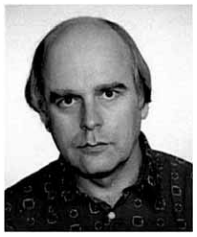
Antiviral Sesqui-, Di- and Sesterterpenes

T. Řezanka[1,*,#], L. Siristova[2] and K. Sigler[1]

[1]*Institute of Microbiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20, Prague 4, Czech Republic;* [2]*Institute of Chemical Technology Prague, Technicka 3, 166 28 Prague, Czech Republic*



Abstract: Terpenoids, biosynthetically related ubiquitous compounds found in virtually all living organisms from marine invertebrates to blooming plants, are derived from the same precursor but their structures and biological and/or pharmacological activities are widely different. Our review concerns terpenoid compounds with antiviral activities, from the simplest sesquiterpenes to diterpenes and sesterterpenes. They include commercially produced therapeutics, compounds with documented antiviral effects and potential future medical use, as well as substances in different stages of clinical research and testing. All of them are based on natural compounds, with only partial man-made changes in the basic structure or mere substituent modifications.

[#]**Author Profile:** Tomáš Řezanka is a Senior Scientist at the Institute of Microbiology, Czech Academy of Sciences. His main research area is the chemistry of natural products and elucidation of their structure via physical methods, especially NMR, MS, and other methods. He is the author of more than 190 papers, including six books. .

INTRODUCTION

Viral infections, whose fast spreading and the sheer numbers of afflicted people (more than 40 million with HIV alone) represent a major medical problem worldwide, have spurred intensive search for efficient antiviral drugs. Although viral infections are so widespread, until recently very few antiviral drugs were available. At present, more than 30 antiviral drugs are available, not only against the AIDS, but also for the treatment of other viral diseases such as hepatitis B, influenza, herpes simplex, and cytomegalovirus infections. The fast replication rate and high variability of the HIV give rise to new drug-resistant strains, whose management calls for new therapeutic approaches and new antivirals. As stated by Tziveleka *et al.* [1]: in spite of current advances in molecular biology, gene therapy and computer – assisted drug design, the need for new drugs effective against drug-resistant pathogens and multi-drug resistant cancers and instrumental in combating Alzheimer disease and the HIV infections is as persistent as before. Besides tailored synthesis, the richest source of products that may prove effective in this context is nature. Screening of natural products derived from numerous species has revealed compounds that exhibit significant antiviral activities. New antiviral compounds are sought in the marine environment, which is still relatively unexplored despite the intensive exploration efforts of the last 5 decades, as well as in the much more thoroughly explored terrestrial plant and animal kingdoms. The main strategies that are being used for discovering new antiviral drugs from nature involve either targeting the producer organism or targeting the therapy. Therapy-targeting approaches make use of *in vitro* drug target-directed biochemical assays that offer specificity and avoid the effects of toxic components, which would dominate intact cell-based assays. They also allow high-throughput screening [2]. Selective extraction and purification protocols are used to optimize the yield of the bioactive compounds, and state-of-the-art spectroscopic techniques and experiments allow the structural elucidation of complex structures isolated even in minute quantities.

Since the spectrum of antiviral and potentially antiviral compounds that are being described, characterized chemically and in terms of biological effects is vast, a selection had to be made along certain lines in writing this article – chemical nature and the structures of the bioactive metabolites, their phylogenetic origin, biological features, therapeutic potential or practical medical relevance. We chose to adhere to the chemical line and focused our attention on terpenoid and steroid antiviral substances of different origin, with special attention being paid to structure-activity relationships.

Natural anti-HIV compounds have been the subject of several reviews in the last years [2-4]. Some reviews were devoted to particular topics such as anti-HIV compounds isolated from plants [5], actinomycetes [6], or marine organisms [1], others were dealing with structurally similar groups of compounds [7] or with the progress in the field of searching for and characterizing anti-HIV agents [8-10].

SESQUITERPENES

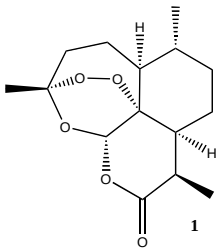
Two recent reviews were devoted to naturally occurring iridoids and secoiridoids and their biological activities [11, 12].

Well-known antimalarial sesquiterpene lactone, artemisinin (**1**), isolated from *Artemisia anuua* [13] showed anti-HIV activity with an IC_{50} of 100 μM and EC_{50} of 100 μM.

*Address correspondence to this author at the Institute of Microbiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20, Prague 4, Czech Republic; E-mail: rezanka@biomed.cas.cz

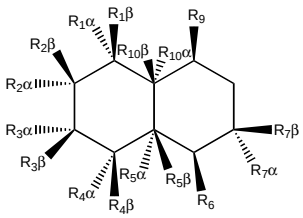
1871-5214/09 $55.00+.00

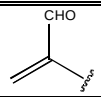
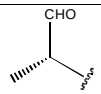
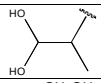
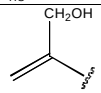
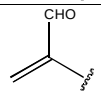
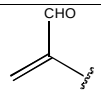
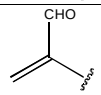
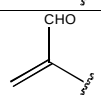
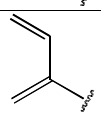
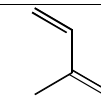
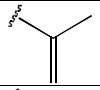
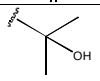
The antiviral activity against flaviviruses of artemisinin, a safe drug obtained from *Artemisia annua* and commonly used to treat malaria, has been investigated [14] using bovine viral diarrhoea virus, which is a member of the Flaviviridae family. Antiviral activity was estimated by comparing it with that of ribavirin (a known antiviral agent), and artemisinin (up to 100 μM) induced no toxicity in host cells. These results suggest a potential usefulness of artemisinin in combination with current pharmacological therapy for the treatment of human and veterinary infections by flaviviruses.



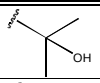
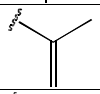
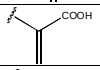
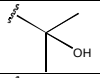
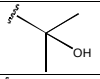
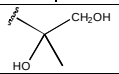
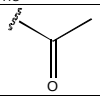
1

HIV-1 integrase, the enzyme responsible for provirus entry into the host cell nucleus and integration into the host

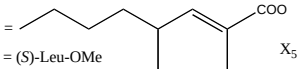


	$R_{1\alpha}$	$R_{1\beta}$	$R_{2\alpha}$	$R_{2\beta}$	$R_{3\alpha}$	$R_{3\beta}$	$R_{4\alpha}$	$R_{4\beta}$	$R_{5\alpha}$	$R_{5\beta}$	R_6	$R_{7\alpha}$	$R_{7\beta}$	R_9	$R_{10\alpha}$	$R_{10\beta}$	Δ^1	Δ^2	Δ^3	Δ^4	Δ^9
2	H	H		H	=O		H	-	-	-	X_1	H	H	COOH	-	Me	-	-	-	=	-
3	H	H		H	=O		H	-	-	-	X_1	H	H	COOH	-	Me	-	-	-	=	-
4	H	H		H	=O		H	-	-	-	X_1	H	H	COOH	-	Me	-	-	-	=	-
5	H	H		H	H	OH	H	-	-	-	X_1	H	H	COOH	-	Me	-	-	-	=	-
6	H	H		H	=O		H	-	-	-	X_1	H	H	$COOX_2$	-	Me	-	-	-	=	-
7	H	H		H	=O		H	-	-	-	X_1	H	H	$COOX_3$	-	Me	-	-	-	=	-
8	H	H		H	=O		H	-	-	-	X_1	H	H	$COOX_4$	-	Me	-	-	-	=	-
9	H	H		H	=O		H	-	-	-	X_1	H	H	$COOX_5$	-	Me	-	-	-	=	-
10	H	H		H	=O		H	-	-	-	X_1	H	H	$COOX_6$	-	Me	-	-	-	=	-
11	H	H		H	=O		H	-	-	-	X_1	H	H	COOH	-	Me	-	-	-	=	-
12	H	H			=O		H	-	-	-	X_1	H	H		COOH	-	Me	-	-	-	=
13	H	OH	H	H	OH	H	$=CH_2$		OH	-	H	H		H	-	Me	-	-	-	-	-
14	H	-	H	-	=O		Me	-	-	-	H	OH		H	-	Me	=	-	-	=	-

Contd...

	$R_{1\alpha}$	$R_{1\beta}$	$R_{2\alpha}$	$R_{2\beta}$	$R_{3\alpha}$	$R_{3\beta}$	$R_{4\alpha}$	$R_{4\beta}$	$R_{5\alpha}$	$R_{5\beta}$	R_6	$R_{7\alpha}$	$R_{7\beta}$	R_9	$R_{10\alpha}$	$R_{10\beta}$	Δ^1	Δ^2	Δ^3	Δ^4	Δ^9
15	=O		H	-	H	-	OH	Me	OH	-	H	H		H	-	Me	-	=	-	-	-
16	H	OH	H	H	H	OH	$=CH_2$		OH	-	H	H		H	-	Me	-	-	-	-	-
17	OH	H	H	H	OH	H	Me	H	-	Me	H	H		-	-	-	-	-	-	-	=
18	OH	H	=O		H	-	Me	-	OH	-	H	H		H	-	H	-	-	=	-	-
19	H	OH	H	-	H	-	Me	OH	H	-	H	H		H	-	H	-	=	-	-	-
20	H	H	H	H	OH	H	Me	H	-	Me	H	H		-	-	-	-	-	-	-	=
21	H	OH	H	H	OH	H	Me	H	-	Me	H	H		-	-	-	-	-	-	-	=
22	OH	H	H	H	H	H	$=CH_2$		-	OH	H		H	H	Me	-	-	-	-	-	-

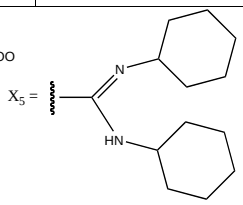
	R_9	$R_{10\alpha}$	$R_{10\beta}$	Δ^1	Δ^2	Δ^3	Δ^4	Δ^9
2	COOH	-	Me	-	-	-	=	-
3	COOH	-	Me	-	-	-	=	-
4	COOH	-	Me	-	-	-	=	-
5	COOH	-	Me	-	-	-	=	-
6	$COOX_2$	-	Me	-	-	-	=	-
7	$COOX_3$	-	Me	-	-	-	=	-
8	$COOX_4$	-	Me	-	-	-	=	-
9	$COOX_5$	-	Me	-	-	-	=	-
10	$COOX_6$	-	Me	-	-	-	=	-
11	COOH	-	Me	-	-	-	=	-
12	COOH	-	Me	-	-	-	=	-
13	H	-	Me	-	-	-	-	-
14	H	-	Me	=	-	-	=	-
15	H	-	Me	-	=	-	-	-
16	H	-	Me	-	-	-	-	-
17	-	-	-	-	-	-	-	=
18	H	-	H	-	-	=	-	-
19	H	-	H	-	=	-	-	-
20	-	-	-	-	-	-	-	=
21	-	-	-	-	-	-	-	=
22	H	Me	-	-	-	-	-	-

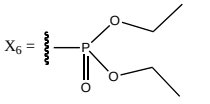
X_1 = 

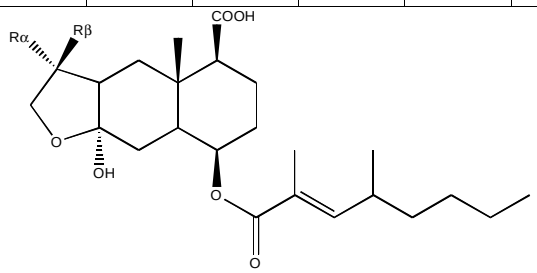
X_2 = (*S*)-Leu-OMe

X_3 = (*S*)-Phenylglycine-OMe

X_4 = (*R*)-Phenylglycine-OMe

X_5 = 

X_6 = 



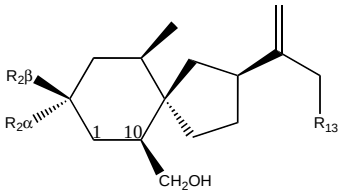
	R_α	R_β
23	H	Me
24	Me	H

genome [15], is critical for viral replication and is absent in the host, and is therefore a potential target for the development of non-toxic antiviral therapy. Integric acid (**2**), a novel eremophilane sesquiterpenoid, has been discovered in a *Xylaria* sp. [16]. Integric acid inhibited 3´-end processing (IC_{50} = 10 μM), and strand transfer (IC_{50} = 10 μM) reactions. It also inhibited the disintegration reactions catalyzed by either truncated core domain (52-212 amino acids) or the full-length integrase enzyme with IC_{50} values of 5 and 15 μM, respectively. Most importantly, it inhibited strand transfer reactions catalyzed by pre-integration complexes isolated from HIV-1 infected cells with an IC_{50} of 30 μM.

Chemical and enzymatic modification of integric acid (**2**), identified as an inhibitor of HIV-1 integrase, led to the preparation of several selective chemical derivatives of integric acid. Preparation, HIV-1 inhibitory activity, and the structure-activity relationship in coupled and strand transfer assays have been described. It appears that most of the groups present in the natural product are required for inhibition of HIV-1 integrase strand transfer activity. In contrast, inhibition of 3' processing activity is less stringent suggesting distinct SAR for the two integrase reactions.

All these compounds were evaluated in the coupled and strand transfer versions of HIV-1 integrase assays. The coupled assay requires both the 30 processing and strand transfer activities of the enzyme. In the coupled assay these compounds exhibited the following IC_{50}; **2**: 3 μM; **3**: 11 μM; **4**: 40 μM; **5**: 73 μM; **6**: 3 μM; **7**: 5 μM; **8**: 5 μM; **9**: 88 μM; **10**: 81 μM; **11**: 30 μM; **12**: 75 μM; **23**: 100 μM; **24**: 45 μM; **25**: 24 μM; and **26**: 10 μM.

The ethyl acetate soluble fraction of a MeOH extract of the dried stems and roots of *Capsicum annum* yielded ten new sesquiterpenes, canusesnols A-J (**14-21**, **25**, **26**) and nine known compounds [17]. Compounds **14-21**, **25**, **26** showed negligible activities as inhibitors of human tumor cell replication or anti-HIV activity.



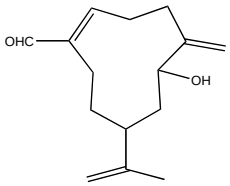
	$R_{2\alpha}$	$R_{2\beta}$	R_{13}	$\Delta^{1,10}$
25	H	OH	H	-
26	=O		OH	=

The eudesmane sesquiterpenoid, verticillatol (**22**), as well as the lignans, (+)-5′-demethoxyepiexcelsin, and (+)-epiexcelsin, were isolated from *Litsea verticillata* [18]. The eudesmane sesquiterpenoid (**22**) demonstrated weak activity against HIV-1 (IC_{50} = 34.5 μg/mL (144.7 μM)) which was notable because of the complete lack of toxicity up to a concentration of 20 μg/mL. The concentration at which **22** mediates a 50% cytotoxic (Table **1**) response (CC_{50}) could not be determined because of the limited quantity of isolated material.

Two new sesquiterpenes, leitneridanin A (**13**) and leitneridanin B (**27**), and seven known compounds were isolated from *Leitneria floridana* [19]. The new compounds **13** and **27** were inactive in both cytotoxic and anti-HIV evaluation.

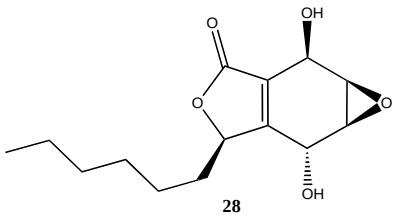
Table 1. Anti-HIV Activity and Cytotoxicity of Compounds Isolated from *Litsea verticillata*

Compound	Cytotoxicity to HOGR5 (CC_{50} μM)	Anti-HIV activity (IC_{50})
22	Nontoxic at 20 mg/mL	144.7
Demethoxyepiexcelsin	59.8	42.7
Epiexcelsin	Nontoxic at 20 mg/mL	Inactive



27

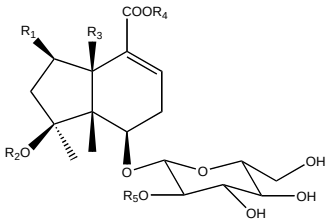
As stated above, HIV-1 integrase is one of the most promising new drug targets for anti-retroviral therapy with potentially significant advantages over existing therapies. The bicyclic dihydroxy epoxide lactone, integrasone (**28**), inhibited the strand transfer reaction of HIV-1 integrase with an IC_{50} of 41 μM [20]. Enantioselective total synthesis of the recently isolated, novel polyketide natural product (+)-integrasone has been published [21].

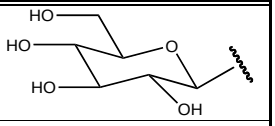
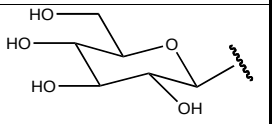


28

A new iridoid diglucoside, lupulinoside (**29**), and eight known iridoid glucosides, acetylbarlerin (**30**), ipolamiidoside (**31**), 6-*O*-acetylshanzhiside methyl ester (**32**), barlerin (**33**), shanzhiside methyl ester (**34**), mussae-nosidic acid (**35**), 8-*O*-acetylshanzhiside (**36**), and shanzhiside (**37**) have been isolated from the flowers of *Barleria lupulina* [22]. When tested for anti-herpes simplex type 1 activity, only compound **31** exhibited antiviral properties. None of the compounds showed cytotoxic effects on Vero cells (IC_{50} > 50 μg/mL) and none of them inhibited cyclooxygenase-2 enzyme. Iridoids **29-34**, **36** and **37** were assayed for antiviral (HSV-1) activity. Only compound **31** was active in the test, with IC_{50} of 41.1 μg/mL. It is interesting to note that compound **31** was the only iridoid with a C-5 hydroxy group. It is thus supposed that one of the structural requirements for an iridoid to exhibit anti-HSV-1 activity could possibly be the presence of a 5-hydroxy group. The sesquiterpene (**38**) had antiviral activity (HSV-1) with IC_{50} 41.1 μg/mL [22].

A novel structural type of sesquiterpene was isolated from the twigs and leaves of *Litsea verticillata* [23]. The litseaverticillol A (**39**) was obtained as a racemate through bioassay-guided fractionation and found to inhibit the replication of HIV-1 with an IC_{50} value of 5.0 μg/mL (21.4 μM). It also demonstrated toxicity to HOGR5 cells, with a CC_{50}



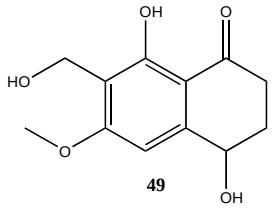
	R_1	R_2	R_3	R_4	R_5
29	OAc	Ac	H	Me	
30	OAc	Ac	H	Me	H
31	H	Ac	OH	Me	H
32	OAc	H	H	Me	H
33	OH	Ac	H	Me	H
34	OH	H	H	Me	H
35	H	H	H	H	H
36	OH	Ac	H	H	H
37	OH	H	H	H	H
38	H	Ac	OH	Me	

value of 13.2 μg/mL (56.4 μM). This yields an unfavorable selectivity index value (CC_{50}/IC_{50}) of 2.6 that excludes **39** from consideration for more advanced studies with *in vivo* models of HIV infection.

Two years later, bioassay directed-fractionation led to the identification of litseaverticillols A-H (**39-46**) from the leaves and twigs of *Litsea verticillata* [24]. These new sesquiterpenes **39-46**, which constitute a new class of anti-HIV agents, inhibited HIV-1 replication in HOGR5 cells with IC_{50} values ranging from 2 to 15 μg/mL (8-58 μM) while affecting the growth of HOGR5 at concentrations 2 - 3-fold higher (Table **2**).

The first total synthesis of litseaverticillols B (**40**), E (**43**), I (**47**), and J (**48**) as well as the structural reassignment of litseaverticillol E have been achieved by means of a biomimetic sequence of transformations [25, 26].

10-Norparvulenone (**49**) is a novel anti-influenza virus antibiotic recently isolated from *Microsphaeropsis* sp.; preliminary *in vitro* assays have shown this compound to be a very promising anti-influenza virus drug [27].



49

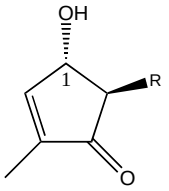
DITERPENES

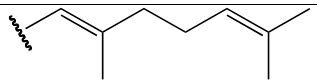
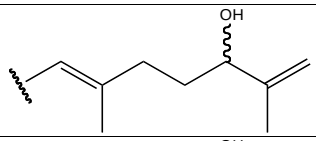
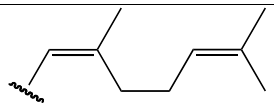
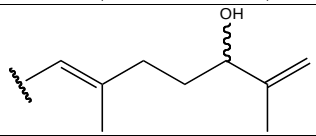
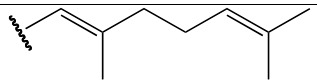
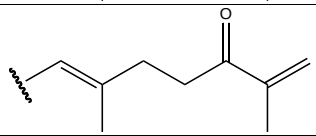
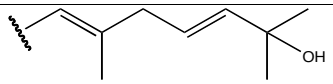
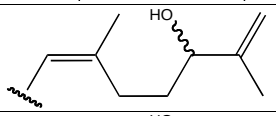
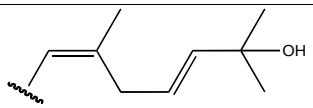
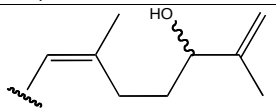
Kaurane diterpenoid, 16*β*,17-dihydroxy-*ent*-kauran-19-oic acid (**50**) isolated from methanolic extracts of the fresh fruits of *Annona squamosa*, significantly inhibited HIV with an EC_{50} value of 0.8 mg/mL (TI > 5) [28]. Linearol (**51**), an *ent*-kaurane diterpenoid isolated from *Sideritis akmanii* and its semisynthetic derivatives showed significant anti-HIV activity against HIV-1 replication in H9 lymphocyte cells [29].

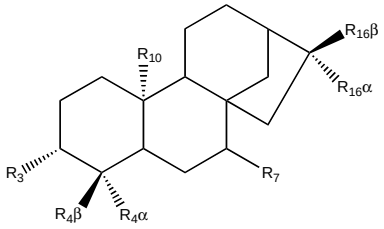
Table 2. Anti-HIV Activity and Cytotoxicity of Compounds (39-46) Isolated from *L. verticillata*

Compound	Cytotoxicity to HOG.R5 CC_{50} (μg/mL (μM))	Anti-HIV activity IC_{50} (μg/mL (μM))	SI[a]
39	13.2 (56.2)	5.0 (21.4)	2.6
40	5.7 (24.4)	2–3 (8.5–12.8)	2.8–1.9
41	17.5 (74.8)	7.1 (30.3)	2.4
42	>20 (80)	14.4 (57.6)	>1
43/44	12.4 (49.6)	4.0 (16)	3.1
45	20.0 (80)	11.3 (45.2)	1.7
46	2.5–5.0 (10.1–20.2)	Toxic	–

[a] SI = selectivity index = CC_{50}/IC_{50}.

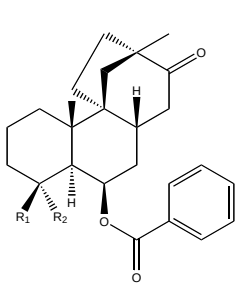


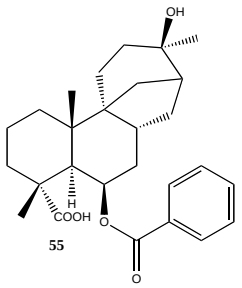
	C-1	R		C-1	R
39	*S*		**44**	*S*	
40	*S*		**45**	*S*	
41	*R*		**46**	*S*	
42	*S*		**47**	*S*	
43	*S*		**48**	*S*	



	R_3	$R_{4\alpha}$	$R_{4\beta}$	R_7	R_{10}	$R_{16\alpha}$	$R_{16\beta}$
50	H	COOH	Me	H	Me	CH_2OH	OH
51	OH	Me	CH_2OAc	OH	Me	$=CH_2$	

The widely distributed plant *Scoparia dulcis* has long been used as a traditional medicine in Paraguay, India, and Taiwan for hypertension, toothaches, blennorhagia and stomach disorders. Due to these diverse medicinal properties, considerable phytochemical investigations were carried out on this plant by different groups to identify the active constituents. Hayashi and co-workers [30, 31] isolated and characterized a number of structurally unique tetracyclic diterpenoids possessing a new carbon skeleton (scopadulane diterpenes), exemplified by scopadulcic acid A (**52**) and B (**53**), from the Paraguayan crude drug prepared from the whole plants of *S. dulcis* [32] and scopadulciol (**54**) from plants collected in Taiwan [30]. Scopadulciol has also been isolated earlier from a Bangladesh collection of *S. dulcis* [33] and is also present in specimens from China and Thailand [31]. During the past decade, Hayashi and co-workers proved that these natural products, and some derivatives, exhibit an amazing





55

	R_1	R_2
52	COOH	CH_2OH
53	H	COOH
54	H	CH_2OH

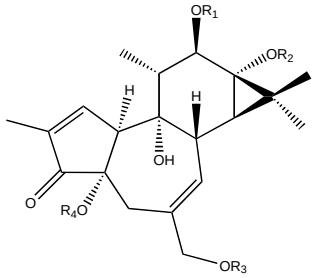


Table 3. Inhibition of HIV-1 Induced CPE and Activation of PKC by Phorbol and its Derivatives

	R_1	R_2	R_3	R_4	IC_{100}	CC_0	%	MAC (μg/mL)
56	H	Ac	$C_{18}H_{31}O$	H	15.6	62.5	0	
57	H	Tig	$C_{18}H_{31}O$	H	7.81	62.5	14	
58	Ac	Tig	H	H	125	500	16	
59	$C_{10}H_{19}O$	2-Me-Bu	H	H	7.81	31.3	0	>50
60	Tig	2-Me-Bu	H	H	31.3	62.5	10	
61	Ac	$C_{10}H_{19}O$	H	H	0.0076	62.5	0	>100
62	2-Me-Bu	$C_{10}H_{19}O$	H	H	15.6	62.5	16	
63	$C_{14}H_{27}O$	Ac	H	H	0.00048	31.3	100	0.01
64	H	H	H	H	-	1000	8	
65	Bz	Bz	Bz	H	-	31.3	100	
66	Ac	Ac	$C_{18}H_{31}O$	H	7.81	62.5	0	
67	$C_{10}H_{19}O$	2-Me-Bu	Ac	H	3.9	15.6	10	>50
68	Ac	$C_{10}H_{19}O$	Ac	H	15.6	31.3	11	
69	Ac	$C_{10}H_{19}O$	Ac	Me	-	1.95	0	
70	$C_{14}H_{27}O$	Ac	Ac	H	15.6	62.5	0	
71	$C_{14}H_{27}O$	Ac	Ac	Me	-	15.6	0	
72	Ac	$C_{14}H_{27}O$	H	H	-	125	0	
73	Ac	$C_{14}H_{27}O$	$C_{14}H_{27}O$	H	62.5	125	0	
74	Ac	H	H	H	-	500	13	
75	H	Ac	H	H	125	>1000	0	
76	Ac	Ac	H	H	-	>1000	57	
77	Ac	Ac	Ac	H	62.5	125	0	
78	Ac	Ac	Ac	Me	31.3	125	0	
79	Ac	Ac	Ac	Ac	125	250	0	
DS8000					3.9	>1000	-	

MAC, minimum concentration for maximum activation of PKC; 2-Me-Bu = 2-Me-butyryl, Tig = tigloyl

pattern of biological activities, including antiviral, antitumor, inhibition of gastric acid secretion and bone resorption as well as potentiation of known antiviral drugs [34]. The continued investigation of Hayashi's group on this plant resulted in isolation and characterization of a novel tetracyclic aphidicolane diterpenoid scopadulin (**55**) in 1990.

A number of phorbol derivatives were evaluated [35] for their inhibition of human immunodeficiency virus (HIV)-1 induced cytopathic effects (CPE) on MT-4 cells, as well as their activation of protein kinase C (PKC), as indices of anti-HIV-1 and tumor promoting activities, respectively.

Through bioactivity-guided fractionation, eight phorbol diesters, including five new ones (**56-60**), were isolated from the seeds of *Croton tiglium* collected in Egypt [36]. Table **3** shows the inhibitory activity of **56-63** against the cytopathic effects (CPE) of HIV-1 in MT-4 cells and their activation of

PKC (protein kinase C). The 13,20-diesters, **56** and **57**, demonstrated complete inhibition of CPE at concentrations (IC_{100}) of 15.6 μg/mL and 7.81 μg/mL, with minimum cytotoxic concentrations (CC_0) of 62.5 μg/mL for both. However, phorbol 12,13-diesters, which contained long-chain and short-chain acyl groups (long-chain at C-12 as in **63** [37], or at C-13 as in **61**), demonstrated potent inhibition of HIV-1-induced CPE at very low concentrations of 0.48 ng/mL and 7.6 ng/mL, respectively. Compound **59**, with C10 and C5 acyl groups, completely inhibited HIV-1 at 7.81 μg/mL, while **62**, with C5 and C12, demonstrated the same inhibitory potency as **56**. Phorbol diesters containing two short acyl residues (**57** and **60**) showed no appreciable anti-HIV CPE activity. It was found that **63**, the most potent tumor promoter known so far, activated PKC by almost 100% at a concentration of 10 ng/mL. However, **61**, which demonstrated potent anti-HIV-1 effects, showed no activation of PKC at concentrations of 10-100 ng/mL. Compounds **56** and **59** did not activate PKC at 10 ng/mL, while **57**, **58**, **60**, and **62** demonstrated 10-16% increases in the activity of PKC. Compound **58** was also a selective inhibitor of HIV-1, and the very potent effects of **61** indicated that the effects of phorbol esters were influenced by chain length and acyl group position.

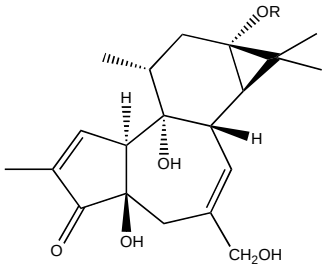
Also, 12-*O*-acetylphorbol-13-decanoate (**61**) effectively inhibited the cytopathic effect of HIV-1 on MT-4 cells with IC_{100} value of 7.6 ng/mL and CC_0 value of 62.5 μg/mL [39].

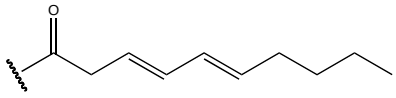
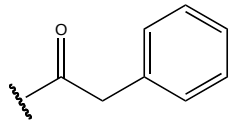
12-*O*-Tetradecanoylphorbol-13-acetate (**63**) was found to be a potent inhibitor of HIV-1-induced cytopathic effect on MT-4 cells with complete inhibitory concentration (IC_{100}) value of 0.48 ng/mL and minimum cytotoxic concentration (CC_0) value of 31.3 μg/mL. In addition, it was found to be an effective activator of PKC (96% activation at 10 ng/mL).

Apart from the potent inhibition of CPE observed in **61** and **63**, the former also showed a strong PKC activation activity, while the latter showed no activity at 10 ng/mL. Both activities were generally observed in those phorbol derivatives with an A/B trans configuration, but not in isophorbol derivatives with an A/B cis configuration. Acetylation of 20-OH in the phorbol derivatives significantly reduced the inhibition of CPE, as shown in **67** (IC_{100} = 15.6 μg/mL) vs. compound **61** (IC_{100} = 7.6 ng/mL), and **69** (IC_{100} = 15.6 μg/mL) vs. **63** (IC_{100} = 0.48 ng/mL), except in the case of **59** and **72**. The reduction of a carbonyl group at C-3 abruptly reduced the inhibition of CPE, as observed in **77** (IC_{100} = 500 μg/mL) vs. **75** (IC_{100} = 62.5 μg/mL). Although **63** was equipotent in the inhibition of CPE and activation of PKC, both activities were abruptly decreased by the acetylation as in **69** and **70**, respectively. On the other hand, its positional isomer **71** showed neither activity. The removal of a long acyl group in **63** led to a substantial loss of both activities, as shown in **74**. Of the 12-*O*-acetyl-13-*O*-acylphorbol derivatives, the highest inhibition of CPE was observed in **61**, which has a dodecanoyl residue at C-13. Both an increase and decrease in the number of fatty acid carbon chains resulted in significant reduction of the inhibition of CPE.

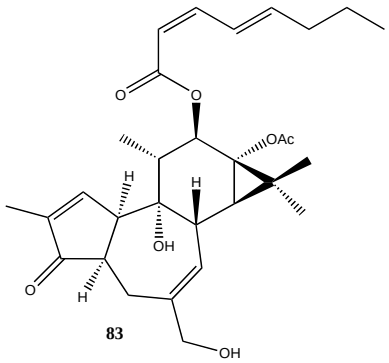
Phorbol ester, prostratin (**80**), isolated from *Homalanthus nutans*, showed a potent HIV inhibitory property with $IC_{100} \geq$ 1 μM (0.39 μg/mL) and weak PKC activation. 12-Deoxyphorbol 13-(3*E*,5*E*-decadienoate) (**81**), isolated from leaves and stems of *Excoecaria agallocha* inhibited HIV-1 RTase [39].

12-Deoxyphorbol-13-phenylacetate (DPP) (**82**), an anti-tumor-promoting phorbol ester originally isolated from the West African plant *Euphorbia poissonii*, induced the expression of HIV-1 in latently infected T cells (IC_{50} = 4 nM, TI = 11 500) and rendered them sensitive to killing by an immunotoxin targeted to the viral envelope glycoprotein. The combination of high potency and anti-tumor promoting activity make DPP an attractive candidate for the adjunctive therapy of persistent HIV-1 infection [40].



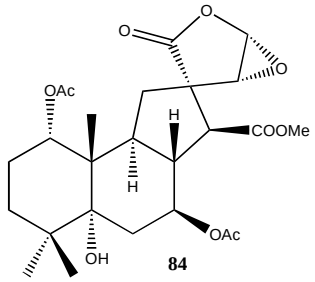
	R
80	Ac
81	
82	

A new cancer cell growth inhibitor designated pedilstatin (**83**) was isolated from *Pedilanthus* sp. collected in Maldives [38]. Pedilstatin was found to significantly inhibit the growth of the P388 lymphocytic leukemia cell line with an ED_{50} of 0.28 μg/mL, to afford, at concentrations of 2-5 μM, protection (to 80%) of human-derived lymphoblastoid CEM-SS cells from infection and cell-killing by HIV-1. The activity of pedilstatin as a ligand for protein kinase C was measured by inhibition of binding of [20-^{3}H]phorbol-12,13-dibutyrate to protein kinase C_α. The K_i for pedilstatin was 620 nM. This value shows good agreement with the measured biological potency of pedilstatin in the P388 assay. The modest potency relative to typical phorbol esters is consistent with the observation that biological activity is dependent on the AB ring system being in a *trans* configuration.



83

Caesalpinia minax is a prickly shrub growing in the tropics and subtropics. The seeds of this plant have long been used as Chinese folk medicine for the treatment of common cold, fever and dysentery. The extract of the seeds was found to show *in vitro* anti-respiratory syncytial virus activity, and a subsequent bioassay-guided study led to the isolation of a novel rearranged vouacapane diterpenoid possessing a new carbon skeleton, now designated spirocaesalmin (**84**) [41]. Spirocaesalmin has been found to exhibit significant activity against respiratory syncytial virus (IC_{50} = 19.5 μg/mL, TC_{50} = 126.9 μg/mL and SI = 6.5) in cell culture, the corresponding values for the positive control (ribavirin) being 3.6 μg/mL, 62.5 μg/mL and 17.4, respectively.



84

A bioassay-guided study led to the isolation of five new cassane furanoditerpenes, designated as caesalmin C (**85**), D (**86**), E (**87**), F (**88**), and G (**89**), along with stigmasterol from the seeds of *Caesalpinia minax* [42]. Furanoditerpenoids **85-89** showed significant activity against the para3 virus, with IC_{50} values ranging between 7.8 and 14.8 μg/mL. However, compound **89**, which is the only furanoditerpenoid lactone, is highly toxic, with a TI value of 3.0. It is noteworthy that the TI value of compound **85** is almost the same as that of ribavirin, which serves as a positive control in the bioassay. Investigation of the chloroform fraction of this extract resulted in the isolation of two new, but inactive, furanoditerpenoid lactones, caesalmin A (**90**) and B (**91**). It can be concluded that the anti-para3 virus activity of tetracyclic furanoditerpenoids is better than that of the furanoditerpenoid lactone.

From the CH_2Cl_2 extract of seed kernels of *Caesalpinia crista* from Myanmar, two rare and biogenetically interesting methyl migrated cassane-type furanoditerpenes, i.e. caesalpinins MM (**92**) and MN (**93**) and two normal cassane-type furanoditerpenes caesalpinins MO (**94**) and MP (**95**) have been isolated, together with eight known cassane-type diterpenes, 1-deacetoxy-1-oxocaesalmin C (**96**), 1-deacetylcaesalmin C (**97**), caesalmin C (**85**), bonducellpin C (**98**), caesaldekarin (**99**), 2-acetoxycaesaldekarin (**100**), 2-acetoxy-3-deacetoxycaesaldekarin (**101**), and norcaesalpinin (**102**) [43]. Among the known compounds, compounds **96** and **97** were isolated for the first time from a natural source.

Further investigation of the active components of the chloroform fraction of the seeds of *Caesalpinia minax* led to the isolation of a new cassane furanoditerpenoid, caesalmin H (**103**), together with two known furanoditerpenoid lactones, caesalmin B (**104**) and bonducellpin D (**105**). Reduction of the naturally abundant caesalmin D (**86**), E (**87**) and F (**88**) resulted in three furanoditerpenoid derivatives **105-107** [44]. The inhibitory activities of these compounds on the para3 virus were evaluated by cytopathogenic effects (CPE) reduction assay (Table **5**). The furanoditerpenoids **91**, **108** showed moderate activity against para3 virus and exhibited high toxicity with TI values of 2.8 and 2.7, respectively. Re-

Table 4. Antiproliferation Activity of Compounds 85-89 Against the Para3 Virus

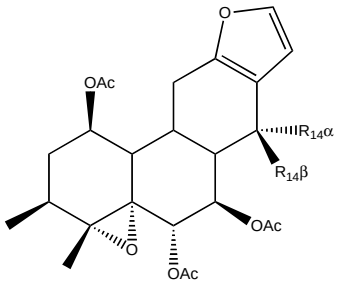
Compound	IC_{50} (μg/mL)	TC_{50} (μg/mL)	TI
85	8.2	196.3	23.9
86	9.6	182.4	19.1
87	10.3	165.0	16.0
88	7.8	136.5	17.5
89	14.8	44.7	3.0
Ribavirin	2.6	62.5	24.0

Table 5. Inhibitory Effects of Compounds on the Para3 Virus Induced Cytopathogenicity

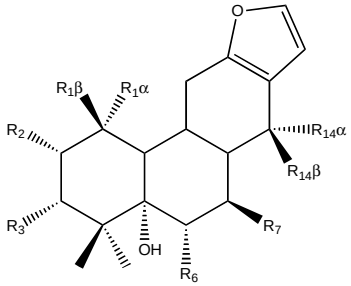
Compound	IC_{50}(Mx10^{-5})	TC_{50} (Mx10^{-5})	TI
91	5.5	15.6	2.8
105	5.2	37.9	7.3
106	6.1	48.9	8.0
107	6.4	120.0	18.8
108	4.8	12.9	2.7
Ribavirin	1.0	24.0	24.0

duction of the acetoxyl group significantly decreased the activity when comparing the IC_{50} values of the compounds with the corresponding parent furanoditerpenoids **86-88**. It is noteworthy that the toxicity of compound **107** is significantly lower than that of other compounds with a TI value comparable to its parent furanoditerpenoid **88**.

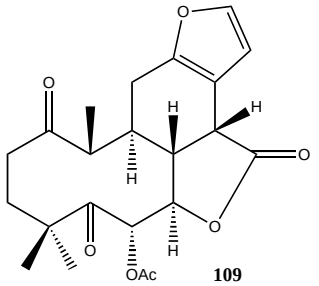
A novel cassane-type furanoditerpenoid lactone, named macrocaesalmin (**109**), possessing a ten-membered macrocyclic 1,5-diketone ring and an unprecedented *cis* B/D ring fusion mode, has been isolated from the seeds of *Caesalpinia minax* [45]. Macrocaesalmin showed inhibitory activity against the RSV with IC_{50} = 24.2 μg/mL, TC_{50} = 138.3 μg/mL and SI = 5.7 in cell culture, and the corresponding values for positive control (ribavirin) were 3.4 μg/mL, 60.6 μg/mL and 17.8, respectively. The antiviral activity of **109** was not better than the positive control; however, the selectivity index SI>4 for natural products was considered significant. However, unlike other furanoditerpenoids, **109** was inactive against the para-3 virus with IC_{50} = 51.9 μg/mL, TC_{50} = 137.5 μg/mL and SI = 2.6, and the corresponding values for the positive control were 2.7 μg/mL, 62.5 μg/mL and 23.1, respectively. Similarly, **109** was also inactive against the Flu-A virus.



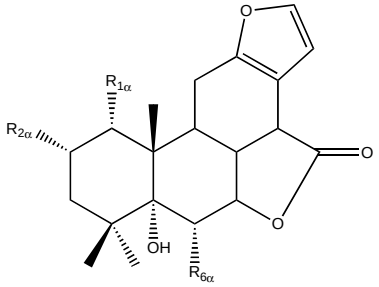
	$R_{14\alpha}$	$R_{14\beta}$
92	OH	Me
93	Me	OH



	$R_{1\beta}$	$R_{1\alpha}$	R_2	R_3	R_6	R_7	$R_{14\alpha}$	$R_{14\beta}$	Δ^2	$\Delta^{8,14}$	$\Delta^{9,11}$
85	H	OAc	H	H	OAc	OAc	$=CH_2$		-	-	-
86	H	OAc	H	H	OAc	OAc	OH	Me	-	-	-
87	H	OAc	H	H	OAc	OAc	Me	OH	-	-	-
93	H	OAc	H	H	OAc	OAc	Me	OMe	-	-	-
94	=O		-	-	OAc	OAc	$=CH_2$		=	-	-
95	H	OAc	H	H	H	H	Me	-	-	=	=
96	=O		H	H	OAc	OAc	$=CH_2$		-	-	-
97	H	OH	H	H	OAc	OAc	$=CH_2$		-	-	-
98	H	OAc	H	H	H	OH	H	COOMe	-	-	-
99	H	OAc	H	OAc	H	H	Me	-	-	=	=
100	H	OAc	OAc	OAc	H	H	Me	-	-	=	=
101	H	OAc	OAc	H	H	H	Me	-	-	=	=
102	H	OAc	H	H	H	OH	=O		-	-	-
104	H	OAc	H	H	H	OH	Me	H	-	-	-
105	H	OH	H	H	OAc	OAc	OH	Me	-	-	-
106	H	OH	H	H	OH	OH	Me	OH	-	-	-
107	H	OH	H	H	OAc	OAc	Me	OMe	-	-	-
108	H	H	H	H	OAc	H	Me	H	-	-	-



109

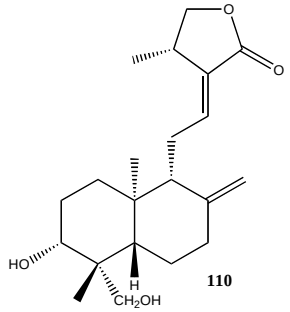


	$R_{1\alpha}$	$R_{2\alpha}$	$R_{6\alpha}$
89	OH	H	H
90	OH	OH	OAc
91	OAc	H	H
104	OH	H	OAc

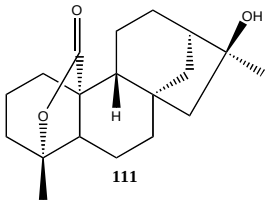
Diterpene lactone, andrographolide (**110**) isolated from *Andrographis paniculata* prevented HIV-infected cells from arresting in G2 phase in which viral replication is optimal. It has also been reported to inhibit cell-to-cell transmission, viral replication and syncytia formation in HIV-infected cells [46]. A phase I dose-escalating clinical trial of andrographolide revealed a significant rise in the mean CD4+ lymphocyte level (from a baseline of 405 cells/mm^3 to 501 cells/mm^3; p = 0.002) of HIV-1 infected subjects after 2 weeks´ administration of 10 mg/kg andrographolide.

Andrographolide (**110**), neoandrographolide and 14-deoxy-11,12-didehydroandrographolide, ent-labdene diterpenes isolated from *Andrographis paniculata* showed viricidal activity against herpes simplex virus 1 (HSV-1) with IC_{50} ~10 μg/mL [47].

Another diterpene lactone, nortripterifordin (**111**) isolated from *Tripterygium wilfordii*, inhibited HIV replication in H9 lymphocytes [48]. Diterpenes from *Homolanthus acuminatus* and *Chrysobalanus icaco* have shown HIV-inhibitory activity in *in vitro* screening [49].

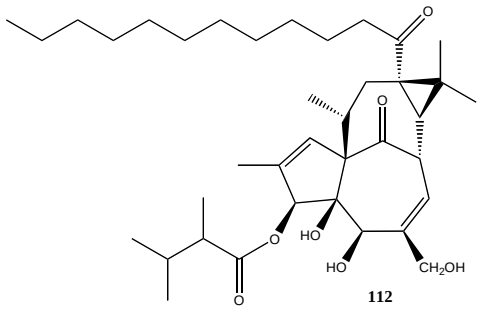


110



111

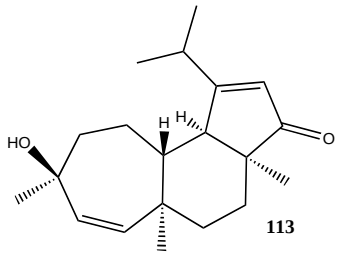
The derivatives extracted from the dried roots of *Euphorbia kansui* have various biological activities, including anti-HIV activity, due to inhibition of virus adsorption to the host cells [50-52]. Among the ingenol derivatives, 13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate (RD4-2138) (**112**) proved to be exquisitely potent (IC_{50}: 0.07 nM) against HIV-1(III_B strain) in MT-4 cells, and selective (50% cytotoxic concentration (CC_{50}): 8.7 mM). The mechanism of anti-HIV action of RD4-2138 could at least in part be attributed to down-regulation of the CD4 receptor for gp120, thus accounting for the inhibitory activity of this class of compounds on virus adsorption.



112

Although ingenol derivatives are highly potent inhibitors of HIV-1 replication in acutely infected cells, it was recently shown that some ingenol derivatives enhance HIV-1 replication in chronically infected cells, whether or not through activation of the nuclear factor κB (NF-κB) and protein kinase C (PKC).

Cyanthiwigin U (**113**) and further cyanthiwigins (A-D), are diterpenes isolated from Jamaican sponge *Myrmekioderma styx* and they exhibited moderate anti-HIV inhibitory activity in cell-based *in vitro* anti-HIV assay [53].



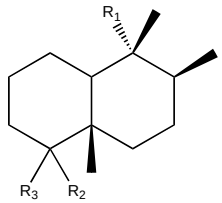
113

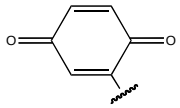
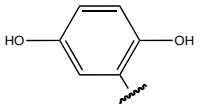
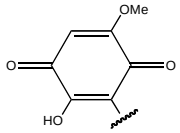
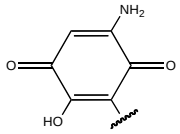
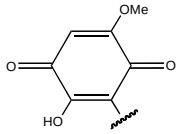
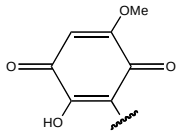
Avarone (**114**) and avarol (**115**) isolated from the sponge *Dysidea avara* showed anti-HIV activity, but controlled studies failed to confirm their utility in treatment of HIV-infection.

Avarol and avarone derivatives (from the Red Sea sponge *Dysidea cinerea*) [54] have all been reported to inhibit the reverse transcriptase (RT) activity of HIV-1, noncompetitively with respect to the natural substrate (dNTP). In neither case was the anti-HIV-1 activity determined in cell culture, so it is not clear whether any of these compounds is a really effective inhibitor of HIV replication, and, if so, whether they inhibit HIV replication through an inhibitory effect on HIV-1 RT.

Illimaquinone (**116**), isolated like avarone and avarol from a Red Sea sponge, i.e. *Smenospongia*, has been reported to inhibit the RNase H activity, associated with the HIV-1 reverse transcriptase (RT), at a concentration of 5-10 μg/mL, while not being active against the RNA dependent

DNA polymerase (RDDP) and DNA-dependent DNA polymerase (DDDP) activities of the enzyme at a concentration of 50 μg/mL [55]. The meaning of this finding is unclear, as the activity of illimaquinone against HIV replication in cell culture was not assessed.



	Δ^3	R_1	R_2	R_3
114	=		Me	-
115	=		Me	-
116	-		=	
117	-		=	
118	-		Me	Me
119	=		Me	-

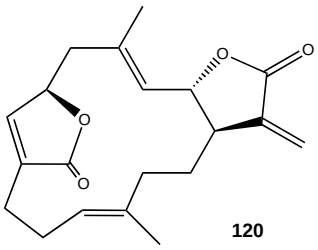
Quinone and hydroquinone subunits are featured in a variety of natural products, including a family of marine metabolites represented by avarone (**114**), avarol (**115**), ilimaquinone (**116**), smenospongine (**117**), mamanuthaquinone (**118**), and avarone E (**119**) [56]. Among the exciting and diverse biological properties exhibited by all members of this family, the antimitotic, antileukemic, and antiviral effects reported (Table **6**) for **114** and **115** are particularly noteworthy. Although the chemical origins of these biological properties remain obscure, the redox properties of the hydroquinone-quinone system present in **114** and **115** may be held accountable for such a profile.

The figures in parentheses (Table **6**) are values calculated for the inhibition of HIV-l RT-associated RDDP activity by the different compounds. These values represent the inhibitor concentrations in μg/mL.

Table 6. Effect of Different Avarol and Avarone Derivatives on HIV-l RT-Associated RNA-Dependent DNA Polymerase (RDDP) and RNase H Activities

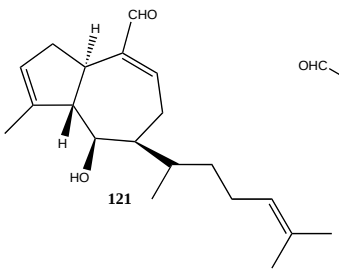
	HIV-l RT enzymatic activity (%)	
	RDDP[a]	RNase H
Avarone A	27 (6.8)	46
Avarone B	30 (5)	59
Avarol C	100 (>50)	86
Avarone D	98 (>50)	96
Avarone E	9 (1.0)	6
Avarol F	28 (7.0)	0

A diterpenoid ovatodiolide (**120**) from *Anisomeles indica* was reported to exhibit anti-HIV activity [57]. Ovatodiolide inhibited the cytopathic effects of HIV-1 infection over a modest concentration range (EC_{50} = 0.10 μg/mL; IC_{50} = 0.10 μg/mL) with maximum cellular protection of 80-90% but was completely cytotoxic to the host cells at 5.0-6.0 μg/mL. The anti-HIV activity of **120** was compared with that produced by a known anti-HIV drug, AZT (EC_{50} 0.0037 μg/mL).

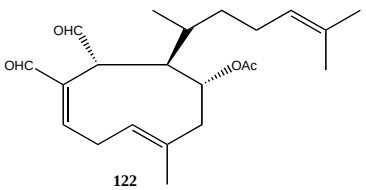


120

Secondary metabolites isolated from the brown alga *Dictyota dichotoma* and the brown alga *D. linearis* [58] included the diterpenes isopachydictyolal (**121**) acquired from *D. dichotoma* and 4α-acetyldictyodial (**122**) from *D. linearis*. The antiviral activity of metabolites isolated in adequate amounts was evaluated in laboratory assays against herpes simplex virus I (HSV I) and poliomyelitis virus I, using Vero cells as hosts. The isolated metabolites did not exhibit significant antiviral activity against the two viruses in concentrations lower than their maximal non-toxic dose (MNTD) and proved to be toxic for Vero cells in different dilutions. Every concentration was tested in duplicate and the highest assayed concentration was 100 μg/mL. The MNTD for the metabolite **120** was found to be 10 μg/mL.



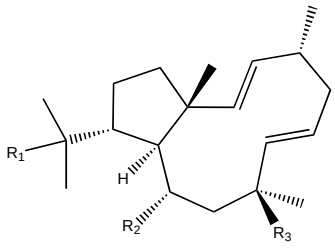
121



122

Specimens of *Dictyota pfaffii* from North-East Brazil afforded the rare dolabellane diterpene 10,18-diacetoxy-8-

hydroxy-2,6-dolabelladiene (**123**) and the new 10-acetoxy-8,18-dihydroxy-2,6-dolabelladiene (**124**) [59]. Reduction of **123** yielded 8,10,18-trihydroxy-2,6-dolabelladiene (**125**), also present in the crude extract of *D. pfaffii*. All these substances showed strong anti-HSV-1 activity *in vitro* but only **125** inhibited the reverse transcriptase enzyme of HIV-1. At a concentration of 50 μM, the compounds **123-125** reached 89, 87 and 81% of cytopathic effect inhibition of herpes virus respectively (Table **7**).



	R_1	R_2	R_3
123	OAc	OAc	OH
124	OH	OH	OAc
125	OH	OH	OH

Table 7. Cytopathic Effect Inhibition of Compounds 123-125 on Herpes Virus

Compound	CC_{50} (μM)	$TCID_{50}$ (%)
123	185	89
124	189	87
125	184	81
Acyclovir	850	79

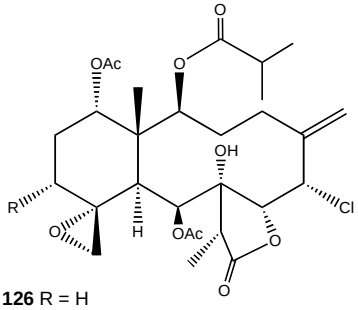
TCID - tissue culture infective dose.

Briaranes are diterpenoid γ-lactones of highly substituted bicyclic six- and ten-membered rings that are extensively produced by marine octocorals including gorgonians [60, 61]. The majority of these compounds are endowed with different biological activities including antiviral ones [62].

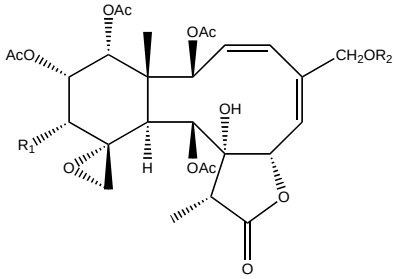
Fractionation of the acetone extract of the red gorgonian coral *Junceella juncea* collected in Taiwan resulted in the isolation of a new briarane, designated juncenolide A (**126**) [63]. General biological study revealed that compound **126** exhibited moderate cytotoxicity against human colon adenocarcinoma and oral epidermoid carcinoma (KB-16) cells at a concentration of 3.4 and 5.9 μg/mL, respectively.

In addition to the known juncenolide A, three new briaranes, juncenolides B (**127**), C (**128**), and D (**129**), have been isolated from the acetone extract of *Junceella juncea* collected in Taiwan [64]. Juncenolide C exhibited mild cytotoxicity against human hepatoadenocarcinoma (HEPA 59T/VGH) and oral epidermoid carcinoma (KB-16) cells at concentrations of 6.6 and 7.8 μg/mL, respectively. However, compounds **127-130** were inactive toward these cell lines.

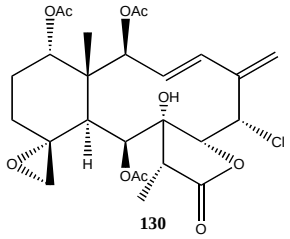
Chemical investigation of *Junceella juncea* has resulted in the isolation of two novel briarane-type diterpenoid compounds, juncenolides F (**131**) and G (**132**) [65].



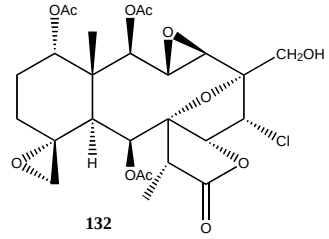
126 R = H
131 R = $OOCCH_2CH(CH_3)_2$



	R_1	R_2
127	H	H
128	OAc	H
129	OAc	Me



130



132

Further, new briarane diterpenes, briarlides A – H (**133**, **135-138**, **140**, **141**, **143**), have been isolated from a gorgonian *Briareum* sp., collected in Japan [66] and their semisynthetic derivatives have also been obtained (**134**, **139**, **142**). Their structures and cytotoxity toward Vero and MDCK cells were described. The inhibitory activity of **133-138** and **140-142** against Vero and MDCK cells was 2.07-62.1 and 2.49-67.1 μg/mL, respectively (Table **8**). Compound **133** showed the strongest inhibitory activity of them all. The compounds **142** and **143**, without a substituent at C-4, and compounds **135-138**, possessing a hydroxyl group(s) at C-2 and/or C-3, were less inhibitory. Compound **138**, with a longer aliphatic chain, was more active than **137**, with a shorter chain. When the octanoyl group at C-4 was rearranged to C-3, the activity was decreased, as seen in the case of **138** and **140**. The activity of compound **135**, possessing an acetyl group at C-12, was stronger than that of **136**, with a hydroxyl group at C-12.

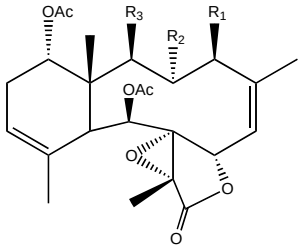
Table 8. Cytotoxic Activity (CC_{50} μg/mL) of Compounds 133-136, 138-141 and 143

	133	134	135	136	138	139	140	141	143
Vero	2.07	9.80	18.9	62.1	4.24	2.26	4.26	22.2	>100
MDCK	4.74	28.8	15.4	38.6	4.91	2.49	3.49	67.1	>100

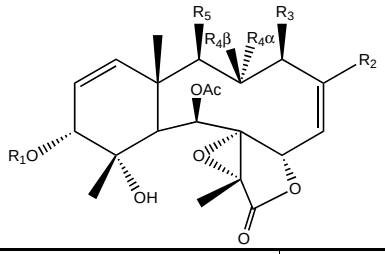
Further investigations of the *Briareum* sp. secondary metabolites have yielded 10 new briarane diterpenes, briarlides I-R (**14-153**) [67]. Bioactivity tests for the new compounds could unfortunately not be performed because of their insufficient amount.

Four new briarane-type diterpenoids, pachyclavulides A (**154**), B (**155**), C (**156**), and D (**156**), were isolated from the Okinawan soft coral *Pachyclavularia violacea* [68].

Chemical investigation of the soft coral *Cespitularia hypotentaculata* resulted in the isolation of eight new diterpenes, cespihypotins E–L (**158-165**) [69]. The new metabolites comprise six verticillene-type diterpenes, one cespitularane derivative, and one derivative with 14-membered lactone ring. Immunomodulatory and antiviral activities of **158-165** were tested and evaluated. The isolated diterpenes **158-165** were tested in vitro against HSV-1 virus. As indicated in Table **9**, they exhibited weak activity as compared with acyclovir. A preliminary study on resting cells and cells acti-

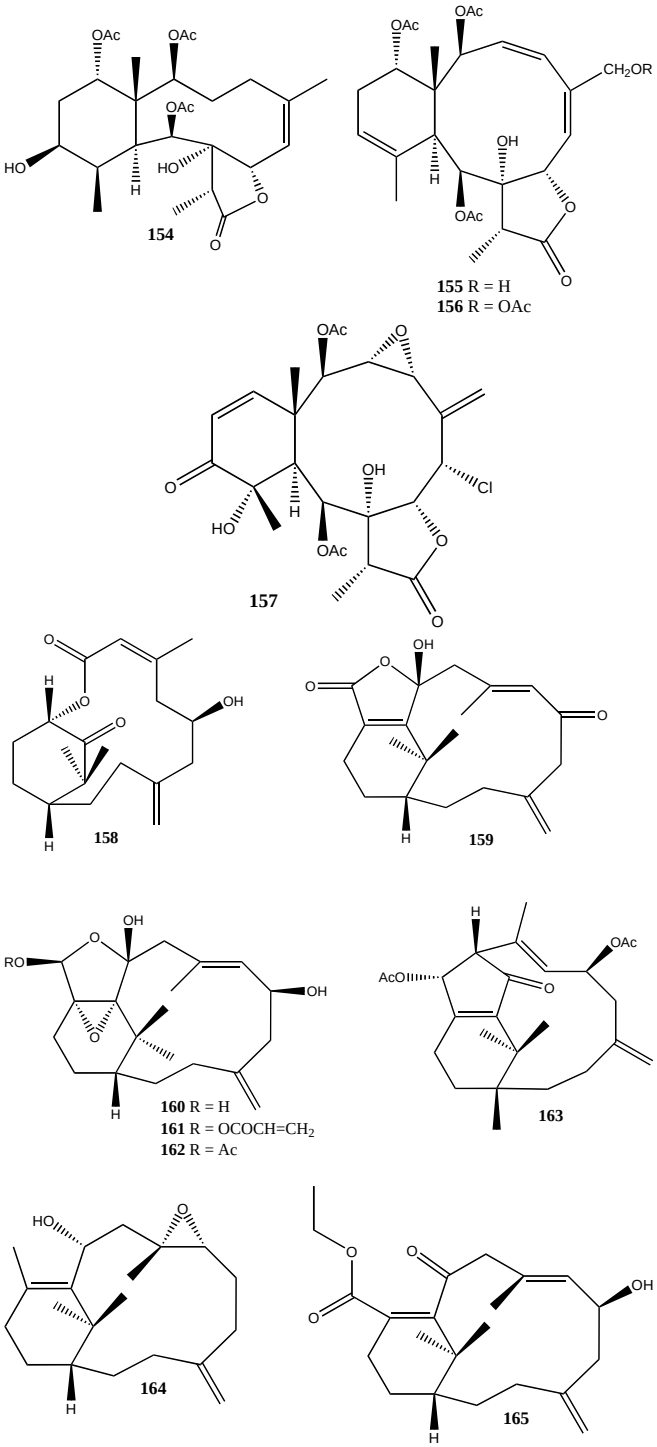


	R_1	R_2	R_3
150	$OOC(CH_2)_6CH_3$	OH	OAc
151	OAc	OH	OAc
152	$OOC(CH_2)_6CH_3$	OAc	OH
153	H	OAc	OH



	R_1	R_2	R_3	$R_{4\beta}$	$R_{4\alpha}$	R_5
133	Ac	Me	OAc	OAc	H	OAc
134	H	Me	OAc	OAc	H	OAc
135	Ac	Me	OAc	OH	H	OAc
136	Ac	Me	OAc	OH	H	H
137	Ac	Me	$OOC(CH_2)_4CH_3$	OH	H	OAc
138	Ac	Me	$OOC(CH_2)_6CH_3$	OH	H	OAc
139	H	Me	$OOC(CH_2)_6CH_3$	OH	H	OAc
140	Ac	Me	OH	$OOC(CH_2)_6CH_3$	H	OAc
141	Ac	Me	H	OAc	H	OAc
142	H	Me	H	OAc	H	OAc
143	H	Me	H	OAc	H	OH
144	Ac	Me	$OOC(CH_2)_6CH_3$	H	OAc	OAc
145	H	Me	OAc	H	OH	OAc
146	Ac	Me	$OOC(CH_2)_2CH_3$	H	OH	OAc
147	Ac	Me	$OOC(CH_2)_6CH_3$	H	H	OAc
148	H	CH_2OH	$OOC(CH_2)_4CH_3$	H	H	OAc
149	Ac	Me	OAc	H	H	OAc

vated with PHA was performed with compounds **158-165** at 100 μM. The inhibition or enhancement of cell proliferation was determined by tritiated thymidine uptake. As indicated in Table **10**, compound **7** showed significant enhancement of cell proliferation, while compound **165** inhibited phytohemagglutinin induced proliferation of peripheral blood mononuclear cells.



Shinjulactone C (**166**), possessing an unusual structure and isolated from *Brucea javanica* and *Brucea antidysenterica* [70], showed anti-HIV activity with therapeutic index of more than 25.

Table 9. Inhibition of [a]HSV-1 Replication by Compounds 158–165

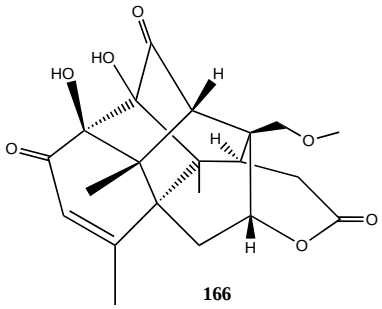
Compound (100 μM)	Inhibitory activity (%)
158	18.5
159	5.2
160	19.4
161	6.6
162	13.7
163	21.8
164	10.0
165	22.3

[a] HSV-1: Herpes simplex virus type 1.

Table 10. Effects of Compounds 158–165 on PBMC Proliferation Induced by PHA

Compound (100 μg/mL)	Activity (%)	
	Resting	PHA (5 μg/mL)
158	−61.9±4.5	89.4±2.4
159	7.0±1.0	−8.6±0.3
160	37.8±8.9	26.7±0.2
161	−37.8±2.6	−2.6±4.0
162	4.3±4.6	−27.8±6.5
163	31.6±8.9	2.9±0.1
164	45.7±8.5	162.6±63.7
165	11.5±1.1	−84.2±1.5
Cyclosporine A (2.5 μg/mL)	−15.9±4.4	−92.2±6.8

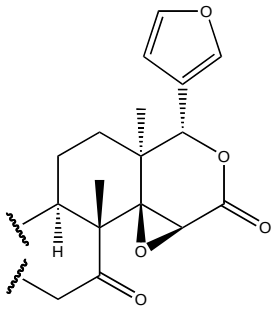
Negative represents inhibitory activity; positive represents enhancement of proliferation.

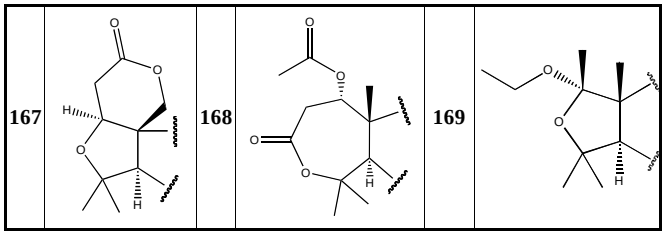


The limonoids, limonin (**167**) and nomilin (**168**), isolated from *Citrus* spp. inhibited HIV-1 replication in PBMC (peripheral blood mononuclear cells) including those with chronic infection and in monocytes/macrophages with EC_{50} values ranging from 20 to 80 μM [71]. A dose-dependent inhibition of viral replication was observed in PMBC isolated from healthy donors and infected with HIV-1 strain after incubation with limonin and nomilin. These also inhib-

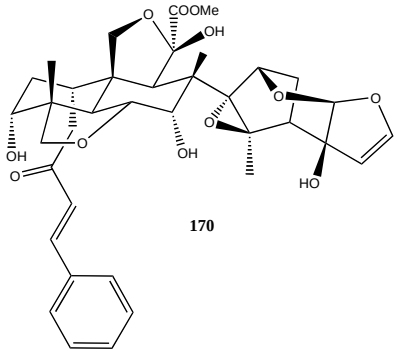
ited the production of HIV-1 p-24 antigen in infected monocytes/macrophages. The mechanism of anti-HIV-1 effect of limonoids was found to be inhibition of HIV-1 protease.

Another limonoid, clausenolide-1-ethyl ether (**169**) isolated from the rhizomes and the roots of *Clausena excavata* showed anti-HIV activity in a syncytium assay with an EC_{50} value of 34.4 μM, exhibiting low cytotoxicity (IC_{50} = 548 μM) [72]. The compound also exhibited HIV inhibitory activity in 1A2 cell line in syncytium assay.



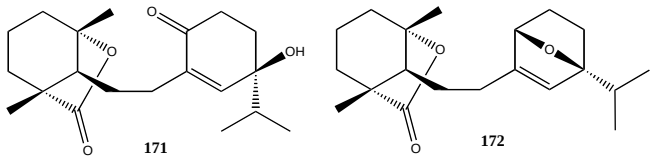


Bioassay guided purification of the ethyl acetate extract of leaves of *Melia azedarach* led to the isolation of the limonoid 1-cinnamoyl-3,11-dihydroxymeliacarpin (**170**), which showed IC_{50} values of 6 μM and 20 μM for vesicular stomatitis (VSV) and herpes simplex (HSV-1) viruses, respectively [73].



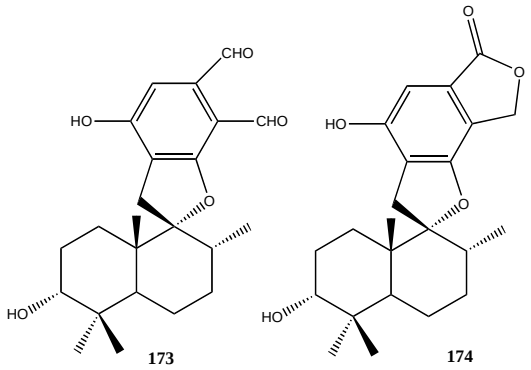
170

A new seco-abietane-type diterpenoid, 13*S*-hydroxy-9-oxo-9,10-seco-abiet-8(14)-en-18,10α-olide (**171**) was isolated along with a known lignan from the stem bark of *Picea glehni* [74]. In order to assess their cancer chemopreventive potential, the inhibition of Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was examined for compound **171**, and its synthetic analogue, 9,10-seco-8*S*,13*S*-epoxy-abiet-8(14)-en-18,10α-olide (**172**). The inhibitory effect of **172** on EBV-EA induction was strong (0, 20.7, 67.1 and 89.2% inhibition at 1000, 500,100 and 10 mol ratio/TPA). The IC_{50} of **172** was 226 mol ratio/32 pmol/TPA.



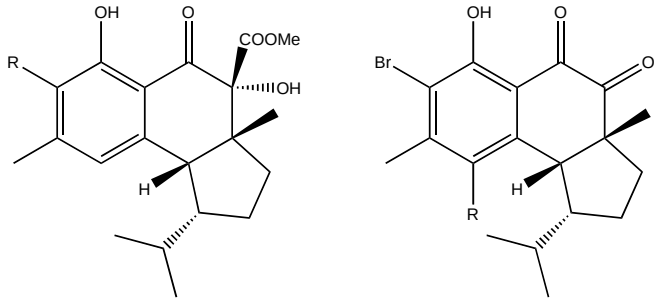
171 **172**

Two known spirodihydrobenzofuran terpenes (**173** and **174**) were isolated from a mycelium extract of the fungus *Stachybotrys nephrospora* [75]. Compound **173** (Mer-NF5003F, stachybotrydial) exhibited potent antiviral activity (an IC_{50} value of 4.32 μg/mL) comparable to the standard drug, acyclovir, while compound **174** was inactive against the HSV-1 virus. Both **173** and **174** possessed antiplasmodial activity (IC_{50} values of 0.85 and 0.15 μg/mL for **173** and **174**, respectively), and were not toxic towards the Vero cell line.



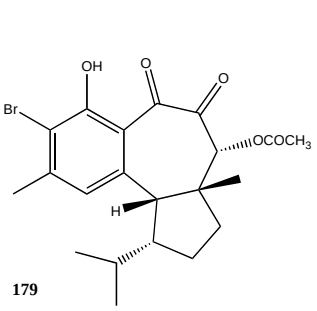
173 **174**

Eight new compounds - hamigeran A (**175**), debromohamigeran A (**176**), hamigeran B (**177**), 4-bromohamigeran B (**178**), hamigeran C (**179**), hamigeran D (**180**), hamigeran E (**181**), and debromohamigeran E (**182**) with a unique carbon skeleton have been isolated from the sponge *Hamigera tarangaensis* [76]. Compounds **178-180** showed moderate *in vitro* cytotoxicity against P-388, while **177** showed 100% *in vitro* virus inhibition against both the herpes and polio viruses, with only slight cytotoxicity.

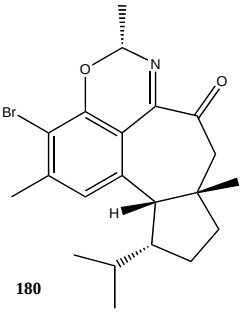


175 R = Br	**177** R = H
176 R = H	**178** R = Br

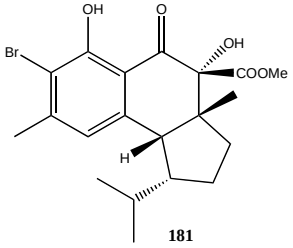
The interesting biological properties of the hamigerans (hamigeran A (**181**) and hamigeran B (**182**)) wherein hamigeran B is a potent antiviral agent with low cytotoxicity to host cells make these deceptively simple looking structures challenging synthetic targets. For this reason, hamigeran B has been repeatedly synthesized – see, e.g., the studies [77, 78].



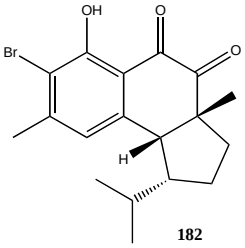
179



180

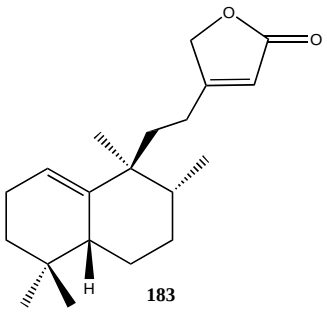


181



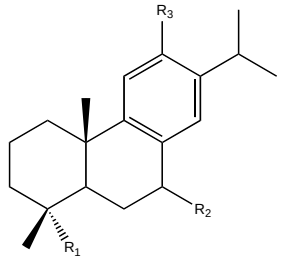
182

In 1995, Hara and co-workers [79] reported the isolation of a great number of clerodanes and ent-halimanes from *Polyalthia langifolia*. Compound **183** is the first ent-halimane diterpene which possesses cytotoxic and antiviral activity against, e.g., HELAM cells (IC_{50} = 5.0 μM), MDCK (IC_{50} = 5.1 μM) and influenza virus (IC_{50} = 6.8 μM).

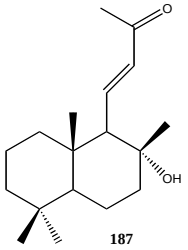


183

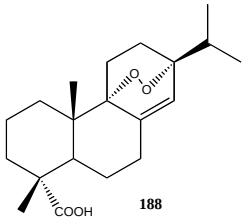
Novel rearranged labdane-type diterpenoids were isolated from the stem bark of *Picea glehni*, together with known diterpenoids (**184-188**) [72]. Compounds **184-188** showed potent inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate (Table **11**).



	R_1	R_2	R_3
184	COOH	H_2	H
185	Me	=O	H
186	COOMe	=O	OH

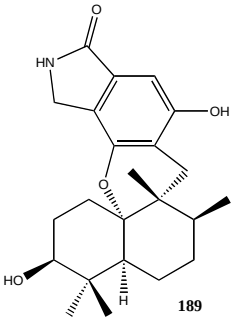


187



188

Two novel compounds, stachyflin (**189**) and acetylstachyflin, have been isolated by solid-state fermentation of *Stachybotrys* sp. RF-7260 [80, 81]. Stachyflin showed antiviral activity against influenza A virus (H1N1) *in vitro* with an IC_{50} value of 0.003 μM. Acetylstachyflin was about 77-fold less active than stachyflin but about 1760 times more than amantadine.



189

Table 11. Percentage of Epstein-Barr Virus Early Antigen Induction in the Presence of Compounds 184-188 with Respect to a Positive Control (100%)

Compound	Concentration (mol ratio/TPA)			
	1000	**500**	**100**	**10**
184	0 (70)	30.6	75.0	95.2
185	0 (60)	20.7	68.4	89.3
186	0 (70)	30.2	74.7	95.0
187	0 (70)	24.2	63.7	90.5
188	0 (70)	28.1	72.9	95.0
β-carotene	9 (70)	34	82.0	100

For decades, gorgonians (Order Gorgonacea, Phylum Cnidaria), commonly known as sea feathers, sea whips and sea fans, have been recognized as a rich source of chemically diverse compounds. Many of these compounds have been isolated and are known to be useful for treating various diseases. Particularly useful among these are the pseudopterosins. They are a family of diterpene pentose glycosides, which have been shown to have potent anti-inflammatory and antiproliferative properties, and analgesic activity equivalent in potency to the industrial standard indomethacin [82-85]. The potential medicinal use of these compounds, which were originally isolated from the Caribbean Sea whip *Pseudoterogorgia elisabethae*, has been intensively studied (see below).

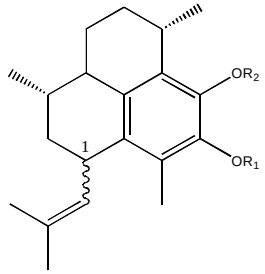
Investigations are reported that identify the biosynthetic source and origins of the pseudopterosins, pharmacologically important diterpene glycosides, in the gorgonian coral *P. elisabethae* [86]. The isolation of physiologically significant levels of endogenous pseudopterosins A, B, C, and D (**190-193**) from purified symbionts identified as the dinoflagellate *Symbiodinium microadricum* was described. These results reveal for the first time that pseudopterosin biosynthesis is occurring within the algal symbiont and suggest the physiological implications of this biosynthesis.

This finding facilitates the production of pseudopterosins from this symbiont as a renewable source and avoids the destruction of coral reefs. *S. microadricum* can be replicated in large numbers in an *in vitro* culture and produce pseudopterosins at a level comparable to that found in naturally occurring coral.

As part of an ongoing program to explore the chemical constituents of Caribbean marine invertebrates, a family of 13 new diterpene glycosides, pseudopterosins P-Z (**194-204**) and seco-pseudopterosins H (**205**) and I (**206**), have been isolated from the organic extracts of two collections of *P. elisabethae* procured on the shore of the Colombian Southwestern Caribbean Sea [87]. Pseudopterosin Q (**195**) inhibited thromboxane B-2 (TXB2) (IC_{50} = 4.7 μM) and superoxide anion $O_2^{\bullet-}$ (IC_{50} = 11.2 μM) generation from *E. coli* lipopolysaccharide (LPS) - activated rat neonatal microglia *in vitro*. In contrast, pseudopterosins P (**194**), U (**199**), V (**200**), W (**201**), and X (**202**) as well as seco-pseudopterosins H (**205**) and I (**206**) demonstrated minimal effects on both TXB_2 and $O_2^{\bullet-}$ release. In addition, some of the new compounds displayed strong antituberculosis, antiviral, antimalarial, and anticancer activity. Pseudopterosin P (**194**) was also subjected to antiviral testing against herpes simplex viruses HSV-1 and HSV-2. Acyclovir (ACV) was used as a control. The tests showed pseudopterosin P to be very toxic against each virus (EC_{50} = 2.9 μM), with SI values of <2.4 (ACV EC_{50} = 0.95 μM). Compound **194** also showed strong antiviral activity against human cytomegalovirus and varicella-zoster virus with EC_{50} values of 2.9 and 2.6 μM (SI values <3.6 and <3.2, respectively).

Seco-pseudopterosins (**207-210**) isolated from a Caribbean Sea whip of the genus *Pseudopterogorgia* [84] are arabinose glycosides possessing aglycones of the serrulatane class; the compounds in the series are mono-acetate positional isomers. The seco-pseudopterosins possess potent anti-inflammatory and analgesic activities equivalent to commercial anti-inflammatory drugs.

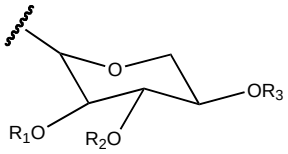
The majority of reef-building corals in the tropical shallow waters belong to the Subclass Hexacoralia whereas only a few species belong to the subclass Octocoralia. The blue coral *Heliopora coerulea* is one of such octocorals. In spite



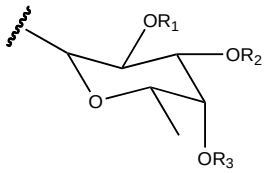
	R_1	R_2	C_1			R_1	R_2	C_1
190	H	a	*R*		**199**	d	H	*S*
191	H	b	*R*		**200**	c	H	*S*
192	H	c	*R*		**201**	f	H	*S*
193	H	d	*R*		**202**	e	H	*S*
194	i	H	*S*		**203**	a	H	*S*
195	j	H	*S*		**204**	f	H	*R*
196	l	H	*S*		**218**	h	H	*R*
197	k	H	*S*		**219**	H	h	*R*
198	h	H	*S*		**223**	b	H	*S*

of extensive chemical investigations since the 1960s on octocorals, i.e. soft corals and gorgonians, blue coral has escaped the attention of organic chemists, presumably because of its calcareous skeleton. In *H. coerulea* were found seven bioactive diterpenes, helioporins A-G (**211-217**). Structurally are these compounds related to the aglycones of anti-inflammatory pseudopterosins isolated from *P. elisabethae*. The pseudopterosins, particularly pseudopterosin E, are reported to be potent anti-inflammatory and analgesic agents, which act by a novel mechanism of pharmacological action. The sugar moiety appears to be important for these compounds to be anti-inflammatory. No activity has been reported with the related terpenes without sugars, which have been isolated from a species of the same genus. Helioporins A and B were found to be inactive in the topical anti-inflammatory assay but they exhibited antiviral activity against HSV1 while helioporins C-G showed cytotoxicity against P388.

Other structurally similar compounds (**218-223**) are given here for the sake of completeness, although their biological effects are not known.

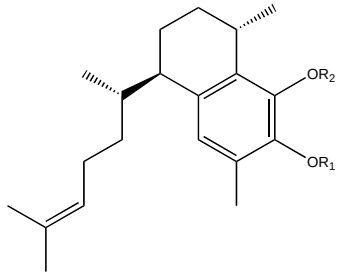


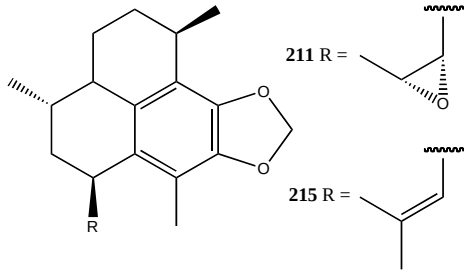
	R_1	R_2	R_3
a	H	H	H
b	Ac	H	H
c	H	Ac	H
d	H	H	Ac
e	Ac	H	Ac
f	H	Ac	Ac

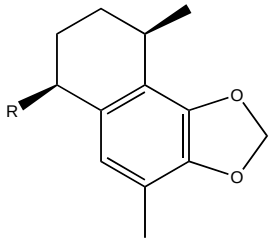


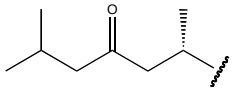
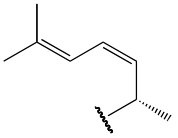
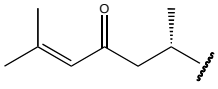
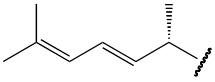
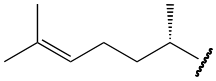
	R_1	R_2	R_3
h	H	H	H
i	H	H	Ac
j	H	Ac	H
k	Ac	H	Ac
l	H	Ac	Ac
m	Ac	H	H

	R_1	R_2
205	d	H
206	b	H
207	H	a
208	H	b
209	H	c
210	H	d
220	m	H
221	j	H
222	i	H

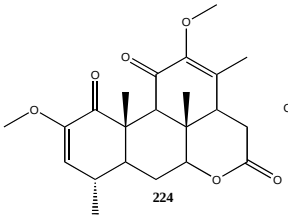




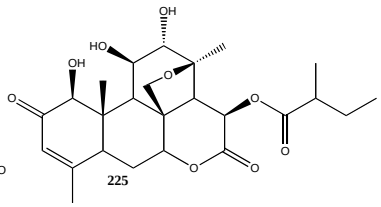


	R		R
212		**216**	
213		**217**	
214			

After removing lipophilic material, the ground root bark of *Quassia africana* was extracted and pronounced activities were shown by the chloroform and ethyl acetate crude extracts against herpes simplex, Semliki forest, coxsackie and vesicular stomatitis viruses [88]. Two quassinoids, i.e., quassin (**224**) and simalikalactone D (**225**) were isolated. Simalikalactone D was responsible, at least in part, for the high antiviral activity observed with the chloroform crude extract. For quassinoids the ester group at C-15 and the epoxymethano bridge between C-8 and C-13 appeared to be important structural features in order to exhibit a pronounced antiviral activity. Both compounds were tested for their antiviral activities in a concentration range from 20 to 0.2 μg/mL. Quassin was not active and showed no cytotoxicity. Simalikalactone D exhibited pronounced activity against herpes simplex virus type 1 and vesicular stomatitis virus, both being enveloped viruses, with an RF of 10^2 at a test concentration of only 0.2 μg/mL. Poliomyelitis and Semliki forest viruses were inhibited at a ten-fold higher concentration. At a test concentration of 5 μg/mL simalikalactone D was cytotoxic.



224



225

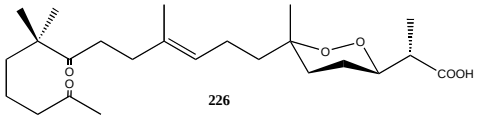
SESTERTERPENES

A relatively small group of terpenopid compounds are called sesterterpenes; their biosynthesis can be derived from five isoprene units.

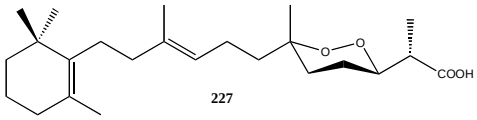
Norsesterterpene peroxide acids and their methyl esters are frequently isolated secondary metabolites from marine sponges. They display a wide range of bioactivity including antiviral activity. A new norsesterterpenoic acid, named muqubilone (**226**), along with the known muqubilin (**227**) and sigmosceptrellin-B (**228**), were isolated from the Red Sea sponge *Diacarnus erythraeanus* [89]. Sigmosceptrellin-B exhibits significant *in vitro* antimalarial activity against *Plasmodium falciparum* (D6 and W2 clones) with IC_{50} values of 1.2 and 3.4 μg/mL, respectively. Muqubilin and muqubilone show *in vitro* antiviral activity against herpes simplex type 1 (HSV-1) with ED_{50} values of 7.5 and 30 μg/mL, respectively. Muqubilin and sigmosceptrellin-B display potent *in vitro* activity against *Toxoplasma gondii* at a concentration of 0.1 μM without significant toxicity.

Variabilin (**229**) is a major component in all New Zealand sponges of the genera *Ircinia*, *Psamminia*, and *Sarcotragus* [90]. The decomposition products of variabilin (**230**-**235**) exhibit biological activity (against Polio vaccine virus type I and Herpes simplex virus type I) similar to that shown by variabilin but that are stable in the presence of light and air.

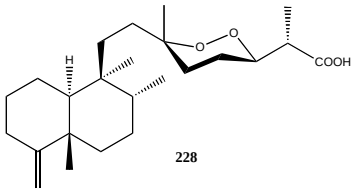
Further paper about of bioactive substances from the massive Indo-Pacific sponge *Fascaplysnopsis reticulata* has yielded unusual salts (reticulatine A **236**, reticulatine B **237**, and fascaplysin B **238**). Each has a sesterterpenoid anion associated with an alkaloid cation [91].



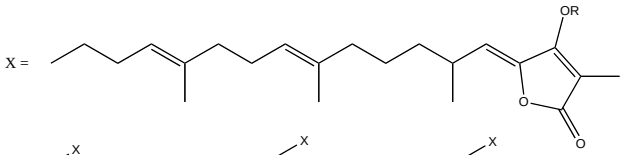
226



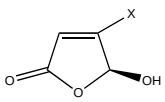
227



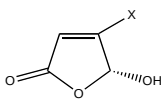
228



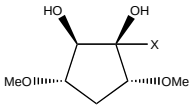
229 R=H
230 R=Me



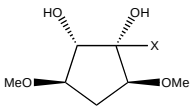
231 R=Me



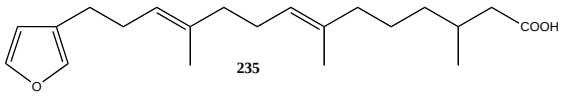
232 R=Me



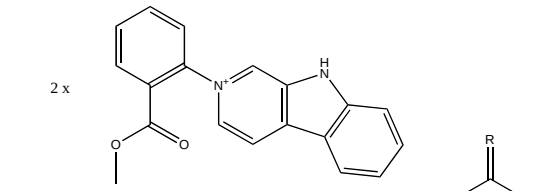
233 R=Me



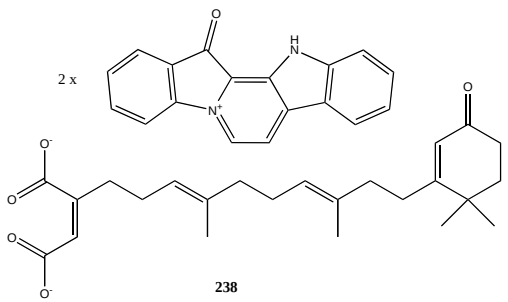
234 R=Me



235

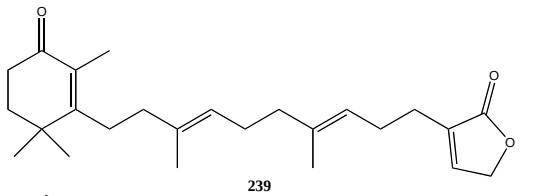


236 R= O
237 R=H_2

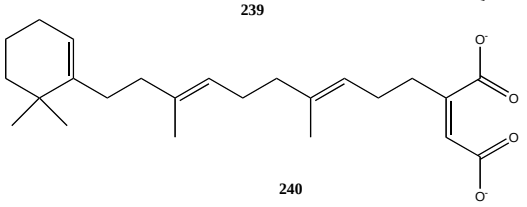


238

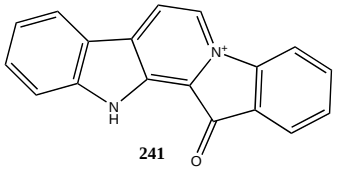
The bioactive constituents of *Fascaplysinopsis reticulata* collected from the Benga Lagoon of the Fiji islands were described [92]. The investigation of *F. reticulata* has revealed new sesterterpenes isodehydrouffariellolide (**239**) and dehydroluffariellolide diacid (**240**); unique alkaloid-sesterterpene salts fascaplysin A (**241**) [fascaplysin cation/ dehydroluffariellolide diacid anion] and homofascaplysin A cation/dehydroluffariellolide diacid anion (**242**), and further neutral alkaloids. The most important finding in this study is biological activity profile against the HIV reverse transcriptase that is reported for selected metabolites. Assay against reverse transcriptase (at 1 mg/mL) revealed inhibitions: **239** = 81%, **240** = not active, **241** = 58%, and **242** =94%.



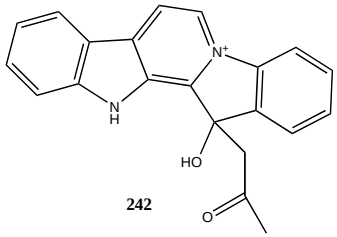
239



240



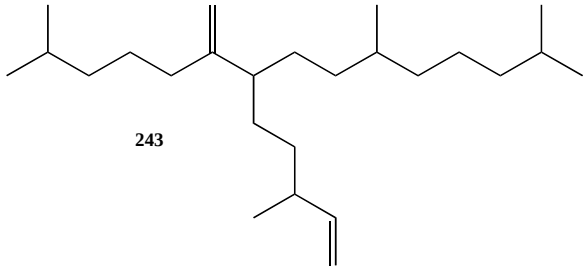
241



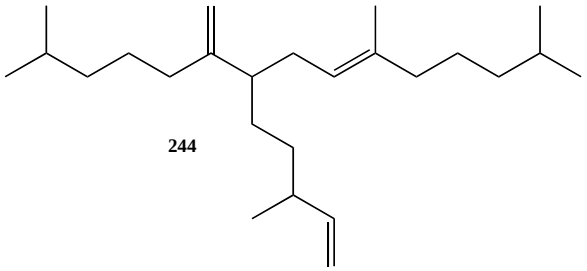
242

Unusual chemicals produced by the 'blue oyster' diatom, *Haslea ostrearia*, include numerous polyunsaturated sesterterpenes – haslenes [93]. Three haslenes (**243**-**245**) exhibit *in vitro* and *in vivo* activities against human lung cancer cells (IC_{50} of **243** is >30, **244** = 13.4 and **245** = 3.8 μg/mL). The most active haslene is the most unsaturated and unsaturation in the haslenes increases with increasing algal growth temperature.

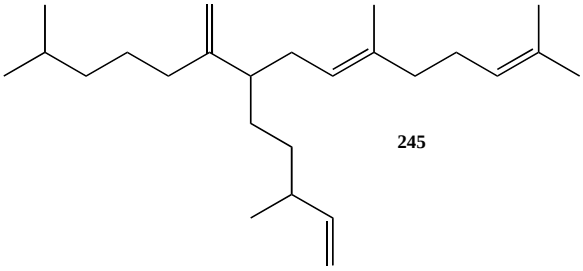
Terpestacin (**246**) is a sesterterpene natural product that is produced by a number of fungi. It was first isolated in 1993 by Oka and co-workers from an *Arthrinium* species [94-96]. In 2001 Gräfe and co-workers isolated terpestacin from a *Ulocladium* fungus; however, they assigned the enantiomeric structure to their isolate [97]. In 2002 Miyagawa and co-workers reported the isolation of siccanol, to which they assigned the 11-*epi*-terpestacin structure, from yet a third fungal source, *Bipolaris sorokiniana* [98], but it was subsequently demonstrated that siccanol is identical to terpestacin.



243

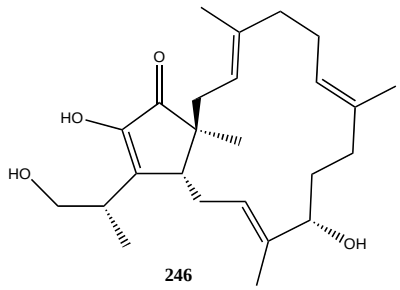


244



245

The C24 acetoxy derivative of terpestacin, fusaproliferin, was isolated by Randazzo and co-workers in 1993 from *Fusarium proliferatum*, a fungal pathogen of maize [99]. Terpestacin is a potent inhibitor (ID_{50} 0.46 μg/mL) of the formation of syncytia, large multinucleated cells that are associated with the pathology of HIV infection [96, 97]. It has also been reported to inhibit angiogenesis on the basis of assays in bovine aortic endothelial cells and in chorioallantoic membrane from chick embryos [100]. Furthermore, terpestacin has been reported to have only modest antimicrobial activity, suggesting that it is not an indiscriminate cytotoxin and may therefore be a useful lead compound for the development of anticancer as well as anti-AIDS chemotherapeutics.



246

CONCLUDING REMARKS

Terpenoids, the largest group of naturally occurring substances produced by a wide variety of plants and animals, provide a rich source of drugs and lead compounds possessing a broad range of biological properties including cancer

chemopreventive effects, antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, and antiparasitic activities. They can be also used as skin penetration enhancers and agents with powerful activity against pathogens that can be used in the prevention and therapy of inflammatory diseases. All this points to the need for larger-scale use of terpenoids in modern medicine. Terpenoids also participate in plant defense responses, and isolation of new secondary metabolites can be used in controlling pests, pathogens and weeds.

In the last decade, terpenoids have therefore been recognized as interesting and valuable biologically active compounds and research into these secondary metabolites has gathered momentum. The low concentration at which some of them can be extracted and isolated from natural sources may be the main reason why the pharmacological properties of these compounds have not been fully explored and the relevant literature covers almost exclusively studies about extraction, isolation and structural characterization. The recent development of new high-yield procedures made possible the synthesis of some of these compounds in larger quantities so that more detailed studies on their pharmacological properties could be carried out. The data on the synthesis and pharmacological properties of terpene derivatives so gathered should pave the way to detailed studies aimed at searching for efficient terpenoids from novel natural sources and development of new environmentally friendly, cheap and high-yield synthetic routes for acquiring these compounds in large amounts. Although progress has been made in elucidating terpenoid biosynthetic pathways at the gene and enzyme levels, regulation of terpenoid metabolism by factors controlling enzymes and genes of secondary metabolism is still largely unknown. Metabolomics approaches revealing the dynamic changes of many primary and secondary metabolites, in combination with transcriptome data, will help to understand these regulatory networks and facilitate genetic engineering of the secondary metabolism of terpenoid-producing organisms. All these efforts will provide further insights into their pharmacological profiles and lead to the improvement of their biological activity and the development of novel antiviral, anti-cancer, anti-inflammatory and antimicrobial compounds.

ACKNOWLEDGEMENT

The review was written within the frames of the Institutional Research Concept AV0Z50200510.

REFERENCES

[1] Tziveleka, L.A.; Vagias, C.; Roussis, V. Natural products with anti-HIV activity from marine organisms. *Curr. Top. Med. Chem.*, **2003**, *3*, 1512-1535.

[2] Singh, I.P.; Bharate, S.B.; Bhutani, K.K. Anti-HIV natural products. *Curr. Sci.*, **2005**, *89*, 269-290.

[3] De Clercq, E.; Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. *Med. Res. Rev.*, **2000**, *20*, 323-349.

[4] Asres, K.; Seyoum, A.; Veeresham, C.; Bucar, F.; Gibbons S. Naturally derived anti-HIV agents. *Phytother. Res.*, **2005**, *19*, 557-581.

[5] Perez, R.M. Antiviral activity of compounds isolated from plants. *Pharm. Biol.*, **2003**, *41*, 107-157.

[6] Uyeda, M. Metabolites produced by actinomycetes - Antiviral antibiotics and enzyme inhibitors. *Yakugaku Zasshi*, **2004**, *124*, 469-479.

[7] Hale, K.J.; Hummersone, M.G.; Manaviazar, S.; Frigerio M. The chemistry and biology of the bryostatin antitumour macrolides. *Nat. Prod. Rep.*, **2002**, *19*, 413-453.

[8] Fortman, J.L.; Sherman, D.H. Utilizing the power of microbial genetics to bridge the gap between the promise and the application of marine natural products. *ChemBioChem.*, **2005**, *6*, 960-978.

[9] Barbaro, G.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C.T. Highly active antiretroviral therapy: Current state of the art, new agents and their pharmacological interactions useful for improving therapeutic outcome. *Curr. Pharm. Des.*, **2005**, *11*, 1805-1843.

[10] De Clercq, E. New developments in anti-HIV chemotherapy. *Curr. Med. Chem.*, **2001**, *8*, 1543-1572.

[11] Dinda, B.; Debnath, S.; Harigaya, Y. Naturally occurring secoiridoids and bioactivity of naturally occurring iridoids and secoiridoids. A review, part 2. *Chem. Pharm. Bull.*, **2007**, *55*, 689-728.

[12] Dinda, B.; Debnath, S.; Harigaya, Y. Naturally occurring iridoids. A review, part 1. *Chem. Pharm. Bull.*, **2007**, *55*, 159-222.

[13] Jung, M.; Schinazi, R. F. Synthesis and in vitro anti-human immunodeficiency virus activity of artemisinin (qinghaosu)-related trioxanes. *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 931-934.

[14] Romero, M.R.; Serrano, M.A.; Vallejo, M.; Efferth, T.; Alvarez, M.; Marin, J.J.G. Antiviral effect of artemisinin from *Artemisia annua* against a model member of the *Flaviviridae* family, the bovine viral diarrhoea virus (BVDV). *Planta Med.*, **2006**, *72*, 1169-1174.

[15] Singh, S.B.; Felock, P.; Hazuda, D.J. Chemical and enzymatic modifications of integric acid and HIV-1 integrase inhibitory activity. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 235-238.

[16] Singh, S.B.; Zink, D.; Polishook, J.; Valentino, D.; Shafiee, A.; Silverman, K.; Felock, P.; Teran, A.; Vilella, D.; Hazuda, D.J.; Lingham, R.B. Structure and absolute stereochemistry of HIV-1 integrase inhibitor integric acid. A novel eremophilane sesquiterpenoid produced by a *Xylaria sp. Tetrahedron Lett.*, **1999**, *40*, 8775-8779.

[17] Kawaguchi, Y.; Ochi, T.; Takaishi, Y.; Kawazoe, K.; Lee, K.H. New Sesquiterpenes from *Capsicum annuum*. *J. Nat. Prod.*, **2004**, *67*, 1893-1896.

[18] Hoang, V.D.; Tan, G.T.; Zhang, H.J.; Tamez, P.A.; Hung, N.V.; Cuong, N.M.; Soejarto, D.D.; Fong, H.H.; Pezzuto, J.M. Natural anti-HIV agents-part I: (+)-demethoxyepiexcelsin and verticillatol from *Litsea verticillata*. *Phytochemistry*, **2002**, *59*, 325-329.

[19] Xu, Z.; Chang, F.R.; Wang, H.K.; Kashiwada, Y.; McPhail, A.T.; Bastow, K.F.; Tachibana, Y.; Cosentino, M.; Lee, K.H. Anti-HIV agents 45 and antitumor agents 205. Two new sesquiterpenes, leitneridanins A and B, and the cytotoxic and anti-HIV principles from *Leitneria floridana*. *J. Nat. Prod.*, **2000**, *63*, 1712-1715.

[20] Herath, K.B.; Jayasuriya, H.; Bills, G.F.; Polishook, J.D.; Dombrowski, A.W.; Guan, Z.; Felock, P.J.; Hazuda, D.J.; Singh, S.B. Isolation, structure, absolute stereochemistry, and HIV-1 integrase inhibitory activity of integrasone, a novel fungal polyketide. *J. Nat. Prod.*, **2004**, *67*, 872-874.

[21] Mehta, G.; Roy, S. Enantioselective total synthesis of a novel polyketide natural product (+)-integrasone, an HIV-1 integrase inhibitor. *Chem. Commun.*, **2005**, 3210-3212.

[22] Suksamrarn, S.; Wongkrajang, K.; Kirtikara, K.; Suksamrarn, A. Iridoid glucosides from the flowers of *Barleria lupulina*. *Planta Med.*, **2003**, *69*, 877-879.

[23] Zhang, H.J.; Tan, G.T.; Hoang, V.D.; Hung, N.V.; Cuong, N.M.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.S. Natural anti-HIV agents. Part 2: Litseaverticillol A, a prototypic litseane sesquiterpene from *Litsea verticillata*. *Tetrahedron Lett.*, **2001**, *42*, 8587-8591.

[24] Zhang, H.J.; Tan, G.T.; Hoang, V.D.; Hung, N.V.; Cuong, N.M.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.S. Natural anti-HIV agents. Part 3: Litseaverticillols A–H, novel sesquiterpenes from *Litsea verticillata*. *Tetrahedron*, **2003**, 59, 141-148.

[25] Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. Biomimetic Total Synthesis of Litseaverticillols B, E, I, and J and Structural Reassignment of Litseaverticillol E. *Org. Lett.*, **2004**, *6*, 2039-2042.

[26] Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. Illustrating the power of singlet oxygen chemistry in a synthetic context: Biomimetic syntheses of litseaverticillols A-G, I and J and the structural reassignment of litseaverticillol E. *Chem. Eur. J.*, **2005**, *11*, 5899-5907.

[27] Fukami, A.; Nakamura, T.; Kim, Y.P.; Shiomi, K.; Hayashi, M.; Nagai, T.; Yamada, H.; Komiyama, K.; Omura, S. A new anti-influenza virus antibiotic, 10-norparvulenone from *Microsphaeropsis sp* FO-5050. *J. Antibiot.*, **2000**, *53*, 1215-1218.

[28] Wu, Y.C.; Hung, Y.C.; Chang, F.R.; Cosentino, M.; Wang, H.K.; Lee, K.H. Identification of ent-16.beta.,17-Dihydroxykauran-19-oic Acid as an Anti-HIV Principle and Isolation of the New Diterpenoids Annosquamosins A and B from Annona squamosa. *J. Nat. Prod.*, **1996**, *59*, 635-637.

[29] Bruno, M.; Rosselli, S.; Pibiri, I.; Kilgore, N.; Lee, K.H. Anti-HIV Agents Derived from the ent-Kaurane Diterpenoid Linearol. *J. Nat. Prod.*, **2002**, *65*, 1594-1597.

[30] Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kojima, T.; Okamura K.; Morita N. Scopadulciol, an inhibitor of gastric hydrogen ion/potassium-ATPase from *Scoparia dulcis*, and its structure-activity relationships. *J. Nat. Prod.*, **1991**, *54*, 802-809.

[31] Hayashi, T.; Okamura, K.; Tamada, Y.; Iida, A.; Fujita T.; Morita. N. A new chemotype of *Scoparia dulcis*. *Phytochemistry*, **1993**, *32*, 349-352.

[32] Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L.H.; Ferro, E.; Basualdo, I. Scopadulcic acid A and B, new diterpenoids with a novel skeleton, from a Paraguayan crude drug "Typycha kuratu" (*Scoparia dulcis L.*). *Tetrahedron Lett.*, **1987**, *28*, 3693-3696.

[33] Ahmed, M.; Jakupovic, J. Diterpenoids from *Scoparia dulcis*. *Phytochemistry*, **1990**, *29*, 3035-3037.

[34] Hayashi, T. Biologically active diterpenoids from *Scoparia dulcis L.* (*Scrophulariaceae*). *Stud. Nat. Prod. Chem.*, **2000**, *21*, 689-727.

[35] El-Mekkawy, S.; Meselhy, M.R.; Abdel-Hafez, A.A.; Nakamura, N.; Hattori, M.; Kawahata, T.; Otake, T. Inhibition of cytopathic effect of human immunodeficiency virus type-1 by various phorbol derivatives. *Chem. Pharm. Bull*., **2002**, *50*, 523-529.

[36] El-Mekkawy, S.; Meselhy, M.R.; Nakamura, N.; Hattori, M.; Kawahata, T.; Otake, T. 12-O-acetylphorbol-13-decanoate potently inhibits cytopathic effects of human immunodeficiency virus type 1 (HIV-1), without activation of protein kinase C. *Chem. Pharm. Bull.*, **1999**, *47*, 1346-1347.

[37] El-Mekkawy, S.; Meselhy, M.R.; Nakamura, N. Anti-HIV-1 phorbol esters from the seeds of *Croton tiglium*. *Phytochemistry*, **2000**, *53*, 457-464.

[38] Pettit, G.R.; Ducki, S.; Tan, R.; Gardella, R.S.; McMahon, J.B.; Boyd, M.R.; Pettit, G.R.; Blumberg, P.M.; Lewin, N.E.; Doubek, D.L.; Tackett, L.P.; Williams, M.D. Isolation and structure of pedilstatin from a Republic of Maldives *Pedilanthus sp. J. Nat. Prod.*, **2002**, *65*, 1262-1265.

[39] Erickson, K.L.; Beutler, J.A.; Cardellina, J.H.; McMahon, J.B.; Newman, D.J.; Boyd, M.R. HIV-Inhibitory natural products. 22. A novel phorbol ester from *Excoecaria agallocha*. *J. Nat. Prod.*, **1995**, *58*, 769-772.

[40] Bocklandt, S.; Blumberg, P.M.; Hamer, D.H. Activation of latent HIV-1 expression by the potent anti-tumor promoter 12-deoxyphorbol 13-phenylacetate. *Antiviral Res.*, **2003**, *59*, 89-98.

[41] Jiang, R.W.; Ma, S.C.; But, P.P.H.; Mak, T.C.W. Isolation and characterization of spirocaesalmin, a novel rearranged vouacapane diterpenoid from *Caesalpinia minax Hance*. *J. Chem. Soc. Perkin Trans. I*, **2001**, 2920-2923.

[42] Jiang, R.W.; Ma, S.C.; But, P.P.; Mak, T.C. New antiviral cassane furanoditerpenes from *Caesalpinia minax*. *J. Nat. Prod.*, **2001**, *64*, 1266-1272.

[43] Kalauni, S.K.; Awale, S.; Tezuka, Y.; Banskota, A.H.; Linn, T.Z.; Kadota, S. Methyl migrated cassane-type furanoditerpenes of *Caesalpinia crista* from Myanmar. *Chem. Pharm. Bull.*, **2005**, *53*, 1300-1304.

[44] Jiang, R.W.; Ma, S.C.; He, Z.D.; Huang, X.S.; But, P.P.; Wang, H.; Chan, S.P.; Ooi, V.E.; Xu, H.X.; Mak, T.C. Molecular structures and antiviral activities of naturally occurring and modified cassane furanoditerpenoids and friedelane triterpenoids from *Caesalpinia minax*. *Bioorg. Med. Chem.*, **2002**, *10*, 2161-2170.

[45] Jiang, R.W.; But P.P.H.; Ma, S.C.; Ye C.W.; Chan S.P.; Mak T.C.W. Structure and antiviral properties of macrocaesalmin, a novel cassane furanoditerpenoid lactone from the seeds of *Caesalpinia minax Hance*. *Tetrahedron Lett.*, **2002**, *43*, 2415-2418.

[46] Calabrese, C.; Berman, S.H.; Babish, J.G.; Ma, X.; Shinto, L.; Dorr, M.; Wells, K.; Wenner, C.A.; Standish, L.J. A phase I trial of andrographolide in HIV positive patients and normal volunteers. *Phytother. Res.*, **2000**, *14*, 333-338.

[47] Wiart, C.; Kumar, K.; Yusof, M.Y.; Hamimah, H.; Fauzi, Z.M.; Sulaiman, M. Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* Nees, inhibitor of herpes simplex virus type 1. *Phytother. Res.*, **2005**, *19*, 1069-1070.

[48] Duan, H.; Takaishi, Y.; Bando, M.; Kido, M.; Imakura, Y.; Lee, K.H. Novel sesquiterpene esters with alkaloid and monoterpene and related compounds from *Tripterygium hypoglaucum*: a new class of potent anti-HIV agents. *Tetrahedron Lett.*, **1999**, *40*, 2969-2972.

[49] Gustafson, K.R.; Munro, M.H.G.; Blunt, J.W.; Cardellina, J.H.; McMahon, J.B.; Gulakowski, R.J.; Cragg, G.M.; Cox, P.A.; Brinen, L.S.; Clardy, J.; Boyd, M.R. HIV inhibitory natural products. 3. Diterpenes from *Homalanthus acuminatus* and *Chrysobalanus icaco*. *Tetrahedron*, **1991**, *47*, 4547-4554.

[50] Fujiwara, M.; Ijichi, K.; Tohuhisa, K.; Katsuura, K.; Wang, G.Y.S.; Uemura, D.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. Ingenol derivatives are highly potent and selective inhibitors of HIV replication *in vitro*. *Antiviral Chem. Chemother.*, **1996**, *7*, 230-236.

[51] Fujiwara, M.; Okamoto, M.; Ijichi, K.; Tokuhisa, K.; Hanasaki, Y.; Katsuura, K.; Uemura, D.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. Upregulation of HIV-1 replication in chronically infected cells by ingenol derivatives. *Arch. Virol.*, **1998**, *143*, 2003-2010.

[52] Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katsuura, K.; Shigeta, S.; Konno, K.; Wang, G.Y.S.; Uemura, D.; Yokota, T.; Baba, M. Mechanism of selective inhibition of human immunodeficiency virus by ingenol triacetate. *Antimicrob. Agents Chemother.*, **1996**, *40*, 271-273.

[53] Rashid, M.A.; Gustafson, K.R.; Boyed, M.R. HIV-inhibitory cembrane derivatives from a Philippines collection of the soft coral *Lobophytum species*. *J. Nat. Prod.*, **2000**, *63*, 531-533.

[54] Hirsch, S.; Rudi, A.; Kashman, Y.; Loya, Y. New avarone and avarol derivatives from the marine sponge *Dysidea cinerea*. *J. Nat. Prod.*, **1991**, *54*, 92-97.

[55] Schroder, H.C.; Begin, M.E.; Klocking, R.; Matthes, E.; Sarma, A.S.; Gai, M.; Muller, W.E.G. Avarol restores the altered prostaglandin and leukotriene metabolism in monocytes infected with human immunodeficiency virus type 1. *Virus Res.*, **1991**, *21*,213-223.

[56] Loya, S.; Hizi, A. The inhibition of human immunodeficiency virus type 1 reverse transcriptase by avarol and avarone derivatives. *FEBS Lett.*, **1990**, *269*, 131-134.

[57] Shahidul, A.M.; Quader, M.A.; Rashid, M.A. HIV-inhibitory diterpenoid from *Anisomeles indica*. *Fitoterapia* **2000**, *71*, 574-576

[58] Siamopoulou, P.; Bimplakis, A.; Iliopoulou, D.; Vagias, C.; Cos, P.; Vanden Berghe, D.; Roussis, V. Diterpenes from the brown algae *Dictyota dichotoma* and *Dictyota linearis*. *Phytochemistry* **2004**, *65*, 2025-2030.

[59] Barbosa, J.P.; Pereira, R.C.; Abrantes, J.L.; dos Santos, C.C.C.; Rebello, M.A.; Frugulhetti, I.C.D.P.; Teixeira, V.L. *In vitro* antiviral diterpenes from the Brazilian brown alga *Dictyota pfaffii*. *Planta Med.*, **2004**, *70*, 856-860.

[60] Rodriguez, A.D.; Ramirez, C.; Cobar, O.M. Briareins C-L, 10 new briarane diterpenoids from the common Caribbean gorgonian *Briareum asbestinum* (Pallas). *J. Nat. Prod.*, **1996**, *59*, 15-22.

[61] Sung, P.J.; Sheu, J.H.; Xu, J.P. Survey of briarane-type diterpenoids of marine origin. *Heterocycles*, **2002**, *57*, 535-579.

[62] Subrahmanyam, C.; Kulatheeswaran, R.; Ward, R.S. Briarane Diterpenes from the Indian Ocean Gorgonian *Gorgonella umbraculum*. *J. Nat. Prod.*, **1998**, *61*, 1120-1122.

[63] Shen, Y.C.; Lin, Y.C.; Chiang, M.Y. Juncenolide A, a new briarane from the Taiwanese gorgonian *Junceella juncea*. *J. Nat. Prod.*, **2002**, *65*, 54-56.

[64] Shen, Y.C.; Lin, Y.C.; Ko, C.L.; Wang, L.T. New briaranes from the Taiwanese gorgonian *Junceella juncea*. *J. Nat. Prod.*, **2003**, *66*, 302-305.

[65] Lin, Y.C.; Huang, Y.L.; Khalil, A.T.; Chen, M.H.; Shen, Y.C. Juncenolides F and G, two new briarane diterpenoids from Taiwanese gorgonian *Junceella juncea*. *Chem. Pharm. Bull.*, **2005**, *53*, 128-130.

[66] Iwagawa, T.; Nishitani, N.; Kurosaki, S.; Okamura, H.; Nakatani, M.; Doe, M.; Takemura, K. Briarlides, briarane diterpenes from a gorgonian *Briareum sp*. *J. Nat. Prod.*, **2003**, *66*, 1412-1415.

[67] Iwagawa, T.; Nishitani, N.; Nakatani, M.; Doe, M.; Morimoto, Y.; Takemura, K. Briarlides I-R, briarane diterpenes from a gorgonian *Briareum sp*. *J. Nat. Prod.*, **2005**, *68*, 31-35.

[68] Iwasaki, J.; Ito, H.; Aoyagi, M.; Sato, Y.; Iguchi, K. Briarane-type diterpenoids from the Okinawan soft coral *Pachyclavularia violacea*. *J. Nat. Prod.*, **2006**, *69*, 2-6.

[69] Shen, Y.C.; Wu, Y.R.; Lin, J.J.; Lo, K.L.; Kuo, Y.C.; Khalil, A.T. Eight new diterpenoids from soft coral *Cespitularia hypotentaculata*. *Tetrahedron*, **2007**, *63* 10914-10920.

[70] Sun, I.C.; Wang, H.K.; Kashiwada, Y.; Shen, J.K.; Cosentino, L.M.; Chen, C.H.; Yang, L.M.; Lee, K.H. Anti-AIDS Agents. 34. Synthesis and Structure-Activity Relationships of Betulin Derivatives as Anti-HIV Agents. *J. Med. Chem.*, **1998**, *41*, 4648-4657.

[71] Battinelli, L.; Mengoni, F.; Lichtner, M.; Mazzanti, G.; Saija, A.; Mastroianni, C.M.; Vullo, V. Effect of limonin and nomilin on HIV-1 replication on infected human mononuclear cells. *Planta Med.*, **2003**, *69*, 910-913.

[72] Sunthitikawinsakul, A.; Kongkathip, N.; Kongkathip, B.; Phonnakhu, S.; Daly, J.W.; Spande, T.F.; Nimit, Y.; Napaswat, C.; Kasisit, J.; Yoosook, C. Anti-HIV-1 limonoid: first isolation from *Clausena excavata*. *Phytother. Res.*, **2003**, *17*, 1101-1103.

[73] Alche, L.E.; Ferek, G.A.; Meo, M.; Coto, C.E.; Maier, M.S. An antiviral meliacarpin from leaves of *Melia azedarach L. Z. Naturforsch. C*, **2003**, *58*, 215-219.

[74] Tanaka, R.; Wada, S.; Kinouchi, Y.; Tokuda, H.; Matsunaga, S. A new seco-abietane-type diterpene from the stem bark of *Picea glehni*. *Planta Med.*, **2004**, *70*, 877-880.

[75] Sawadjoon, S.; Kittakoop, P.; Isaka, M.; Kirtikara, K.; Madla, S.; Thebtaranonth, Y. Antiviral and antiplasmodial spirodihydrobenzofuran terpenes from the fungus *Stachybotrys nephrospora*. *Planta Med.*, **2004**, *70*, 1085-1087.

[76] Wellington, K.D.; Cambie, R.C.; Rutledge, P.S.; Bergquist, P.R. Chemistry of sponges., 19. Novel bioactive metabolites from *Hamigera tarangaensis*. *J. Nat. Prod.*, **2000**, *63*, 79-85.

[77] Clive, D.L.J.; Wang, J. Synthesis of (±)-hamigeran B, (-)-hamigeran B, and (±)-1-epi-hamigeran B: use of bulky silyl groups to protect a benzylic carbon-oxygen bond from hydrogenolysis. *J. Org. Chem.*, **2004**, *69*, 2773-2784.

[78] Trost, B.M.; Pissot-Soldermann, C.; Chen, I. A short and concise asymmetric synthesis of hamigeran B. *Chem-A Eur. J.*, **2005**, *11*, 951-959.

[79] Hara, N.; Asaki, H.; Fujimoto, Y.; Gupta, Y.K.; Singh, A.K.; Sahai, M. Clerodane and ent-halimane diterpenes from *Polyalthia longifolia*. *Phytochemistry*, **1995**, *38*, 189-194.

[80] Kinouchi, Y.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. Potential antitumor-promoting diterpenoids from the stem bark of *Picea glehni*. *J. Nat. Prod.*, **2000**, *63*, 817-820.

[81] Minagawa, K.; Kouzuki, S.; Yoshimoto, J.; Kawamura, Y.; Tani, H.; Iwata, T.; Terui, Y.; Nakai, H.; Yagi, S.; Hattori, N.; Fujiwara, T.; Kamigauchi, T. Stachyflin and acetylstachyflin, novel anti-influenza A virus substances, produced by *Stachybotrys sp*. RF-7260. I. Isolation, structure elucidation and biological activities. *J. Antibiot.*, **2002**, *55*, 155-164.

[82] Look, S.A.; Fenical, W.; Jacobs, R.S.; Clardy, J. The pseudopterosins: anti-inflammatory and analgesic natural products from the sea whip *Pseudopterogorgia elisabethae*. *Proc. Natl. Acad. Sci. USA*, **1986**, *83*, 6238-6240.

[83] Look, S.A.; Fenical, W.; Matsumoto, G.K.; Clardy, J. The pseudopterosins: a new class of antiinflammatory and analgesic diterpene pentosides from the marine sea whip *Pseudopterogorgia elisabethae* (*Octocorallia*). *J. Org. Chem.*, **1986**, *51*, 5140-5145.

[84] Look, S.A.; Fenical, W. The seco-pseudopterosins, new anti-inflammatory diterpene-glycosides from a Caribbean gorgonian octocoral of the genus *Pseudopterogorgia*. *Tetrahedron*, **1987**, *43*, 3363-3370.

[85] Roussis, V.;Wu, Z.; Fenical, W.; Strobel, S.A.; Van Duyne, G.D.; Clardy, J. New anti-inflammatory pseudopterosins from the marine octocoral *Pseudopterogorgia elisabethae*. *J. Org. Chem.*, **1990**, *55*, 4916-4922.

[86] Mydlarz, L.D.; Jacobs, R.S.; Boehnlein, J.; Kerr, R.G. Pseudopterosin biosynthesis in *Symbiodinium sp*., the dinoflagellate symbiont of *Pseudopterogorgia elisabethae*. *Chem. Biol.*, **2003**, *10*, 1051-1056.

[87] Rodriguez, I.I.; Shi, Y.P.; Garcia, O.J.; Rodriguez, A.D.; Mayer, A.M.S.; Sanchez, J.A.; Ortega-Barria, E.; Gonzalez, J. New pseudopterosin and seco-pseudopterosin diterpene glycosides from two Colombian isolates of *Pseudopterogorgia elisabethae* and their diverse biological activities. *J. Nat. Prod.*, **2004**, *67*, 1672-1680.

[88] Apers, S.; Cimanga, K.; Vanden Berghe, D.; Van Meenen, E.; Longanga, A.O.; Foriers, A.; Vlietinck, A.; Pieters, L. Antiviral activity of simalikalactone D, a quassinoid from *Quassia africana*. *Planta Med.*, **2002**, *68*, 20-24.

[89] El Sayed, K.A.; Hamann, M.T.; Hashish, N.E.; Shier, W.T.; Kelly, M.; Khan, A.A. Antimalarial, antiviral, and antitoxoplasmosis norsesterterpene peroxide acids from the Red Sea sponge *Diacarnus erythraeanus*. *J. Nat. Prod.*, **2001**, *64*, 522-524.

[90] Barrow, C.J.; Blunt, J.W.; Munro, M.H.G. Autooxidation studies on the marine sesterterpene tetronic acid, variabilin. *J. Nat. Prod.*, **1989**, *52*, 346-359.

[91] Jimenez, C.; Quinoa, E.; Crews, P. Novel marine sponge alkaloids. 3. .beta.-Carbolinium salts from *Fascaplysinopsis reticulata*. *Tetrahedron Lett.*, **1991**, *32*, 1843-1846.

[92] Jimenez, C.; Quinoa, E.; Adamczeski, M.; Hunter, L.M.; Crews, P. Tryptophan-derived pigments and accompanying sesterterpenes from *Fascaplysinopsis reticulata*. *J. Org. Chem.*, **1991**, *56*, 3403-3410.

[93] Rowland, S.J.; Belt, S.T.; Wraige, E.J.; Masse, G.; Roussakis, C.; Robert, J.M.; Effects of temperature on polyunsaturation in cytostatic lipids of *Haslea ostrearia*. *Phytochemistry*, **2001**, *56*, 597-602.

[94] Iimura, S.; Oka, M.; Narita, Y.; Konishi, M.; Kakisawa, H.; Gao, Q.; Oki, T. Terpestacin, a novel syncytium formation inhibitor, isolated from *Arthrinium species*. *Tetrahedron Lett.*, **1993**, *34*, 493-496.

[95] Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. Terpestacin, a new syncytium formation inhibitor from *Arthrinium sp*. *J. Antibiot.*, **1993**, *46*, 367-373.

[96] Oka, M.; Iimura, S.; Narita, Y.; Furumai, T.; Konishi, M.; Oki, T.; Gao, Q.; Kakisawa, H. Stereochemistry and biosynthesis of terpestacin, a new syncytium formation inhibitor. *J. Org. Chem.*, **1993**, *58*, 1875-1881.

[97] Schlegel, B.; Schmidtke, M.; Dorfelt, H.; Kleinwachter, P.; Gräfe, U. (-)-Terpestacin and L-tenuazonic acid, inducers of pigment and aerial mycelium formation by Fusarium *culmorum* JP 15. *J. Basic Microbiol.*, **2001**, *41*, 179-183.

[98] Nihashi, Y.; Lim, C.-H.; Tanaka, C.; Miyagawa, H.; Ueno, T. Phytotoxic sesterterpene, 11-epiterpestacin, from *Bipolaris sorokiniana* NSDR-011. *Biosci. Biotechnol. Biochem.*, **2002**, *66*, 685-688.

[99] Randazzo, G.; Fogliano, V.; Ritieni, A.; Mannina, L.; Rossi, E.; Scarallo, A.; Segre, A.L. Proliferin, a new sesterterpene from *Fusarium proliferatum*. *Tetrahedron*, **1993**, *49*, 10883-10896.

[100] Jung, H. J.; Lee, H. B.; Kim, C. J.; Rho, J.R.; Shin, J.; Kwon, H. J. Anti-angiogenic activity of terpestacin, a bicyclo sesterterpene from *Embellisia chlamydospora*. *J. Antibiot.*, **2003**, *56*, 492-496.

Received: September 01, 2008 Revised: February 01, 2009 Accepted: February 01, 2009