SURVEY OF OXYGENATED 2,11-CYCLIZED CEMBRANOIDS OF MARINE ORIGIN‡

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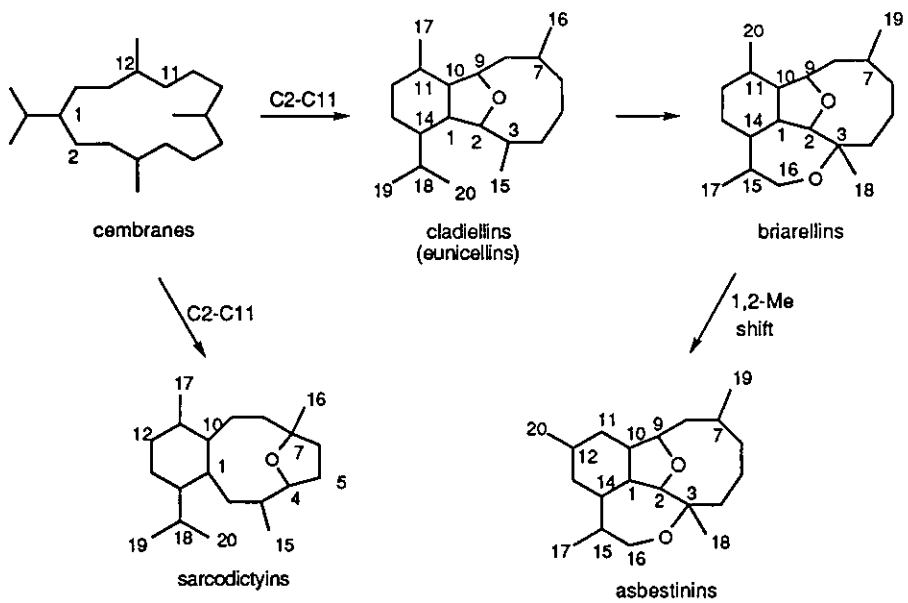
Abstract - The structure, source, and biological activities of the many known members of the four classes of oxygenated 2,11-cyclized cembranoid natural products are compiled in tabular form. The cladiellins, briarellins, asbestinins, and sarcodictyins have been purposefully organized to highlight biological activity interrelationships.

During the past thirty years, many 2,11-cyclized cembranoids containing one of the heterocyclic frameworks shown in Scheme 1 have been isolated from marine invertebrates.[1,2] These natural products are all found in coelenterates (phylum: Coelenterata (also called Cnidaria), class Anthozoa, subclass Octocorallia). A survey (up to December 1997) of the cyclized cembranoids extracted from octocorals[3]



Scheme 1. Presumed biosynthesis of the four known classes of oxygenated 2,11-cyclized cembranoids. The numbering schemes shown are those presently in use.

‡This paper is dedicated to Dr. Bernhard Withop on the occasion of his 80th birthday.

is presented herein. The focus is on the large structural diversity of this class of natural products as well as the varied biological and pharmacological activities of its members. As a consequence, the compounds have been arranged, when possible, so that any structure-activity relationship is brought to light.

The 2,11-cyclized cembranoids have been classified into four categories:[1] the cladiellins (also known as eunicellins), the briarellins, the asbestinins, and the sarcodictyins. A lack of general agreement has surrounded the nomenclature of these related systems. Select authors have made recourse uniquely to cladiellane (or eunicellane) and asbestinane nomenclature, which only gives specific consideration to the carbon framework involved. However, according to these guidelines, the cladiellins, briarellins, and sarcodictyins should all be called cladiellanes. Proper distinction of compounds that possess different structures and distinctive chemical properties can consequently not be made For instance, the sarcodictyins, unlike the cladiellins, are known to be unstable when their C11-OH functionality is not esterified.[4,5] In our view, a nomenclature system that allows differentiation of the 2,11-cyclized cembranoids according to the presence of characteristic ether rings in their structure is greatly preferred.

These marine metabolites have unique structures that, so far, have not been found in natural products isolated from terrestrial sources. The cladiellins, the briarellins, and the asbestinins are seen to be characterized by a novel tricyclic diterpenoid structure associated with an unusual ether bridge between C-2 and C-9. The briarellins and the asbestinins feature an additional seven-membered ether ring between C-8 and C-16. In the sarcodictyins, there is only one ether bridge and it is found between C-4 and C-7 unlike the others.

Eunicellin (**2**) (Table 1), a cladiellin isolated in 1968 from the Mediterranean gorgonian *Eunicella stricta*,[6] was the first reported 2,11-cyclized cembranoid marine natural product. The structure of the first isolated asbestinin was determined and published only in 1980.[7] In this report, Faulkner proposed that the cladiellins are biosynthesized by 2,11-cyclization (cembrane nomenclature) of the cembrane ring skeleton and that the asbestinins are derived from the cladiellins by seven-membered ether formation between C-3 and C-16 (asbertinin nomenclature) and migration of a methyl group from C-11 to C-12 (Scheme 1). Although no systematic study of the biosynthesis of these cyclized cembranoids has been reported, the discovery of a cembrane metabolite with cladiellin metabolites in *Alcyonium molle* and with asbestinins in the Australian gorgonian *Briareum steckii* is consistent with this hypothesis.[8]

The first briarellins were isolated by Rodríguez and Cóbar in 1995 .[9] They initially suggested that this class constituted biosynthetic intermediates between the cladiellins and asbestinins as depicted in Scheme 1. Subsequent to formation of the oxepane ring, asbestinins might originate upon migration of a methyl group. The hypothesis that a suprafacial 1,2-methyl shift is involved requires that the methyl at C-12 in the asbestinins be on the same structural surface as the methyl at C-11 in the briarellins.[10] This is the case for briarellins E-I (**69-73**). However, the fact that briarellins A-D (**65-68**) (Table 2) possess opposite stereochemistry at C-11 with respect to the asbestinins (Table 3) appears inconsistent with the

biosynthetic hypothesis since a very unlikely antarafacial methyl migration must operate.[10] At this moment, it is unclear whether briarellins are true biosynthetic precursors of asbestinins.

The sarcodictyins are also believed to be secondary metabolites that derive biosynthetically from cembrane precursors by 2,11-cyclization.[1,4]

In Tables 1-4, the title compounds are compiled by chemical class. The structure, source, and biological activities are indicated.

1. THE CLADIELLINS (Table 1):

The cladiellins (also called eunicellins) represent the most abundant class of 2,11-cyclized cembranoid natural products. Most cladiellins have been isolated from octocorals of the orders Alcyonacea and Gorgonacea. On the other hand, (6*E*)-11-acetoxycladiellin (**48**) has been extracted from *Pachyclavularia* species that belong to the order Stolonifera.[11]

The 64 cladiellins feature a large array of functionalities (Figure 1). In these secondary metabolites, the C-3, C-6, C-7, C-11 carbons (indicated with #) are always either oxygenated or sp^2-hybridized. The C-3 center is the same in all the cladiellins isolated so far. The degree of functionalization at the other centers (indicated with *) varies. As shown at the end of Table 1, a few products lacking the ether bridge have also been isolated. Nevertheless, they are considered to be cladiellins.

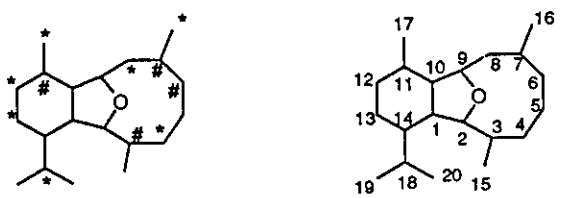


Figure 1: Functionalized centers in the cladiellins.

In Table 1, these cladiellins not previously assigned a common name were named according to a semi-systematic nomenclature based on the cladiellin framework (Figure 1), as has become the norm.[1,8,12,13]

Several cladiellins have been subjected to X-Ray crystallographic analysis in order to establish their relative configuration as indicated in Table 1. Determination of the absolute configuration of a cladiellin was first realized with litophynin C (**8**).[14] Due to the complexity of the macrocyclic system, the graphical representation of the cladiellins is not trivial. The stereocenters C-2 and C-9 of the ether bridge are usually represented as depicted in Table 1. As a reference, the absolute configurations of C-2 and C-9 in

sclerophytin C (**18**) are respectively *R* and *S*. [15] Later, the absolute configuration of the cladiellins was confirmed by the modified Mosher method.[16] The absolute configuration of 6-acetoxycladiella-7(16),11-dien-3-ol (**44**) was corroborated by total synthesis.[17]

The cladiellins exhibit interesting and varied biological activities of ecological, agrochemical, and pharmacological significance. Their molluscicidal and repellent activity against the muricid gastropods of the genus Drupella, ichthyotoxicity, brine shrimp lethality, and inhibition of cell division in fertilized starfish eggs suggest the natural function of these secondary metabolites appears to be the defense of octocorals from predators.[3] Interestingly, the presence of an acetate at C-3 is necessary for good toxicity against brine shrimp larvae.[18] 3-Acetoxycladiella-6,11-diene (**42**) is over 100 times more toxic to brine shrimp larvae than its corresponding non-esterified analog **41**. Ophirin (**37**) is also more toxic than its hydrolyzed analog. Since 3-acetoxycladiella-6,11-diene (**42**) is more active than calicophirin B (**40**) which, in turn, is more toxic than ophirin (**37**), the influence of acetoxy groups on the biological activity does not seem to be additive. Further comparison between 3-acetoxycladiella-6,11-diene (**42**) and cladiellin (**5**) shows that the C-11/C-12 endocyclic double bond in the six-membered ring is preferable to the C-11/C-17 exocyclic option for improved brine shrimp lethality. In another comparison, cladiellaperoxide (**23**) displays toxicity at a concentration of 30 ppm but cladielisin (**20**), its reduced analog, is inactive.[19]

Certain cladiellins such as litophynin A (**6**) and B (**7**) are recognized to exhibit insect growth inhibitory activity against the silkworm *Bombyx mori L.*[20] The presence of a butanoyloxy substituent at C-8 in litophynin B is responsible for its increased inhibitory activity compared to lytophinin A. However, a hydroxyl group at C-12 is detrimental because litophynin C is less active than litophynin A.

The cladiellins also possess pharmacological potential. Several members have been reported to be antiinflammatory and antitumor agents. Palmonine B (**54**) is active against P-388 mice lymphoma and MEL28 human melanoma. However, the other palmonines show low *in vitro* cytotoxicity against various cell lines.[21] The seemingly most potent cladiellin is sclerophytin A (**28**). This natural product is cytotoxic against L1210 leukemia cells at a concentration of only 1 ng/mL.[22a] This very powerful compound or one of its analogs could therefore have the potential to become an important antitumor drug. Knowledge of the selectivity and mechanism of action of this secondary metabolite would be welcomed. No systematic study of this type has been undertaken on any bioactive cladiellin. Very recently, cladiellin (**5**), astrogorgin (**39**), ophirin (**37**), and calicophirin B (**40**) were reported to be inhibitors of cAMP phosphodiesterase.[22b] This appears to be the underlying reason for their antiinflammatory activity.

Very few reports have appeared dealing with the chemistry of the cladiellin system. Recently, Overman published an enantioselective synthesis of acetoxycladiella-7(16),11-dien-3-ol (**44**).[17] In this approach, the tetrahydrofuran was constructed by a stereoselective Prins-pinacol condensation-rearrangement and the nine-membered ring was ultimately closed by a Nozaki-Utimoto-Kishi Cr(II)/Ni(II)-mediated cyclization. The construction of a model of a nine-membered ring ether similar to the one present in the

cladiellins was achieved by Hoffmann via an annulation-fragmentation strategy.[23] Otherwise, interesting indications of the chemical behavior of the cladiellin system have been provided in several isolation reports.[24-27] These reactions were performed in order to confirm the structure of the reported natural products by chemical interconversion.

2. THE BRIARELLINS (Table 2):

Only two recent papers report the isolation of briarellin compounds from the Caribbean gorgonian *Briareum asbestinum*.[9,10] As a consequence, there are only ten known members of this class. Although the absolute configuration of these 2,11-cyclized cembranoids has not been established, it is reasonable to assume that it is identical to that of the corresponding cladiellins since the latter likely serve as their biosynthetic precursors. As a consequence, the stereochemical formulas provided in Table 2 are consistent with the cladiellin absolute configuration and differ from that utilized by their discoverers. However, one must be mindful that the absolute configuration of the briarellins remains to be confirmed. Interestingly, a *seco*-briarellin (**74**) in which the macrocyclic ring is cleaved has been isolated.[9]

Only two briarellins have been tested for pharmacological activity . Briarellins A (**65**) and E (**69**) displayed modest *in vitro* cytotoxicity against HeLa cells with an estimated IC_{50} of 20 μg/mL.[9]

There exists no report giving any indication on the chemistry of the briarellins.

3. THE ASBESTININS (Table 3):

The 33 asbestinins presented in Table 3 have all been isolated from *Briareum asbestinum* of the order Gorgonacea. Since the asbestinins are believed to be derived biosynthetically from the cladiellins, their absolute configuration can be expected to correspond to that of the cladiellins. Therefore, unlike the structural formulas depicted in the literature, it was elected to depict the asbestinins herein with the corresponding absolute stereochemistry. However, it should be emphasized that, so far, the absolute stereochemistry of no asbestinin has been established. Like the cladiellins, the asbestinins feature a variety of functionalities (Figure 2). Unlike the cladiellins, C-12, C-13 and C-15 in the asbestinins are never oxygenated. Unlike the briarellins, no asbestinin containing a carbonyl at C-16 has been isolated.

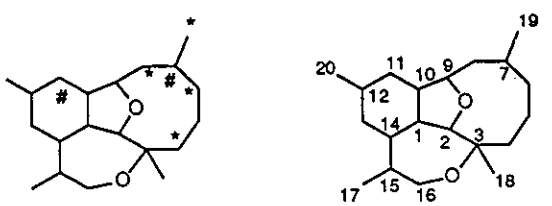


Figure 2: Functionalized centers in the asbestinins.

The asbestinins feature interesting pharmacological activities different from the two previous families (Table 3). Some asbestinins exhibit not only strong antitumor and antimicrobial activities, but also histamine and acetylcholine antagonism.

Antimicrobial activity has been reported only for several 4-deoxyasbestinin derivatives. On the other hand, asbestinin-6 (79), asbestinin-7 (97), asbestinin-8 (82), asbestinin-9 (107), and asbestinin-10 (108), which are all oxygenated at C-4, exhibit no antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, or *Staphylococcus aureus*.[28] Accordingly, it seems that oxygenation of C-4 inhibits antimicrobial activity. This is seemingly not the case for the stereochemistry of the double bond in the nine-membered ring ether, since 11-acetoxy-4-deoxyasbestinins B (75) and D (77) exhibit comparable activities, as do deoxyasbestinins A (76) and C (78).[29] Similarly, upon comparison of the antimicrobial activities of 77 and 78, it appears that substitution at C-11 with either an acetoxy or butanoyl group is inconsequential.

Asbestinin-5 (95) antagonizes the effect of acetylcholine at a higher level than asbestinin-1 (81) at the same concentration.[30] Therefore, an allylic alcohol moiety in the nine-membered ring is more conducive than an (*E*)-C-6/C-7 double bond to improved acetylcholine antagonism. However, both of these functional groups seem to have approximately the same effect on antitumor activity, as suggested by comparison of the IC_{50} values for asbestinin-6 (79) and asbestinin-7 (97)[28] toward various cell lines. As previously noted in the case of antimicrobial properties, the stereochemistry of the double bond in the nine-membered ring ether similarly has no influence on antitumor activity.

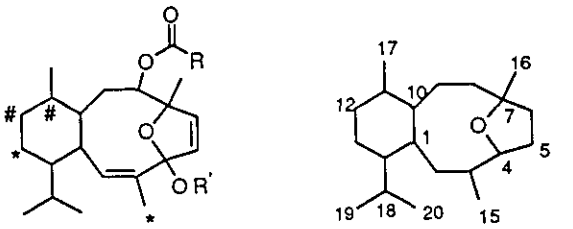
The presence of a carbonyl at C-11 as in asbestinin-8 (82) is detrimental to antitumor activity. When viewed in the context of asbestinin-6 (79), the same functionality is seen to affect cytotoxicity levels against various human tumor cell lines.[28] Asbestinin-9 (107) and asbestinin-10 (108) also show different selectivities, another indicator that the substituent at C-11 is an important factor in controlling antitumor activity. Since 87 is not cytotoxic against CHO-K1 cell lines[31] unlike 11-acetoxy-4-deoxyasbestinins B (75) and D (77), the possibility exists that the nine-membered ring ether may possibly play a role in the antitumor properties of the asbestinins.

Only few indicators of the chemistry of the asbestinins have been reported.[7, 30, 31] The total synthesis of an asbestinin has yet to be achieved.

4. THE SARCODICTYINS (Table 4):

Sarcodictyins A-F (109-114) were the first natural products possessing the skeleton shown in Figure 3 to be isolated.[4,5] The valdivones (115-119),[32] eleuthosides (120-121)[33] and the recently reported compound, eleutherobin (122),[34] feature a very similar framework. Therefore, they have been collectively classified as sarcodictyins. Taxonomically, the sarcodictyins, except for sarcodictyin A, have been

extracted from species derived from entirely different orders. The producing organism of the valdivones, *Alcyonium valdivae*, as well as that responsible for generation of the eleuthosides and eleutherobin, *Eleutherobia* species, belong to the order Alcyonacea. In contrast, the source of sarcodictyins B-F, *Sarcodictyon roseum*, is from the order Stolonifera. In contrast, sarcodictyin A has been extracted from both *Sarcodictyon roseum* and *Eleutherobia aurea*.



oxygenated or unsaturated carbons in all of the sarcodictyins
• oxygenated or unsaturated carbons in some sarcodictyins
R' = H, Me

Figure 3: Functionalized centers in the sarcodictyins.

Few sarcodictyins have been reported so far. Unlike the other 2,11-cyclized cembranoids, the ether bridge in the sarcodictyins is located between C-4 and C-7 (Figure 3). In all the known members, C-2/C-3 and C-5/C-6 double bonds are present, and the C-4 and C-8 centers are oxygenated. We note that the methyl ketals(**116**)and(**118**)of valdivone A (**115**) and B (**117**) should be regarded as artifacts of the isolation procedure since the products were extracted with methanol.[32] Eleuthosides A and B, sarcodictyins A-F, and eleutherobin feature *N*-methylurocanic esters at C-8. Various other ester residues are found at this position in the valdivones. Arabinose acetate subunits are linked to C-15 in the eleuthosides and eleutherobin.

The absolute configuration of sarcodictyin A and B was determined according to Horeau's method.[4] The structure and absolute configuration of sarcodictyin A and eleutherobin were very recently confirmed by total synthesis.[35,36] Satisfyingly, the sarcodictyin absolute configuration corresponds to that of the cladiellin family.

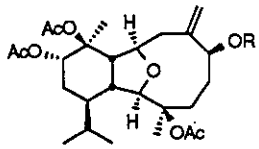
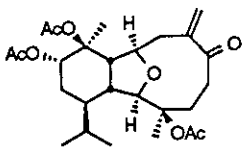
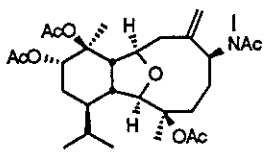
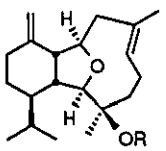
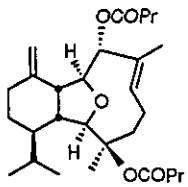
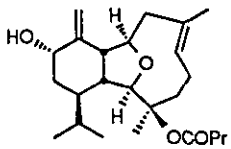
As a class, the sarcodictyins possess fascinating pharmacological activities. Although the valdivones exhibit anti-inflammatory properties, they proved to be inactive against a standard panel of bacteria and fungi.[32] On the other hand, sarcodictyins A and B, and, particularly, eleutherobin exhibit potent antitumor activities.[34,37] Eleutherobin is roughly 10-fold more cytotoxic than sarcodictyins A and B against breast, renal ovarian and lung cancer cells. Amazingly, eleutherobin featured a 100-fold higher potency over the average for compounds tested against the National Cancer Institute's cell line panel.[34] Sarcodictyin A and B as well as eleutherobin were proven to display the same mechanism of action as

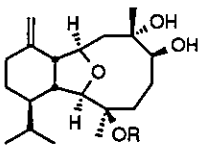
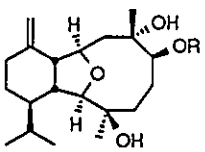
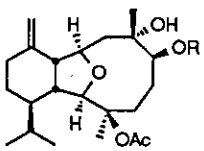
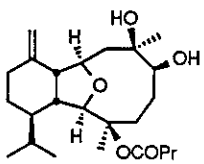
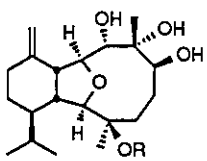
taxol: they prevent cell division by inducing tubulin polymerization and microtubule stabilization.[37,38] Therefore, eleutherobin constitutes a very promising lead candidate for use as an anticancer drug.

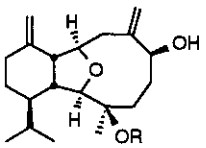
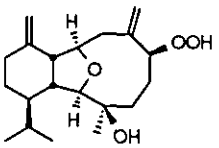
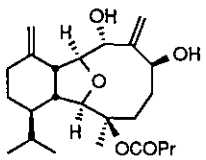
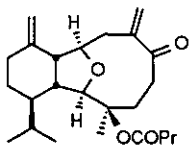
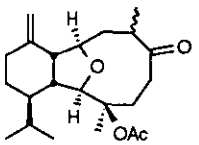
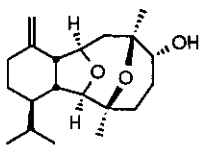
As mentioned previously, sarcodictyin A and eleutherobin have very recently been synthesized by Nicolaou.[35,36] In their approach, the macrocyclic ring was constructed by an acetylide-aldehyde addition. Two active analogs of eleutherobin have also been designed and prepared.[36] More complete structure-activity relationship studies have been undertaken.

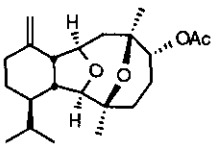
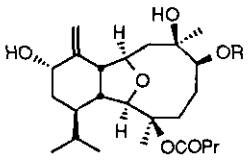
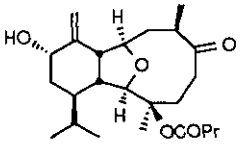
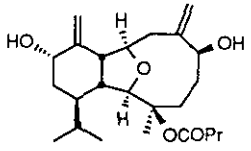
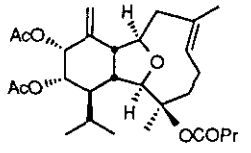
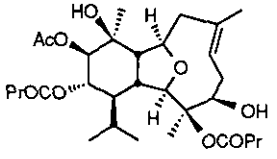
In conclusion, a large variety of 2,11-cyclized cembranoid natural products has been discovered in recent years. The structural diversity of the four constituent classes and their diverse biological activities have been presented. These compounds, similarly to many other natural products,[39] could have important ecological, agrochemical and pharmaceutical applications. The present compilation constitutes a potentially useful resource for the design and synthesis of unnatural analogs with improved biological activity.

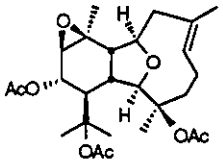
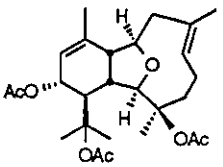
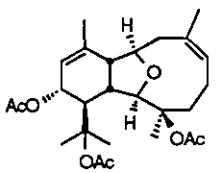
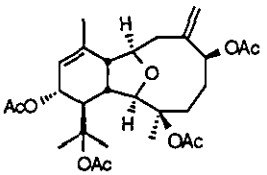
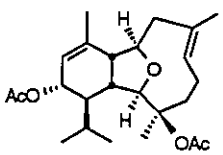
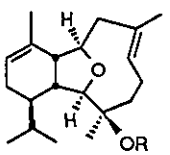
Table 1: The Cladiellins.

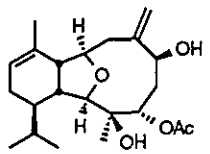
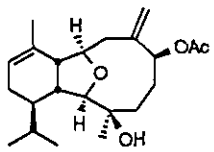
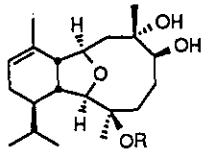
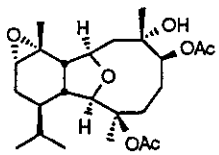
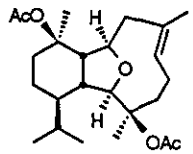
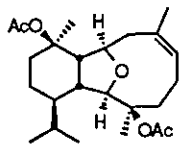
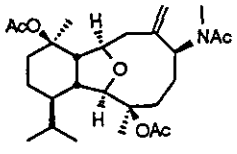
Structure	No.	Name	Source	Biological activity
	1	Labiatin C (R=H)	*Eunicella labiata*[40]	
	2	Eunicellin (R=Ac) [a]	*Eunicella stricta*[6] and *Eunicella labiata*[41]	
	3	Labiatin B	*Eunicella labiata*[40,41]	Cytotoxic against human colon cancer cells HCT-116 (ED_{50}=0.85 μg/mL)
	4	Labiatamide A	*Eunicella labiata*[40]	
	5	Cladiellin (R=Ac)	*Cladiella* species,[24] *Muricella* species[18]	Antiinflammatory effect;[42] cAMP phosphodiesterase inhibitor;[22b] LD_{50}(brine shrimp)=1.3 ppm[18]
	6	Litophynin A (R=COPr)	*Litophyton* species[20]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=12 ppm[20]
	7	Litophynin B	*Litophyton* species[20]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=2.7 ppm[20]
	8	Litophynin C [b]	*Litophyton* species[14]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=25 ppm

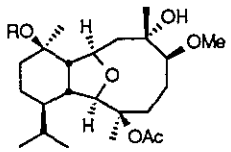
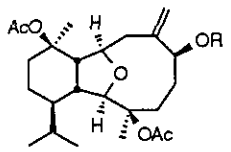
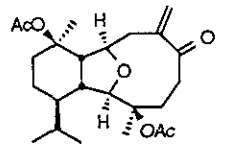
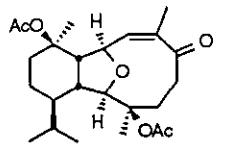
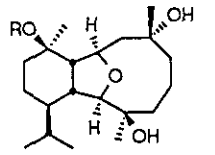
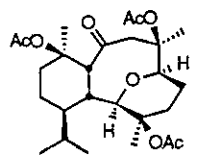
Structure	No.	Name	Source	Biological activity
	**9**	Sclerophytin F (R=H)	*Sclerophytum capitalis*[15]	
	10	3-Butanoyloxycladiell-11(17)-ene-6,7-diol (R=COPr)	*Cladiella australis*[12]	
	11	Sclerophytin E (R=Ac)	*Cladiella australis*[12] and *Sclerophytum capitalis*[15]	
	**12**	6-Acetoxycladiell-11(17)-ene-3,7-diol (R=Ac)	*Cladiella australis*[13]	
	13	Sclerophytin F methyl ether (R=Me) [c]	*Cladiella krempfi*[43]	
	14	Patagonicol (R=Et) [d]	*Alcyonium patagonicum*[44]	Inactive against P388 murine leukemia cells and *Candida albicans*
	**15**	3-Acetoxy-6-(3-methylbutanoyloxy) cladiell-11(17)-en-7-ol ($R=COCH_2CHMe_2$)	*Cladiella australis*[12]	
	**16**	Litophynin E [e]	*Litophyton* species[25,45]	Hemolytic activity; ichthyotoxic (IC_{100}=20 ppm)[25]
	**17**	Sclerophytin D (R=H)	*Sclerophytum capitalis*[15]	
	18	Sclerophytin C (R=Ac) [c]	*Sclerophytum capitalis*[15] and *Cladiella australis*[12]	
	19	Litophynol B (R=COPr) [f]	*Litophyton* species[25]	Hemolytic activity; ichthyotoxic (IC_{100}=20 ppm)

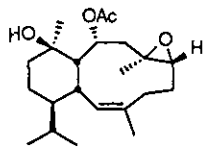
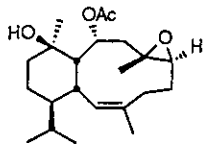
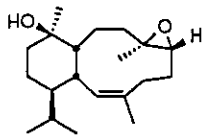
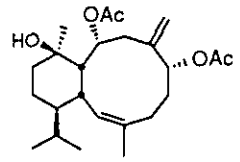
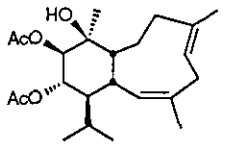
Structure	No.	Name	Source	Biological activity
	20	Cladiellisin (R=H) [e]	*Cladiella australis*,[13] *Cladiella sphaeroides*,[19] *Cladiella similis*[46]	Inactive in the brine shrimp lethality bioassay[19]
	21	3-Acetoxycladiella-7(16),11(17)-dien-6-ol (R=Ac)	*Cladiella australis*[12]	
	22	Litophynin F (R=OCOPr)	*Litophyton* species[47]	
	23	Cladiellaperoxide [e]	*Cladiella* sphaeroides[19]	LD_{50}(brine shrimp)=30 ppm
	24	Litophynol A [f]	*Litophyton* species[25]	Hemolytic activity; ichthyotoxic (IC_{100}=20 ppm)
	25	Litophynin G	*Litophyton* species[17]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=42 ppm
	26/27	3-Acetoxycladiell-11(17)-en-6-ones	*Cladiella australis*[12]	
	28	Sclerophytin A	*Sclerophytum capitalis*[15,22a]	Cytotoxic activity against the L1210 cell line at 1 ng/mL[22a]

Structure	No.	Name	Source	Biological activity
	**29**	Sclerophytin B	*Sclerophytum capitalis*[15,22a]	
	**30**	Litophynin I (R=H)	*Litophyton* species[48]	Molluscicidal and repellent activities against the muricid gastropod *Drupella fragum*; LD_{100}(snail)=30 ppm
	31	Litophynin I monoacetate (R=Ac)	*Litophyton* species[25]	Positive in hemolytic reaction test; ichthyotoxic (IC_{100}=20 ppm)
	**32**	Litophynin J	*Litophyton* species[48]	Molluscicidal and repellent activities against the muricid gastropod *Drupella fragum*; LD_{100}(snail)=30 ppm
	**33**	Litophynin H	*Litophyton* species[25,47]	Hemolytic activity; ichthyotoxic (IC_{100}=20 ppm)
	**34**	Litophynin D	*Litophyton* species[45]	LD_{50}(brine shrimp)=0.9 ppm[25]
	**35**	12-Acetoxy-3,13-dibutanoyloxycladiell-6-ene-4,11-diol *g*	*Alcyonium molle*[8]	

Structure	No.	Name	Source	Biological activity
	**36**	Calicophirin A	*Calicogorgia* species[49]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=20 ppm
	**37**	Ophirin	*Astrogorgia* species[50] *Calicogorgia* species[49] and *Muricella* species[18,51]	Inhibitor of cell division in fertilized starfish eggs at 10 μg/mL;[50] cAMP phosphodiesterase inhibitor;[22b] LD_{50}(brine shrimp)=8.7 ppm[18]
	**38**	(6Z)-3,13,18-Triacetoxycladiella-6,11-diene	*Muricella* species[18]	
	**39**	Astrogorgin	*Astrogorgia* species[50] and *Muricella* species[18]	Inhibitor of cell division in fertilized starfish eggs at 10 μg/mL;[50] LD_{50}(brine shrimp)=1.8 ppm[18]
	**40**	Calicophirin B	*Calicogorgia* species[49] and *Muricella* species[18]	Inhibitory activity against the silkworm *Bombyx mori* L; ED_{50}=52 ppm;[49] cAMP phosphodiesterase inhibitor;[22b] LD_{50}(brine shrimp) = 1.0 ppm[18]
	**41**	Cladiella-6,11-dien-3-ol (R=H)	*Cladiella* species[52]	LD_{50}(brine shrimp)=1.8 ppm[18]
	42	3-Acetoxycladiella-6,11-diene (R=Ac)	*Muricella* species[18]	LD_{50}(brine shrimp) = 0.3 ppm; cytotoxic against human A-549 lung (ED_{50}=12.7 μg/mL), SKOV-3 ovarian (ED_{50}=21.3 μg/mL), SK-MEL-2 melanoma (ED_{50}=11.6 μg/mL), and HCT-15 colon cancer cell lines (ED_{50}=13.9 μg/mL)

Structure	No.	Name	Source	Biological activity
	**43**	Alcyonin	*Sinularia flexibilis*[26]	Cytotoxic activity against Vero cells; IC_{50}=55 μg/mL
	**44**	6-Acetoxycladiella-7(16),11-dien-3-ol [h]	*Cladiella* species[27]	
	**45**	Cladiell-11-ene-3,6,7-triol (R=H) [d]	*Cladiella* species[53]	
	46	3-Acetoxycladiell-11-ene-6,7-diol (R=Ac)	*Cladiella* species[27]	
	**47**	3,6-Diacetoxy-11,12-epoxycladiellan-7-ol	*Cladiella* species[27]	
	**48**	(6*E*)-11-Acetoxy-cladiellin [d]	*Cladiella* species[24] *Pachyclavularia* species[11]	
	**49**	(6*Z*)-11-Acetoxy-cladiellin	*Eunicella cavolini*[54]	
	**50**	Labiatamide B	*Eunicella labiata*[40]	

Structure	No.	Name	Source	Biological activity
	51	Palmonine C (R=H)	*Eunicella verrucosa*[55]	Low cytotoxicity against various cancer cells; (ED_{50}>10 μg/mL)[21]
	52	Palmonine A (R=Ac)	*Eunicella verrucosa*[55]	Low cytotoxicity against various cancer cells; (ED_{50}>10 μg/mL)[21]
	53	Palmonine F (R=H) [i]	*Eunicella verrucosa*[21]	Low cytotoxicity against various cancer cells; (ED_{50}>10 μg/mL) [21]
	54	Palmonine B (R=Ac)	*Eunicella verrucosa*[55]	Cytotoxic against P-388 mice lymphoma and MEL28 human melanoma cell lines; ED_{50}=5 μg/mL[21]
	55	Palmonine D	*Eunicella verrucosa*[55] and *Eunicella labiata*[41]	Low cytotoxicity against various cancer cells; (ED_{50}>10 μg/mL)[21]
	56	Palmonine E	*Eunicella verrucosa*[55]	Low cytotoxicity against various cancer cells (ED_{50}>10 μg/mL)[21]
	57	Cladiellane-3,7,11-triol (R=H)	*Briareum* species[56]	
	58	11-Acetoxy-cladiellane-3,7-diol (R=Ac)	*Briareum* species[56]	
	59	Labiatin A	*Eunicella labiata*[40]	

Structure	No.	Name	Source	Biological activity
	60	Solenopodin A	*Solenopodium stechei*[57]	
	61	Solenopodin B	*Solenopodium stechei*[57]	
	62	Solenopodin C	*Solenopodium stechei*[57]	
	63	Solenopodin D[d]	*Solenopodium stechei*[57]	
	64	12,13-Diacetoxycladiella-2,6-dien-11-ol	*Eunicella labiata*[41]	

[a]Relative configuration established by X-Ray analysis of the dibromide derivative.[6]

[b]Absolute configuration established on the basis of the CD spectrum of the *p*-bromobenzoate derivative.

[c]Absolute configuration established by X-Ray analysis.

[d] Relative configuration established by X-Ray analysis.

[e]Absolute configuration established by the modified Mosher method.

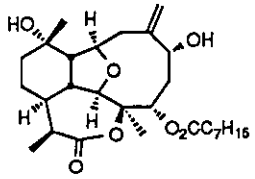
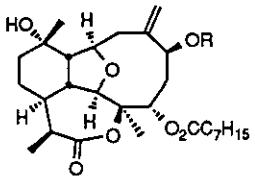
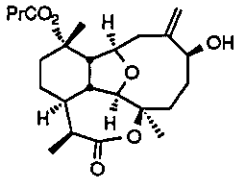
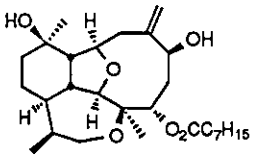
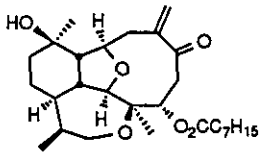
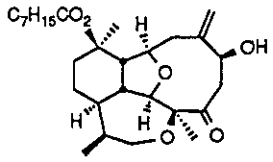
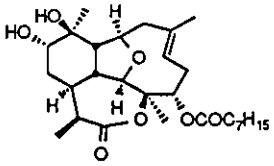
[f]Absolute configuration established by the CD exciton method on the dibenzoate derivative.

[g]Absolute configuration established by the Horeau method.

[h]Absolute configuration confirmed by total synthesis.[17]

[i]Absolute configuration confirmed by the Mosher method.

Table 2: The Briarellins.

Structure	No.	Name	Source	Biological activity
	65	Briarellin A	*Briareum asbestinum*[9]	Cytotoxic activity against HeLa cells; IC_{50}=20.0 μg/mL
	66	Briarellin B (R=H)	*Briareum asbestinum*[9]	
	67	Briarellin C (R=COPr)	*Briareum asbestinum*[9]	
	68	Briarellin D	*Briareum asbestinum*[9]	
	69	Briarellin E	*Briareum asbestinum*[10]	Cytotoxic activity against HeLa cells; IC_{50}=20.0 μg/mL
	70	Briarellin F	*Briareum asbestinum*[10]	
	71	Briarellin G	*Briareum asbestinum*[10]	
	72	Briarellin H	*Briareum asbestinum*[10]	

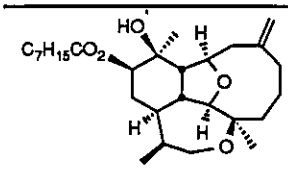
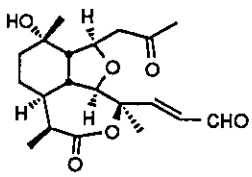
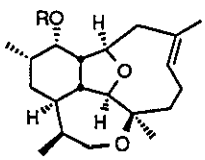
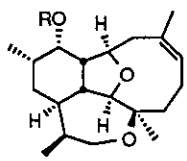
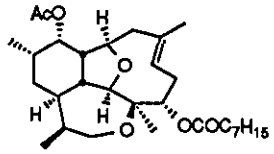
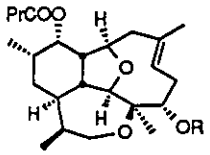
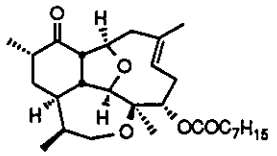
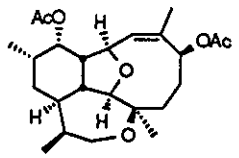
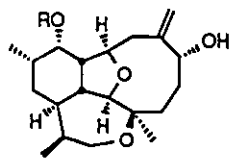
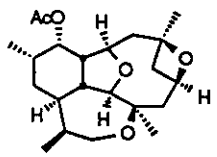
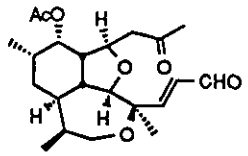
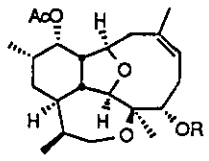
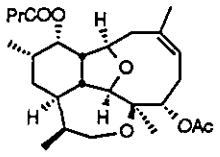
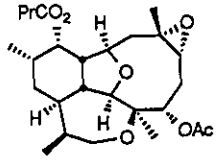
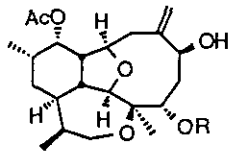
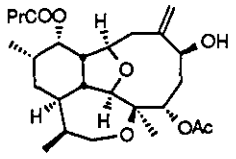
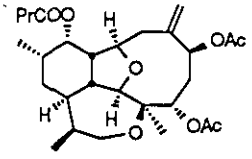
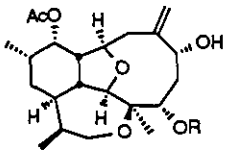
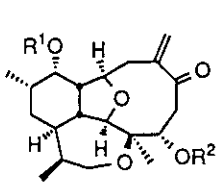
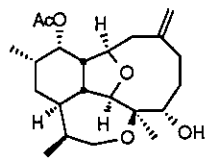
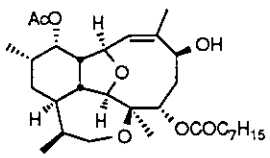
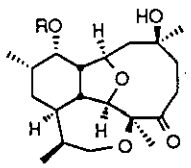
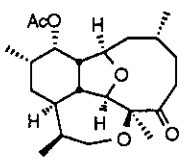
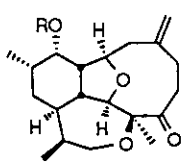
Structure	No.	Name	Source	Biological activity
	73	Briarellin I	*Briareum asbestinum*[10]	
	74	*seco*-Briarellin	*Briareum asbestinum*[10]	

Table 3: The Asbestinins.

Structure	No.	Name	Source	Biological activity
	75	11-Acetoxy-4-deoxyasbestinin B (R=Ac)	*Briareum asbestinum*[29]	Cytotoxic effect against CHO-K1 cells; ED_{50}=2.50 μg/mL; strong antimicrobial activity against *Klebsiella pneumoniae*; inactive against HIV
	76	4-Deoxyasbestinin A (R=COPr)	*Briareum asbestinum*[29]	Cytotoxic effect against CHO-K1 cells; ED_{50}=3.55 μg/mL; strong antimicrobial activity against *Klebsiella pneumoniae*
	77	11-Acetoxy-4-deoxyasbestinin D (R=Ac)	*Briareum asbestinum*[29]	Cytotoxic effect against CHO-K1 cells; ED_{50}=4.82 μg/mL; strong antimicrobial activity against *Klebsiella pneumoniae*
	78	4-Deoxyasbestinin C (R=COPr)	*Briareum asbestinum*[29]	Cytotoxic effect against CHO-K1 cells; ED_{50}=3.55 μg/mL; strong antimicrobial activity against *Klebsiella pneumoniae*

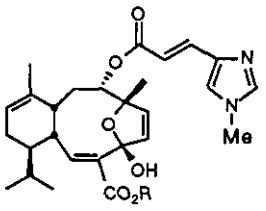
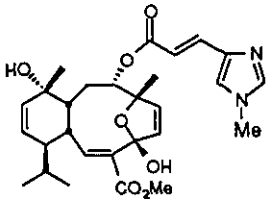
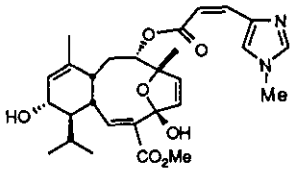
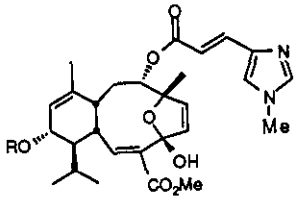
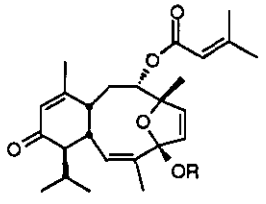
Structure	No.	Name	Source	Biological activity
	79	Asbestinin-6	*Briareum asbestinum*[28,58]	Cytotoxic activity against MCF-7 (IC_{50}=1.5 μg/mL), CCRF-CEM (IC_{50}=0.5 μg/mL), and HCT 116 (IC_{50}=5 μg/mL) cell lines[28]
	80	Asbestinin-3 (R=H)	*Briareum asbestinum*[7]	
	81	Asbestinin-1 (R=Ac) [a]	*Briareum asbestinum*[7,30]	Antagonizes the effect of acetylcholine on guinea pig ileum preparations to the 13% level at a concentration of 16 μg/mL[30]
	82	Asbestinin-8	*Briareum asbestinum*[28]	Cytotoxic activity against MCF-7 (IC_{50}>50 μg/mL), CCRF-CEM (IC_{50}=2.5 μg/mL), and HCT 116 (IC_{50}=10 μg/mL) cell lines[28]
	83	11-Acetoxy-4-deoxyasbestinin E	*Briareum asbestinum*[58]	
	84	11-Acetoxy-4-deoxyasbestinin F (R=Ac)	*Briareum asbestinum*[58]	
	85	4-Deoxyasbestinin G (R=COPr)	*Briareum asbestinum*[58]	
	86		*Briareum asbestinum*[59]	Inactive against HeLa and CHO-K1 cell lines
	87		*Briareum asbestinum*[31]	Not cytotoxic against HeLa and CHO-K1 cell lines within 5 to 250 μg/mL

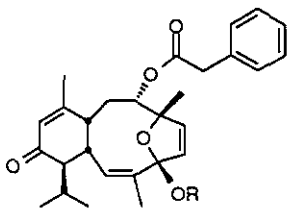
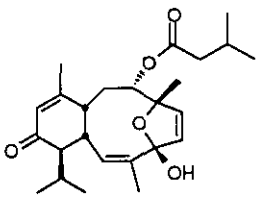
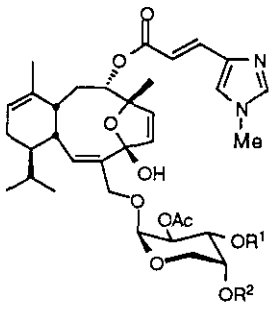
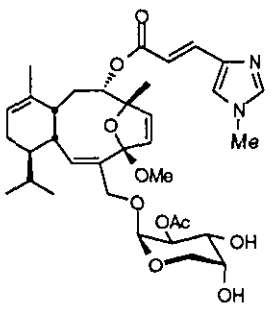
Structure	No.	Name	Source	Biological activity
	88	Asbestinin-12 (R=Ac)	*Briareum asbestinum*[58]	
	89	Asbestinin-11 (R=COC_7H_{15})	*Briareum asbestinum*[58]	
	90	Asbestinin-2	*Briareum asbestinum*[7,30]	
	91	Asbestinin epoxide	*Briareum asbestinum*[30]	
	92	Asbestinin-17 (R=Ac)	*Briareum asbestinum*[58]	
	93	Asbestinin-13 (R=COC_7H_{15})	*Briareum asbestinum*[58]	
	94	Asbestinin-14 (R=COC_5H_{11})	*Briareum asbestinum*[58]	
	95	Asbestinin-5	*Briareum asbestinum*[7,30]	Exhibits 40% histamine antagonism at 16 μg/mL; antagonizes the effect of acetylcholine on guinea pig ileum preparations to the 38% level to the concentration of 16 μg/mL[30]
	96	Asbestinin-5 acetate	*Briareum asbestinum*[30]	
	97	Asbestinin-7 (R=COC_7H_{15})	*Briareum asbestinum*[28,58]	Cytotoxic activity against MCF-7 (IC_{50}=9 μg/mL), CCRF-CEM (IC_{50}=0.15 μg/mL), and HCT 116 (IC_{50}=5 μg/mL) cell lines[28]
	98	Asbestinin-15 (R=Ac)	*Briareum asbestinum*[58]	

Structure	No.	Name	Source	Biological activity
	99	Asbestinin-19 (R^1=Ac; R^2=Ac)	*Briareum asbestinum*[58]	
	100	Asbestinin-16 (R^1=Ac; R^2=COC_7H_{15})	*Briareum asbestinum*[58]	
	101	Asbestinin-4 (R^1=COPr; R^2=Ac)	*Briareum asbestinum*[7,30]	
	102	Asbestinin-20	*Briareum asbestinum*[58]	
	103	Asbestinin-18	*Briareum asbestinum*[58]	
	104	Asbestinin-21 (R=Ac)	*Briareum asbestinum*[58]	
	105	Asbestinin-22 (R=COPr)	*Briareum asbestinum*[58]	
	106	Asbestinin-23	*Briareum asbestinum*[58]	
	107	Asbestinin-9 (R=COPr)	*Briareum asbestinum*[28]	Cytotoxic activity against SK5-MEL (IC_{50}>50 μg/mL), A498 (IC_{50}>50 μg/mL), and HCT 116 (IC_{50}=20 μg/mL) cell lines
	108	Asbestinin-10 (R=Ac)	*Briareum asbestinum*[28]	Cytotoxic activity against SK5-MEL (IC_{50}>50 μg/mL), A498 (IC_{50}=15 μg/mL), and HCT 116 (IC_{50}>50 μg/mL) cell lines

[a] Relative configuration established by X-Ray analysis of the diol.

Table 4: The Sarcodictyins

Structure	No.	Name	Source	Biological activity
	109	Sarcodictyin A (R=Me) [a]	*Sarcodictyon roseum*,[4] *Eleutherobia aurea*[33]	Potent antitumor activity against a variety of cells (IC_{50}=400-900 nM); induces tubulin polymerization and microtubule stabilization[37]
	110	Sarcodictyin B (R=Et) [b]	*Sarcodictyon roseum*[4]	Potent antitumor activity against a variety of cells (IC_{50}=400-900 nM); induces tubulin polymerization and microtubule stabilization[37]
	111	Sarcodictyin F	*Sarcodictyon roseum*[5]	
	112	Sarcodictyin E	*Sarcodictyon roseum*[5]	
	113	Sarcodictyin C (R=H)	*Sarcodictyon roseum*[5]	
	114	Sarcodictyin D (R=Ac)	*Sarcodictyon roseum*[5]	
	115	Valdivone A (R=H)	*Alcyonium valdivae*[32]	Inhibitor of chemically-induced inflammation at the 93% level in the mouse ear assay at 50 μg/ear
	116	Valdivone A methoxyketal (R=Me)	*Alcyonium valdivae*[32]	

Structure	No.	Name	Source	Biological activity
	117	Valdivone B (R=H)	*Alcyonium valdivae*[32]	Inhibitor of chemically-induced inflammation at the 72% level in the mouse ear assay at 50 μg/ear
	118	Valdivone B methoxyketal (R=Me)	*Alcyonium valdivae*[32]	
	119	Dihydrovaldivone A	*Alcyonium valdivae*[32]	
	120	Eleuthoside A (R^1=Ac, R^2=H)	*Eleutherobia aurea*[33]	
	121	Eleuthoside B (R^1=H, R^2=Ac)	*Eleutherobia aurea*[33]	
	122	Eleutherobin [c]	*Eleutherobia* species[34]	Potent antitumor activity against a variety of cells (IC_{50}=10-15 nM);[60] induces tubulin polymerization and microtubule stabilization[34,38]

[a]Absolute configuration established by Horeau's method;[4] structure proven by total synthesis.[35]

[b]Absolute configuration established by Horeau's method.[4]

[c]Structure proven by total synthesis.[36]

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