; Baba, M.; Ito, M.; Shigeta, S.; Nakashima, H.; Yamamoto, N. Antiviral Activities of Glycerrhizin and its Modified Compounds Against Human Immunodeficiency Virus Type 1 (HIV-1) and *Herpes simplex* type 1 (HSV-1) *In Vitro*. *Chem. Pharm. Bull.* **1991**, *39*, 112-115.

[117] Bloor, S.J.; Qi, L. Cytotoxic Saponins from New Zealand *Myrsine* Species *J. Nat. Prod.* **1994**, *57*, 1354-1360.

[118] Sidambiwe, J.B.; Balde, A.M.; De Bruyne, T.; Pieters, L.; Van den Huevel, H.; Claeys, M.; Vanden Berghe, D.; Vlietinck, A.J. Triterpenoid Saponins from *Maesa lanceolata*. *Phytochemistry.* **1996**, *41*, 269-277.

[119] Konoshima, T.; Yasuda, I.; Kashiwada, Y.; Corentino, C.M.; Lee, K.H. Anti-AIDS Agents, 21. Triterpenoid Saponins as Anti-HIV Principles from Fruits of *Gleditsia japonica* and *Gymnocladus chinensis* and A Structure Activity Correlation. *J. Nat. Prod.* **1995**, *58*, 1372-1375.

[120] Xi, H.X.; Zong, F.Q.; Wan, M.; Sim, K.Y. Anti-HIV Triterpene Acids from *Geum Japonicum*. *J. Nat. Prod.* **1996**, *59*, 643-649.

[121] Fujioka, T.; Kashiwada, Y.; Kilkuskie, R.E.; Cosentino, L.M.; Ballas, L.M.; Jiang, J.B.; Janzen, W.P.; Chen, I.S.; Lee, K.-H. Anti-AIDS Agenta, 11. Betulinic Acid and Platanic Acid as Anti-HIV Principles from *Syzigum claviflorum* and The Anti-HIV Activity of Structurally Related Triterpenoids. *J. Nat. Prod.* **1994**, *57*, 243-247.

[122] Evers, M.; Pouyade, C.; Soler, F.; Ribeill, Y.; Janus, C.; Lelievre, Y.; Gueguen, J.C.; Reisdorf, D.; Morize, I.; Pauwels, R.; De Clercq, E.; Henin, Y.; Rousseau, A.; Mayeux, J.F.; Le Pecq, J.B.; Derue, N. Betulinic Acid Derivatives: A New Class of Human Immunodeficiency Virus Type 1 Specific Inhibitors with a New Mode of Action. *J. Med. Chem.* **1996**, *39*, 1056-1068.

[123] Soler, F.; Pouyade, C.; Evers, M.; Carry, J.C.; Henin, Y.; Bousseau, A.; Huet, I.T.; Pauwels, R.; De Clerq, E.; Mayaux, J.F.; Le Pecq, J.B.; Derue, N. Betulinic Acid Derivatives: A New Class of Specific Inhibitors of Human Immunodeficiency Virus Type 1 Entry. *J. Med. Chem.* **1996**, *39*, 1069-1083.

[124] Fukushima, Y.; Bastow, K.F.; Ohba, T.; Lee, K.H. Antiviral Activity of Dammarane Saponins Against *Herpes Simplex* Virus I. *Int. J. Pharmacognosy.* **1995**, *33*, 2-6.

[125] Kashiwada, Y.; Wang, H-K.; Nagao, T.; Kitanaka, S.; Yasuda, I.; Fujioka, T.; Yamagishi, T.; Cosentino, M.L.; Kozuka, M.; Okabe, H.; Ikeshiro, Y.; Hu, C-Q.; Yeh, E.; Lee, K-H. Anti- AIDS Agents. 30. Anti-HIV Activity of Oleanolic Acid, Pomolic Acid and Structurally Related Triterpenoids. *J. Nat. Prod.* **1998**, *61*, 1090-1095.

[126] Sun, H.D.; Qiu, S.X.; Lin, L.Z.; Warg, Z.Y.; Lin, Z.W.; Pengsuparp, T.; Pezutto, J.M.; Fong, H.R.S.; Cordell, G.A.; Farnsworth, N. Nigranoic Acid, a Triterpenoid from *Schisandra sphaerandra* That Inhibits HIV-1 Reverse Transcriptase. *J. Nat. Prod.* **1996**, *59*, 525-527.

[127] Ishikawa, T.; Nishigaya, K.; Uchikoshi, H.; Chen, I-S. Cochinolide, a New γ-Alkylidene Bicyclic Butenolide with Antiviral Activity and Its β-Glucopyranoside from *Homalium cochinchinensis*. *J. Nat. Prod.* **1998**, *61*, 534-537.

[128] Cooper, D.C.; Mort, K.A.; Allan, N.L.; Kinchington, D.; McGuian, C. Molecular Similarity of Anti-HIV Phospholipids. *J. Am. Chem. Soc.* **1993**, *115*, 12615.

[129] Siegall, C.B.; Gawlak, S.L.; Marquardt, H. Bryodin 2 a Ribosome-Inactivating Protein from the Plant *Bryonia dioica*, **1990**, US patent, U.S. Ser. No. 141,891, US 5597569 A 970128 Application: US 94-324301 941020.

[130] Balasarawathi, R.; Sadasivam, S.; Ward, M.; Walker, J.M. An Antiviral Protein from *Bougainvillea spectabilis* Roots; Purification and Characterization. *Phytochemistry*. **1998**, *47*, 1561-1565.

[131] Stripe, F. Ribosome-Inactivating Proteins. Protein Toxins and Their Use in Cell Biology. Rappuoli, R.; Montecucco, C. Eds**1997**. Oxfod University Press, Oxford, U.K. p 57-58.

[132] Hur, Y.; Han, C-T.; Maeng, J. Expression Characteristics of Pokeweed Antiviral Proteins (PAPs): Two Distinct Types of Proteins. *J. Plant Biol.* **1997**, *40*, 53-60.

[133] Watanabe, K.; Kawasaki, T.; Sako, N.; Funatsu, G.; Actions of Pokeweed Antiviral Protein on Virus-Infected Protoplasts. *Japan. Biosci., Biotech., Biochem.* **1997**, *61*, 994-997.

[134] Talwar, G.P.; Raghuvanshi, P.; Misra, R.; Mukherjee, S.; Shah, S. Plant Immunomo- dulators for Termination of Unwanted Pregnancy and for Contraception and Reproductive Health. *Immunol. Cell Biol.* **1997**, *75*, 190-192.

[135] Wachsman, M.B.; Castilla, V.; Coto, C.E. Inhibition of Foot and Mouth Virus (FMDV) Uncoating by a Plant-Derived Peptide Isolated from *Melia azedarach* L. Leaves. *Argent. Arch. Virol.* **1998**, *143*, 581-590.

[136] Hancock, R.E.W.; The Therapeutic Potential of Cationic Peptides. *Can. Expert. Opin. Invest. Drugs.***1998**, *7*, 167-174.

[137] Lowery, D.T.; Eastwell, K.C.; Smirle, M. Neem Seed Oil Inhibits Aphid Transmission of Potato virus Y to Pepper. *Can. Ann. Appl. Biol.* **1997**, *130*, 217-225.

[138] Serkedjieva, J. Antiinfective Activity of a Plant Preparation from *Geranium sanguineum* L. *Pharmazie.* **1997**, *52*, 799-802.

[139] Serkedjieva, J.; Hay, A. *In Vitro* Anti-influenza Virus Activity of a plant preparation from *Geranium sanguineum* L. *Antiviral Res.* **1998**, *37*, 121-130.

[140] Ott, M.; Thyagarajan, S.P.; Gupta, S. *Phyllanthus amarus* Suppresses Hepatitis B Virus by Interrupting Interaction Between HBV Enhancer I and Cellular Transcription Factors. *Eur. J. Clin. Invest.* **1997**, *27*, 908-915.

[141] Calixto, J.B.; Santos, A.R.S.; Paulino N.; Filho, V.C.; Yunes, R.A. The Plants of The Genus *Phyllanthus* as a Potential Source of New Drugs. *Brazil. Cienc. Cult.* **1997**, *49*, 422-432.

[142] Calixto, J.B.; Santos, A.R.S.; Paulino N.; Filho, V.C.; Yunes, R.A. A Review of The Plants of The Genus *Phyllanthus*: Their Chemistry, Pharmacology and Therapeutic Potential. *Med. Res. Rev.* **1998**, *18*, 225-258.

[143] Sinot, R.A.; Clark, D.W.; De Boer, K.F. Nontoxic Therapeutic Extracts of *Larrea tridentata.* **1997** U.S. Patent, Application: WO 97-US18103 971007. CAN 128:275069.

[144] Miranda, M.M.F.S.; Almeida, A.P.; Costa, S.S.; Santos, M.G.M.; Lagrota, M.H.C.; Wigg, M.D. *In Vitro* Activity of Extracts of *Persea americana* Leaves on Acyclovir-Resistant and Phosphonoacetic Resistant *Herpes simplex* Virus. *Phytomedicine.* **1997**, *4*, 347-352.

[145] Summerfield, A.; Keil, G.M.; Mettenleiter, T.C.; Rziha, H-J.; Saalmueller, A. Antiviral Activity of an Extract from Leaves of the Tropical Plant *Acanthospermum hispidum. Antiviral Res.* **1997**, *36*, 55-62.

[146] Woo, E.R.; Yoon, S.H.; Kwak, J.H.; Kim, H.J.; Park, H. Inhibition of gp 120-CD4 Interaction by Various Plant Extracts. *Phytomedicine.* **1997**, *4*, 53-58.

[147] Woo, E.R.; Kim, H.Ja. Kwak, J.H.; Lim, Y.K.; Park, S.K.; Kim, H.S.; Lee, C-K.; Park, H. Anti-herpetic Activity of Various Medicinal Plant Extracts. *Arch. Pharmacol. Res.* **1997**, *20*, 58- 67.

[148] El Sayed, K.A. Study of *Stapelia* Pregnanes and *Veratrum* Alkaloids. Ph.D. Dissertation, Mansoura University, Egypt, **1993**, p 191-198.

[149] Nakano, M. Anti-HIV Activity of Alkaline Extracts of Rooibos Tea Leaves. *Aromatopia.* **1997**, *24*, 28-30.

[150] De Vries, D.J.; Hall, M.R. Marine Biodiversity as a Source of Chemical Diversity. *Drug Development Research.* **1994**, *33*, 161-173.

[151] Jimeno, J.M.; Faircloth, G.; Cameron, L.; Meely, K.; Vega, E.; Gomez, A.; Sousa-Faro, J.M.F.; Rinehart, K. Progress in The Acquisition of New Marine-Derived Anticancer Compounds: Development of Ecteinascidin-743 (ET-743). *Drugs of the Future.* **1996**, *21*, 1155-1165.

[152] Woerdenbag, H.J.; Koulman, A.; Proksch, P.; Ebel, R.; Van Uden, W.; Pras, N.; Beijnen, J.H. Pharmacologically Active Compounds from Marine Invertebrates: Drugs from the Sea. *Neth. Weekbl.* **1995**, *130*, 1290-1301.

[153] Rinehart, K.L. Dideminins A, B, C and Derivatives Thereof, as Antiviral Agents. **1983**, US Patent: US 80--217768 801218; US 83-461346 830127, CAN 103: 76241.

[154] Che, C-T. Marine Products as a Source of Antiviral Drug Leads. *Drug Development Research.* **1991**, *23*, 201-218.

[155] Rinehart, K.L.; Shield, L.S.; Cohen-Parsons, M. Antiviral Substances. In: Marine Biotechnology, Volume 1, Pharmacutical and Bioactive Natural Products. Attaway, D.H.; Zaborsky, O.R. Eds., Plenium Press, New York, London, **1993**, p 309-342.

[156] Rinehart, K.L.; Gloer, J.B.; Welson, G.R.; Hughes, Jr. G.R.; Li, L.H.; Renis, H.E.; McGovren, J.P. Antiviral and Antitumor Compounds from Tunicates. *Fed. Proc.* **1983**, *42*, 87-90.

[157] Rinehart, K.L.; Gloer, J.B.; Cook, J.C.; Mizsak, S.A.; Scahill, T.A. Structures of The Didemnins, Antiviral and Antitumor Depsipeptides from a Caribbean Tunicate. *J. Am. Chem. Soc.* **1981**, *103*, 1857-1859.

[158] Rinehart, K.L.; Gloer, J.B.; Hughes, Jr. G.R.; Renis, H.E., McGovren, J.P. Didemnins, Antiviral and Antitumor Compounds from a Caribbean Tunicate. *Science.* **1981**, *212*, 933-935.

[159] Hamann, M.T.; Otto, C.S.; Scheuer, P.J.; Dunbar, D.C. Kahalalides: Bioactive Peptides from a Marine Mollusk *Elysia rufescens* and Its Algal Diet *Bryopsis* sp. *J. Org. Chem.***1996**, *61*, 6594-6600.

[160] Zampella, A.; D'Auria, V.M.; Paloma, L.G.; Casapullo, A.; Minale. L.; Debitus, C.; Henin, Y. Callipeltin A, an Anti-HIV Cyclic Depsipeptide from the New Caledonian Lithistida Sponge *Callipelta* sp. *J. Am. Chem. Soc.* **1996**, *118*, 6202-6209.

[161] Rinehart, K.L.; Kobayashi, J.; Harbour, G.C.; Hughes, R.G.; Mizsak, S.A.; Scahill, T.A. Eudistomins C; E; K and L; Potent Antiviral Compounds Containing Novel Oxathiazepine Ring from Caribbean Tunicate *Eudistoma olivaceum. J. Am. Chem. Soc.* **1984**, *106*, 1524-1526.

[162] Tsujii, S.; Rinehart, K.L.; Gunasekera, S.P.; Kashman, Y.; Cross, S.S.; Lui, M.S.; Pomponi, S.A.; Diaz, M.C. Topsentin, Bromotopsentin and Dihydroxybromotopsentin: Antiviral and Antitumor Bis(Indolyl) Imidazoles from Caribbean Deep-Sea Sponges of the family Halichon. *J. Org. Chem.* **1988**, *53*, 5446-5453.

[163] Gunawardana, G.P.; Kohmoto, S.; Gunasekera, S.P.; McConnoell, O.J.; Koehn, F.E. Dercitin, A Biologically Active Acridine Alkaloid from a sponge *Dercitus* sp. *J. Am. Chem. Soc.* **1988**, *110*, 4856-4858.

[164] Sakai, R.; Higa, T. Tubastrine, A New Guanidinostyrene from the Coral *Tubastrea aurea. Chem. Lett.* **1987**, *0*, 127-128.

[165] Carter, G.T.; Rinehart, K.L. Acarnidines; Novel Antiviral and Antimicrobial Compounds from the Sponge *Acarnus erithacus* (De Laubenfles). *J. Am. Chem. Soc.* **1978**, *100*, 4302-4304.

[166] Carte, B.; Faulkner, D.J. Revised Structures of Polyandrocarpidines. *Tetrahedron Lett.* **1982**, *23*, 3863-3866.

[167] Rinehart, K.L. Antiviral and Antibacterial Bromopyrrols from *Agelas coniferin* and Halo Derivatives Thereof. U.S. Patent No. 4,737,510, 12 Apr. **1988**, CAN *109*:216002u.

[168] Rinehart, K.L. Biologically Active Marine Natural Products. *Pure & Appl. Chem.* **1989**, *61*, 525-528.

[169] Rinehart, K.L.; Holt, T.G.; Fregeau, N.L.; Keifer, P.A.; Wilson, G.R.; Perun, T.J., Jr.; Sakai, R.; Thompson, A.G.; Stroh, J.G., Shield, L.S., Seigler, D.S.; Li, L.H.; Martin, D.G.; Grimme-likhuijzen, C.J.P.; Gade, G. Bioactive Compounds from Aquatic and Terrestrial Sources. *J. Nat. Prod.* **1990**, *53*, 771-792.

[170] Perry, N.B., Blunt, J.W., Munro, M.H.G.; Pannel, L.K. Mycalamide A, An Antiviral Compound from a New Zealand Sponge of the Genus *Mycale*. *J. Am. Chem. Soc.* **1988**, *110*, 4850-4851.

[171] Perry, N.B., Blunt, J.W., Munro, M.H.G.; Thompson, A.M. Antiviral and Antitumor Agents from a New Zealand Sponge, *Mycale* sp. 2. Structures and Solution Conformations of Mycalamides A and B. *J. Org. Chem.* **1990**, *55*, 223-227.

[172] Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. Isolation and Structure Elucidation of Onnamide A, a New Metabolite of a Marine Sponge, *Theonella* sp. *J. Am. Chem. Soc.* **1988**, 110, 4851-4853.

[173] Kashman, Y.; Hirsh, S.; McConnell, O.J.; Ohanti, I.; Kusumi, T.; Kakisawa, H. Ptilomycalin A: A Novel Polycyclic Guanidine Alkaloid of Marine Origin. *J. Am. Chem. Soc.* **1989**, *111*, 8925-8926.

[174] Jares-Erijman, E.A.; Sakai, R.; Rinehart, K.L. Crambescidins, New Antiviral and Cytotoxic Compounds from the Sponge Crambe crambe. *J. Org. Chem.* **1991**, *56*, 5712-5715.

[175] Ichiba, T.; Yoshiba, W.Y.; Scheuer, P.J. Hennoxazoles: Bioactive Bisoxazoles from a Marine Sponge. *J. Am. Chem. Soc.* **1991**, *113*, 3173-3174.

[176] Knubel, G.; Larsen, L.K.; Moore, R.E.; Levine, I.A. and Patterson, G.M.L. Cytotoxic, Antiviral Indolocarbazoles from a Blue-Green Alga Belonging to the Nostocaceae. *J. Antibiot.* **1990**, *43*, 1236-1239.

[177] Carter, G.; Rinehart, K.L. Aplidiasphingosine, an Antimicrobial and Antitumor Terpenoid from an *Aplidium* sp. (Marine Tunicate). *J. Am. Chem. Soc.* **1978**,*100*, 7441-7442.

[178] Patil, A.D.; Kumar, N.V.; Kokke, W.C.; Bean, M.F.; Freyer, A.J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D.J.; Carte, B.; Breen, A.L.; Hertzberg, R.P.; Johnson, R.K.; Westley, J.W.; Potts, B.C.M. Novel Alkaloids from the Sponge *Batzella* sp.: Inhibitors of HIV gp120-Human CD4 Binding. *J. Org. Chem.* **1995**, *60*, 1182-1188.

[179] Larsen, L.K.; Moore, R.E.; Patterson, G.M.L. b-Carbolines from the Blue-Green Alga *Dichothrix baueriana*. *J. Nat. Prod.* **1994**, *57*, 419-421.

[180] Perry, N.B.; Ettouati, L.; Litaudon, M.; Blunt, J.W.; Munro, M. H.G.; Parkin, S.; Hope, H. Alkaloids from Antarctic Sponge *Kirkpatrickia varialosa*. Part 1: Variolin B, a New Antitumor and Antiviral Compound. *Tetrahedron*. **1994**, *50*, 3987-3792.

[181] Loukaci, A.; Guyot, M. Trikendiol, an Unusual Red Pigment from The Sponge *Trikentrion loeve*, Anti-HIV-1 Metabolite. *Tetrahedron Lett.* **1994**, *35*, 6869-6872.

[182] Bergmann, W.; Feeney, R.J. The Isolation of a New Thymine Pentoside from Sponges. *J. Am. Chem. Soc.* **1950**, *72*, 2809-2810.

[183] Bergmann, W.; Feeney, R.J. Contribution to The Study of Marine Products. XXXII. The Nucleosides of Sponges. *J. Org. Chem.* **1951**, *16*, 981-987.

[184] Cimino, G.; De Rosa, S.; De Stefano, S. Antiviral Agents from a Gorgonian, *Euncella cavolini*, *Experientia.* **1984**, *30*, 18-20.

[185] Driscoll, P.C.; Clore, G.M.; Beress, L.; Gronenborn, A.M. A Proton Nuclear Magnetic Resonance Study of The Antihypertensive and Antiviral Protein BDS-1 from The Sea Anemone *Anemonia sulcata*: Sequential and Stereospecific Resonance Assignment and Secondary Structure. *Biochemistry.* **1989**, *28*, 2178-2187.

[186] O'Keefe, B.R.; Beutler, J.A.; Cardellina, J.H. II; Gulakowski, R.J.; Kreps, B.L.; McMahon, J.D.; Raymond, C. II; Henderson, L.E.; Pannell, L.K.; Pomponi, S.A.; Boyd, M.R. *Eur. J. Biochem.* **1997**, *245*, 47-53.

[187] Gustafson, K.R.; Raymond, C.S.; Henderson, L.E.; Cardellina, J.H. II; McMahon, J.B.; Rajamani, U.; Pannel, L.K.; Boyd, M.R. *Biochem. Bioph. Res. Comm.* **1997**, *238*, 223- 228.

[188] Higa, T. 2-(1-Chloro-2-hydroxyethyl)-4,4-Dimethylcyclohexa-2,5-dienone: A Precursor of 4,5-Dimethylbenzo[*b*]furan from The Red Alga *Desmia hornemanni. Tetrahedron Lett.* **1985**, *26*, 2335-2336.

[189] Sarin, P.S.; Sun, D.; Thornton, A.; Muller, W.E.G. Inhibition of the Replication of Etiologic Agent of Acquired Immune Deficiency Syndrome (Human T-Lymphotropic Retrovirus /Lymphadenopathy-Associated Virus) by Avarol and Avarone. *J. Natl. Cancer Inst.* **1987**, *78*, 663-666.

[190] Sander, K.M.; Higa, T. Antiviral Chamigrene Derivative, PCT International Application WO 86 03,739, July 3, **1986**; U.S. Patent Application 682,896, December 18, 1984. CAN 106: 12959q.

[191] Wright, A.E.; McCarthy, P.; Cross, S.S.; Rake, J.B.; McConnel, O.J. Sesquiterpenoid Isocyanide Purification from a Marine Sponge and Its Use As a Neoplasm Inhibitor, Virucide and Fungicide. **1988**. European Patent Application EP 285,302, October 5, 1988; U.S. Patent Application 32,289, March 30, 1987. CAN 111:50414u.

[192] Wright, A.E.; Rueth, S.A.; Cross, S.S. An Antiviral Sesquiterpene Hydroquinone from The Marine Sponge *Strongylophora hartmani. J. Nat. Prod.* **1991**, *54*, 1108-1111.

[193] Hamann, M.T,; Scheuer, P.J. Cyanopuupehenol, an Antiviral Metabolite of a Sponge of The Order Verongida. *Tetrahedron Lett.* **1991**, *32*, 5671-5672.

[194] Talpir, R.; Rudi, A.; Kashman, Y.; Loya, Y.; Hizi, A. Three New Sesquiterpene Hydroquin- ones from Marine Origin. *Tetrahedron.* **1994**, *50*, 4179-4184.

[195] Hallock, Y.F.; Cardellina, J.H. II; Boyd, M.R. (-)-Frondosins A and D, HIV-Inhibitory Sesquiterpene Hydroquinone Derivatives from *Euryspongia* sp. *Nat. Prod. Lett.*, **1998**, *11*, 53-160.

[196] Kohmoto, S.; McConnell, O.J.; Wright, A.E.; Cross, S.S. Isospongiadiol, a Cytotoxic and Antiviral Diterpene from a Caribbean Deep Water Marine Sponge, *Spongia* sp. *Chem. Lett.* **1987**, *0*, 1687-1690.

[197] Groweiss, A.; Look, S.A.; Fenical, W. Solenolides, New Antiinflammatory and Antiviral Diterpenoids from a Marine Octocoral of The Genus *Solenopodium. J. Org. Chem.* **1988**, *53*, 2401-2406.

[198] Coval, S.J.; Cross, S.S.; Bernardinelli, G.; Jefford, C.W. Brianthein V, a New Cytotoxic and Antiviral Diterpene Isolated from *Briareum asbestinum. J. Nat. Prod.* **1988**, *51*, 981-984.

[199] Koehn, F.E.; Gunasekera, S.P.; Niel, D.N.; Cross, S.S. Halitunal, an Unusual Diterpene Aldehyde from The Marine Alga *Halimeda tuna. Tetrahedron Lett.* **1991**, *32*, 169-172.

[200] Kashman, Y.; Hirsch, S.; Koehn, F.; Cross, S.S. Reiswigins A and B, Novel Antiviral Diterpenes from a Deep Water Sponge. *Tetrahedron Lett.* **1987**, *28*, 5461-5464.

[201] Tanaka, J.; Higa, T.; Suwanborirux, K.; Kopol, U.; Bernardinelli, G.; Jefford, C.W. Bioactive Norsesterterpene 1,2-Dioxanes froma Thia Sponge, *Mycale* sp. *J. Org. Chem.* **1993**, *58*, 2999-3002.

[202] Barrow, C.J.; Blunt, J.W.; Munro, M.H.G.; Perry, N.B. Variabilin and Related Compounds from a Sponge genus *Sarcotragus*. *J. Nat. Prod.* **1988**, *51*, 275-281.

[203] Sakemi, S.; Higa, T.; Jefford, C.W.; Bernardinelli, G. Venustatriol: A New Antiviral Triterpene Tetracyclic Ether from *Laurencia venusta*. *Tetrahedron Lett.* **1986**, *27*, 4287- 4290.

[204] Rodriguez, J.; Castro, R.; Riguera, R. Holothurinosides: New Antitumor Non Sulphated Triterpenoid Glycosides from The Sea Cucumber *Holothuria forskalii*. *Tetrahedron.* **1991**, *47*, 4753-4762.

[205] Anderson, L.; Bohlin, L.; Iorizzi, M.; Riccio, R.; Minale, L.; Moreno-Lopez, W. Biologically Active Saponins and Saponin-Like Compounds from Starfish and Brittle-Stars. *Toxicon.* **1989**, *27*, 179-188.

[206] Seo, Y.; Shin, J.; Song, J-I. New Secosteroids from an Undescribed Gorgonian of The Genus *Muricella*. *J. Nat. Prod.* **1995**, *58*, 1291-1296.

[207] McKee, T.C.; Cardellina, J.H. II; Riccio, R.; D'Auria, M.V.; Iorizzi, M.; Minale, L.; Moran, R.A.; Gulakowski, R.J.; McMahon, J.B.; Buckheit, R.W. Jr.; Snader, K.M.; Boyd, M.R. HIV-Inhibitory Natural Products. 11. Comparative Studies of Sulfated Sterols from Marine Invertebrates. *J. Med. Chem.* **1994**, *37*, 793-797.

[208] Sun, H.H.; Cross, S.S.; Gunasekera, M.; Koehn, F.E. Weinbersterol Disulfates A and B, Antiviral Steroid Sulfates from The Sponge *Petrosia weinbergi*. *Tetrahedron*, **1991**, *47*, 1185-1190.

[209] Koehn, F.E.; Gunasekera, M.; Cross, S.S. New Antiviral Sterol Disulfate *Ortho* Esters from The Marine Sponge *Petrosia weinbergi*. *J. Org. Chem.* **1991**, *56*, 1322-1325.

[210] Urones, J.G.; Araujo, M.E.M.; Brito, P.F.M.S.; Basabe, P.; Marcos, I.S.; Moro, R.F.; Lithgo, A.M., Pineda, J. Meroterpenes from *Cystoseira usneoides* II. *Phytochemistry.* **1992**, *31*, 2105-2109.

[211] Tsushima M.; Fujiwara, Y.; Matsunon, T. Novel Marine Di-*Z*-Carotenoids: Cucumaria- xanthins A, B and C from The Sea Cucumber *Cucumaria japonica*. *J. Nat. Prod.* **1996**, *59*, 30-34.

[212] Ferri-Di Martino, M.; Ba, D.; Kornprobst, J-M., Combaut, G.; Digoutte, J-P. Caracterisation Chimique et Activite Virostatique *in Vitro* Vis du Virus de la Fevere Jaune Quelques Carraghenanes Extraits D'algues Rouge Senegalaises. In: Vth IUPAC, Paris, **1985**, Abstract PA-44.

[213] Gonzalez, M.E.; Alarcon, B.; Carrasco, L. Polysaccharides as Antiviral Agents: Antiviral Activity of Carrageenan, *Antimicrob. Agents Chemother.***1987**, *31*, 1388-1393.

[214] Neushul, M. Antiviral Carbohydrates from Marine Red Algae, In: Bioactive Compounds from Marine Organisms, Thompson, M.-F.; Sarojini, R.; Nagabhushanam, R. Eds., Oxford & IBH Publishing Co. Pvt. Ltd., New Delhi, India, **1991**, p 275-281.

[215] Bruhn, T.; Duerig, J.; Kraiselburd, E.N.; De Clercq, E.; Bruhn, H-D.; Beress, L. Antiviral and Anticoagulant Activity of Polysaccharides from marine brown algae.

Aspects Mar. Pharmacol. Lazarovici, P.; Spira, M.; Zlotkin, E. Eds.; Alaken, Fort Collins, Colorado,**1996**, p 187-208.

[216] Okutani, K. Antiviral Activities of Sulfated Derivatives of a Fucosamine-Containing Polysaccharide of Marine Bacterial Origin. *Nippon Suisan Gakkaishi.* **1992**, *58*, 927-930.

[217] Okutani, K.; Shigeta, S. Inhibitory Effect of Sulfated Derivatives of a Marine Bacterial Polysaccharide on Replication of Human Immunodeficiency Virus *in Vitro*. *Nippon Suisan Gakkaishi.* **1993**, *59*, 1433-1436.

[218] Ivanova, V.; Rouseva, R.; Kolarova, M.; Serkedjieva, J.; Rachev, R.; Manolova, N. Isolation of a Polysaccharide with Antiviral Effect from *Ulva lactuca*. *Prep. Biochem.* **1994**, *24*, 83-97.

[219] Elykova, L.A.; Reunov, A.V.; Mozhaeva, K.A. Protection of Tobacco Plants Against Tobacco Mosaic Virus by b-1,3;1,6-Glucan "Antivir" Obtained by Enzymatic Transformation of Laminarin. *Dokl. Akad. Nauk.* **1994**, *336*, 710-711. CAN 122:5729.

[220] Hasui, M.; Matsuda, M.; Okutani, K.; Shigeta, S. *In Vitro* Antiviral Activities of Sulfated Polysaccharides from a Marine Microalga (*Cochlodinium polykrikoides*) Against Human Immunodeficiency Virus and Other Enveloped Viruses. Int. *J. Biol. Macromol.* **1995**, *17*, 293-297.

[221] Riccio, R.; Kinnel, R.B.; Bifulco, G. Sheuer, P.J. Kakelokelose, a Sulfated Mannose Polysaccharide with Anti-HIV Activity from The Pacific Tunicate *Didemnum molle*. *Tetrahedron Lett.* **1996**, *37*, 1979-1982.

[222] Hashimoto, K.; Kodama, E.; Mori, S.; Watanabe, J.; Baba, M.; Okutani, K.; Matsuda, M.; Shigeta, S. Antiviral Activity of a Sulfated Polysaccharide Extracted from The Marine *Pseudomonas* and Marine Plant *Dinoflagellata* Against Human Immunodeficiency Viruses and Other Enveloped Viruses. *Antiviral Chem. Chemother.* **1996**, *7*, 189-196.

[223] Patil, A.D.; Kokke, W.C.; Cochran, S.; Francis, T.A.; Tomszek, T.; Westley, J.W. Brominated Polyacetylenic Avids from The Marine Sponge *Xestospongia muta*: Inhibitors of HIV Protease. *J. Nat. Prod.* **1992**, *55*, 1170-1177.

[224] Isaacs, S.; Kashman, Y.; Loya, S.; Hizi, A.; Loya, Y. Petrosynol and Petrosolic Acid, Two Novel Natural Inhibitors of The Reverse Transcriptase of Human Immunodeficiency Virus from *Petrosia* sp. *Tetrahedron.* **1993**, *49*, 10435-10438.

[225] Rodriguez, J.; Riguera, R.; Debitus, C. New Marine Cytotoxic Bipyrones. Absolute Stereo- chemistry of Onchitriols I and II. *Tetrahedron Lett.* **1992**, *33*, 1089-1092.

[226] Loya, S.; Rudi, A.; Kashman, Y.; Hizi, A. Mode of Inhibition of HIV Reverse Transcriptase by 2-Hexaprenylhydroquinone, a Novel General Inhibitor of RNA- and DNA-Directed DNA Polymerases. *Israel. Biochem. J.* **1997**, *324*, 721-727.

[227] Higa, T.; Sakai, R.; Lui, M.S. Antibiotic and Antitumor Misakinolide Composition and Their Derivatives. PCT International Application WO 88 00,195, January 14, **1988**. CAN 111:1702p.

[228] Shu, Y-Z.; Ye, Q.; Kolb, J.M.; Huang, S.; Veitch, J.A.; Lowe, S.E.; Manly, S.P. Bripiodionen, A New Inhibitor of Human Cytomegalovirus Protease from *Streptomyces* sp. *J. Nat. Prod.* **1997**, *60*, 529-532.

[229] Tomassini, J.E.; Davies, M.E.; Hasting, J.C.; Lingham, R.; Mojena, M.; Raghoobar, S.L.; Singh, S.B.; Tkacz, J.S.; Goetz, M.A. A Novel Antiviral Agents Which Inhibits The Endounclease of Influenza Viruses. *Antimicrob. Agents Chemother.* **1996**, *40*, 1189- 1193.

[230] Lampis, G.; Deidda, D.; Maullu, C.; Madeddu, M.A.; Pompei, R.; Delle, M.; Franco, S.G. Sattabacins and Sattazolins: New Biologically Active Compounds with Antiviral Properties Extracted from a *Bacillus* sp. *J. Antibiot.* **1995**, *48*, 967-972.

[231] Naurse, N.; Tenmyo, O.; Kobaru, S.; Hatori, M.; Tomita, K.; Hamagishi, Y.; Oki, T. New Antiviral Antibiotics, Kistamicins A and B. I. Taxonomy, Production, Isolation, Physico- Chemical Properties and Biological Activities. *J. Antibiotic.* **1993**, *46*, 1804-1811.

[232] Davidson, B.S.; Schumacher, R.W. Isolation and Synthesis of Caprolactins A and B, New Caprolactams from a Marine Bacterium. *Tetrahedron.* **1993**, *49*, 6569-6574.

[233] Hashimoto, T.; Takaoka, S.; Yasuda, A.; Akazawa, K.; Tori, M.; Asakawa, Y. Structures of New Polyacetylene Triglycerides and Indolocarbazoles from The Myxomycetes *Lycogala epidendrum. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu.* **1992**, *34*, 470-477. CAN 120:212133.

[234] Hunsman, G.; Jurkiwicz, E.; Reichenbach, H.; Forche, E.; Gerth, K.; Irschik, H.; Kunze, B.; Sasse, F.; Hoefle, G. International Patent Application DE 90-4041688 901224. **1994**. CAN 117:232213.

[235] Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Hoefle, G. Antibiotics from Gliding Bacteria XLVII. Thiangazole: A Novel Inhibitor of HIV-1 from *Polyangium* sp. *Liebigs Ann. Chem.* **1992**, *0*, 357-359. CAN 116:210829.

[236] Naurse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Tenmyo, O.; Kawano, K; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. Fluvirucins A1, A2, B1, B2, B3, B4 and B5, New Antibiotics Active Against Influenza A Virus. I. Production, Isolation, Chemical Properties and Biological Activities. *J. Antibiot.* **1991**, *44*, 733-740.

[237] Luk, K.; Readshaw, S.A. Structural Studies of MM46115, A Novel Tetronic Acid Containing Macrolide with Antiviral and Antibacterial Activity Isolated from Actinomadura pelletieri. *J. Chem Soc., Perkin Trans. 1.* **1991**, *0*, 1641-1644.

[238] Jansen, R.; Kunze, B.; Wray, V.; Reichenbach, H.; Jurkiewicz, E. Hunsmann, G.; Hoefle, G. Antibiotics from Gliding Bacteria. XLIII. Phenoxan: A Novel Inhibitor of HIV-1 Infection in Cell Cultures from Polygonium sp., Strain P1 VO19 (Myxobacteria). *Liebigs Ann. Chem.* **1991**, *0*, 707-708.

[239] Naruse, N.; Tenmyo, O.; Kobaru, S.; Kamei, H.; Miyaki, T.; Konishi, M.; Oki, T. Pumilacidin, A complex of New Antiviral Antibiotics: Production, Isolation, Chemical Properties, Structure and Biological Activity. *J. Antibiot.* **1990**, *43*, 267-280.

[240] Naruse, N.; Tenmyo, O.; Tomita, K.; Konishi, M.; Miyaki, T.; Kawaguchi, H.; Fukase, K.; Wakamiya, T.; Shiba, T. Lanthiopeptin, A New Peptide Antibiotic. Production, Isolation, and Properties of Lanthiopeptin. *J. Antibiot.* **1989**, *42*, 837-845.

[241] Tenmyo, O.; Ohkuma, H.; Konishi, M. Manufacture of Diaminobutyric Acid Homopolymer with Streptoalloteichus for Use as Antibiotic and Virucide. US Patent. Application US 86- 857878 860501. **1987**, CAN 110:171791.

[242] Shimada, N.; Hasegawa, S.; Saito, S.; Nishikiori, T.; Fujii, A.; Takita, T. Derivatives of Oxetanocin: Oxetanocins H, X and G and 2-Aminooxetanocin A. *J. Antibiot.* **1987**, *40*, 1788-1790.

[243] Omura, S.; Imamura, N.; Kuga, H.; Ishikawa, H.; Yamazaki, Y.; Okano, K.; Kimura, K.; Takahashi, Y.; Tanaka, H. Adechlorin, A New Adenosine Deaminase Inhibitor Containing Chlorine. Production, Isolation and Properties. *J. Antibiot.* **1985**, *38*, 1008-1015.

[244] Inouye, Y.; Manabe, N.; Mukai, H.; Nakamura, S.; Matsugi, T.; Amanuma, H.; Ikawa, Y. Chromostin, A Novel Specific Inhibitor Against Reverse Transcriptase. *J. Antibiot.* **1985**, *38*, 519-521.

[245] Omura, S.; Nakagawa, A. Structure of Virantmycin, A Novel Antiviral Antibiotic. *Tetrahedron Lett.* **1981**, *22*, 2199-2202.

[246] Iwata, M.; Kodama, Y.; Asada, B.; Iwamatsu, H.; Suzuki, Y.; Watanabe, T.; Ito, T.; Sekizawa, Y. Studies on SF-1836C Substance. *Meiji Seika Kenkyu Nempo.* **1979**, *0*, 18- 26. CAN 92:158272.

[247] Uyeda, M.; Yokomizo, K.; Ito, A.; Nakayama, K.; Watanabe, H.; Kido, Y. A New Antiherpetic Agent, AH-1763 Iia, Produced by *Streptomyces cyaneus* Strain No. 1763. *J. Antibiot.* **1997**, *50*, 828-832.

[248] Chu, M.; Mierzwa, R.; Truumees, I.; King, A.; Patel, M.; Berrie, R.; Hart, A.; Butkiewicz, N.; DasMahapatra, B. Structure of Sch 68631: A New Hepatitis C Virus Proteinase Inhibitor from *Streptomyces* sp. *Tetrahedron Lett.* **1996**, *37*, 7229-7232.

[249] Tenmyo, O.; Saitoh, K.; Hatori, M.; Furumai, T.; Oki, T. Pradimicin Antibiotics and Their Manufacture with Actinomadura. Eur. Pat. Appl. EP 92-108232 920515. **1995**. CAN 118:146238.

[250] Tao, P.; Wang, S.; Zhang, G.; Cai, S.; Li, H.; Jin, W. New Antiviral Antibiotic: Mutactimycin A. *Zhongguo Kangshengsu Zazhi.* **1990**, *15*, 170-174. CAN 115:154890.

[251] Tsanakawa, M.; Komiyama, N.; Tenmyo, O.; Tomita, K.; Kawano, K.; Kotake, C.; Konishi, M.; Oki, T. New Antiviral Antibiotics, Cycloviracins B1 and B2. I. Production, Isolation, Physico-Chemical Properties and Biological Activities. *J. Antibiot.* **1992**, *45*, 1467- 1471.

[252] Kusumi, T.; Ichikawa, A.; Kakisawa, H.; Tsunakawa, M.; Konishi, M.; Oki, T. The Structures of Quartromicins A1, A2 and A3: Novel Macrocyclic Antiviral Antibiotics Possessing Four Tetronic Acid Moieties. *J. Am. Chem. Soc.* **1991**, *113*, 8947-8948.

[253] Erkel, G.; Anke, T.; Velten, R.; Steglich, W. Antibiotics from Basidiomycetes. XXXIX. Podoscyphic Acid, A New Inhibitor of Avian Myeloblastosis Virus and Moloney Murine Leukemia Virus Reverse Transcriptase from a *Podoscypha* Species. *Biosci.* **1991**, *46*, 442-450.