Scalarane Sesterterpenoids

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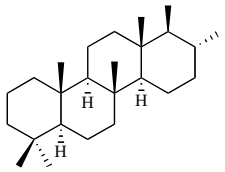
Abstract: In this review we cover the names, structures, and occurrence of all the scalaranes since their discovery in 1972. We have given special attention to the biological properties of these polycyclic terpenoids of exclusive marine origin.



Scalarane skeleton

Keywords: ?????

1. INTRODUCTION

Marine organisms have provided a large number of terpenoids, possessing novel carbon skeletons different from those present in terrestrial species. Several sesterterpenoids isolated from marine organisms have shown a wide variety of biological activities. In this review, we focus our attention on sesterterpenoids characterised by polycyclic structures having the scalarane (**I**, C_{25}) (Fig. **1**) carbon framework as well as nor- and alkylated members.

Scalarane sesterterpenoids are bioactive natural products isolated exclusively from sponges and shell-less molluscs (nudibranchs), which are believed to be able of sequestering the scalarane-based metabolites from the sponges on which they feed. Most of these compounds play a key role as eco-physiological mediators (chemical defense) and are of interest for potential applications as therapeutic agents. In addition, scalarane sesterterpenoids are considered to represent useful chemotaxonomic markers within sponges.

Scalaranes having the characteristic carbon skeleton **I** (Fig. **1**) have been reviewed up to 1990 and listed in the Dictionary of terpenoids [1]. During the last two decades, many new members of this family of natural products have been isolated and described in a few specific reviews on naturally occurring sesterterpenoids by Professor Hanson [2], and Professor Liu [3]. The excellent reviewing work on marine natural products by Professor Faulkner [4], now continued by the team of Professor Blunt [5], has also covered mainly the isolation and structural aspects of scalaranes. A recent review on bioactive marine sesterterpenoids has also included articles on isolation and structure determination of scalaranes up to 2004 [6]. The scalarane sesterterpenoids have attracted the attention of synthetic chemists and two reviews have covered the studies on the synthesis of scalaranes [7]. We now provide full coverage of past and recent advances in the field which have been reported in the literature up to December 2009.

2. STRUCTURE, OCCURRENCE AND BIOLOGICAL ACTIVITY

The semisystematic naming of this family of sesterterpenoids was introduced in 1980, by Kazlauskas *et al.* [8], following the isolation of the first member of the family from the Mediterranean sponge *Cacospongia scalaris*. Thus, in accordance with the IUPAC recommendations, the saturated hydrocarbon **I**, named 'scalarane', was chosen as the fundamental parent structure with the numbering pattern as depicted in Fig. (**1**). This numbering system will be used throughout the article, though other numbering systems have been used by other authors.

The first known member of the scalarane family of terpenoids, scalarin (**1**), was discovered by Fattorusso *et al.* from the sponge *Cacospongia scalaris* nearly forty years ago. Structure (**1**) was assigned based on chemical and spectroscopic data [9].

To date, there are around two hundred known compounds belonging to this family of marine natural products, including nor- and alkylated members, normally at C-19 or C-20 and/or C-24. Alkylated scalaranes, are sometimes called homoscalaranes. Homoscalaranes

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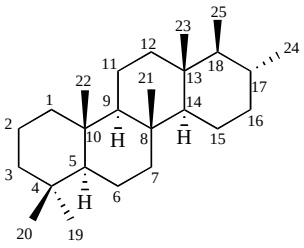
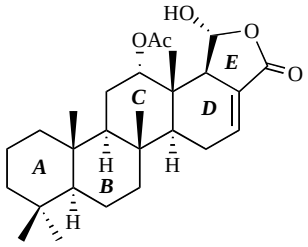


I, scalarane skeleton



1, scalarin

Fig. (1). Scalarane numbering system and scalarin (**1**).

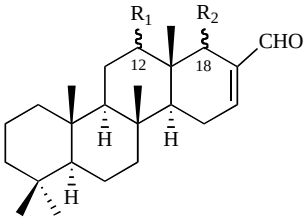
show methylation at C-20 or C-24, while methylations at both C-20 and C-24 are typical in bishomoscalaranes. Generally, scalaranes are not functionalised on A- or B-ring carbons. Most of them present a different degree of oxidation in their C- and D-ring carbons, particularly at positions C-12 and C-16.

Given the variety of chemical structures found in the scalarane family, we could group them according to the type of carbocyclic framework, normally either the characteristic 6/6/6/6-tetracyclic fused ring system or a 6/6/6/6/5-pentacyclic fused ring system. Thus, we have integrated most of them into two main groups: compounds having a tetracyclic scalarane skeleton and compounds with a pentacyclic skeleton. We have also included another group containing scalarane-derived metabolites with unusual carbon frameworks.

Sponges are exposed to a variety of dangers in their environment and this has led to the development of chemical defense mechanisms against predation. Nudibranchs feed on a variety of sponges and are able of storing selected metabolites, even transforming them, for their own self-defense. Thus, sponges and nudibranchs are a rich source of biologically active metabolites, and the scalaranes, in particular, have displayed a wide spectrum of interesting biological properties (see Tables **1-3**) including antifeedant, antimicrobial, antifungal, ichthyotoxicity, antitubercular, antitumour, cytotoxicity, anti-HIV, antifouling, inhibition of platelet-aggregation, inhibition of transactivation for the nuclear hormone receptor (FXR, farnesoid X-activated receptor), stimulation of nerve growth factor synthesis, as well as anti-inflammatory activity.

2.1. Tetracyclic Scalaranes

The first group of tetracyclic scalaranes is composed mainly of 1,4-dicarbonyl compounds, of which the earliest example is the biologically active scalaradial (**2**)(Fig. **2**)[10], which posseses a 1,4-dialdehyde moiety. Other metabolites related to scalaradial (**2**) have been isolated and differ from the stereochemistry and substituent type at C-12, as well as the stereochemistry of the aldehyde group at C-18 (Fig. **2**).



2, R_1= α-OAc; R_2= β–CHO
3, R_1= α–OH; R_2= β-CHO
4, R_1= H; R_2= β-CHO
5, R_1= β-OAc; R_2= β-CHO
6, R_1= β-OH; R_2= β–CHO
7, R_1= α–OAc; R_2= β-CH_2OH
8, R_1= α-OAc; R_2= α–CHO
9, R_1= β-OAc; R_2= α-CHO
10, R_1= β-OH; R_2= α-CHO
11, R_1= =O; R_2= α-CHO
12, R_1= =O; R_2= β-CHO

Fig. (2). Scalaradial (**2**) and related metabolites.

Scalaradial (**2**) was first isolated in 1974 from the sponge *Cacospongia mollior* collected at the Mediterranean sea, and the gross structure was reported [10]. The X-ray study of scalaradial confirmed his structure [11]. Scalaradial (**2**) has also been found in other *Cacospongia mollior* specimens [12], as well as in other sponges and as chemical constituents of nudibranchs. For example, scalaradial (**2**) has been isolated from the sponge *Cacospongia scalaris* collected at Wakayama (Japan)[13], and collected at Tarifa Island (Spain)[14]. The sponges *Spongia oceania* collected at Pupukea (Hawai)[15], *Cacospongia* sp. collected at the Gulf of Naples and collected at Apra Harbor, Guam (Micronesia)[16,17], *Dysidea villosa* and *Dysidea marshalla* collected at the South China Sea [18], and other sponges collected at the South China Sea of the order Dictyoceratida have also shown to contain scalaradial (**2**)[19]. Finally, the nudibranchs *Glossodoris pallida* and *Glossodoris cincta* from Guam have demostrated to possess diet-derived scalaradial (**2**)[16,20].

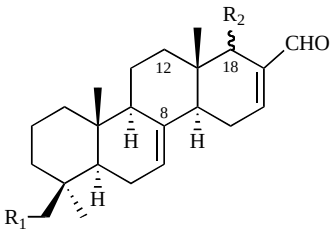
The biological properties of scalaradial (**2**) have long been studied. Scalaradial (**2**) displays not only antifeedant and ichthyotoxic properties but also cytotoxic, antitumour and anti inflammatory effects (Table

1). The majority of terpenoids, containing an unsaturated 1,4-dialdehyde functionality, are intensely pungent and are generally versatile repellents [21,22]. This activity has been explained by their interaction with vanilloid receptors [23]. Scalaradial (**2**) is tasteless but is part of an effective defense against predation by reef fishes and crabs (*Leptodius* sp.)[16,17]. Scalaradial (**2**) is very toxic at 10 ppm when evaluated for its ichthyotoxicity in the mosquito fish *Gambusia affinis* test [19]. Scalaradial (**2**) is cytotoxic in the *Artemia salina* shrimp bioassay (LD_{50}= 0.18 μg/mL)[12b]. Compound **2** showed strong antitumour activity against several human cancer cell lines (leukemia HL60, IC_{50}= 3.4 μM; hepatocarcinoma BEL7402, IC_{50}= 5.8 μM; breast cancer MDA-MB435, IC_{50}= 4.8 μM)[18]. Finally, scalaradial (**2**) exhibits potent activity against phospholipase A_2 (PLA_2) enzymes, which are involved in the biosyntesis of eicosanoids responsible for the inflammatory response. Thus, scalaradial (**2**) was found to inhibit PLA_2 from bee venom (IC_{50}= 0.07 μM)[24], and human recombinant PLA_2 (IC_{50}= 0.07 μM)[25].

Desacetylscalaradial (**3**) was first isolated in 1981 from a Japanese specimen of the sponge *Cacospongia scalaris* and showed interesting cytotoxic activity against L1210 cancer cells (IC_{50}= 0.58 μg/mL)[13]. Desacetylscalaradial (**3**) has also been isolated from the nudibranch *Chromodoris youngbleuthi* (currently known as *Glossodoris rufomarginata*) and the sponge *Spongia oceania* on which the nudibranch feeds, collected at Hawai [15]. Similarly, compound **3** was found in the nudibranch *Glossodoris pallida* and its sponge prey *Cacospongia* sp, collected at Guam [17,20], and in the nudibranch *Glossodoris rufomarginata* and its dietary sponge collected at the South China Sea [19]. Desacetylscalaradial (**3**) is very toxic at 10 ppm when evaluated for its ichthyotoxicity in the *Gambusia affinis* test [19].

12-Deacetoxyscalaradial (scalarenedial, **4**) was first isolated in 1994 from the Mediterranean sponge *Cacospongia mollior* and showed cytotoxic activity in the *Artemia salina* shrimp bioassay (LD_{50}= 0.77 μg/mL) [12b]. The structure of 12-deacetoxyscalaradial (**4**) proposed by spectral data was confirmed by X-ray diffraction analysis and represents the first scalarane sesterterpenoid without a substituent at C-12 [12b]. Compound **4** was active in a fish (*Carassius carassius*) feeding inhibition bioassay at a concentration of 30 μg/cm^2 and was hot in taste [12b]. Later, 12-deacetoxyscalaradial (**4**) has also been found in the sponge *Cacospongia scalaris* collected at Tarifa Island (Spain) [14], and has been prepared by total synthesis [26].

12-Epi-scalaradial (**5**) was first isolated in 1979 from the Mediterranean sponge *Spongia nitens* [27]. Later, it has been found in the Tongan sponge *Hyrtios erecta* [28], in the Great Barrier Reef sponge *Collospongia auris* [29], and in the sponge *Spongia agaricina* collected near Tarifa Island (Spain)[30]. Finally, the nudibranchs *Glossodoris hikeurensis* and *Glossodoris cincta* from Guam have also demostrated to contain 12-epi-scalaradial (**5**)[16b]. Recently, 12-epi-scalaradial (**5**) has been prepared by semisynthesis from natural pentacyclic scalaranes [31,32]. Compound **5** showed antimicrobial activity using the standard disk assay against *Staphylococcus aureus* (10 μg/disk), *Bacillus subtilis* (10 μg/disk), and *Candida albicans* (10 μg/disk)[29]. 12-Epi-scalaradial (**5**) is an inhibitor of human recombinant PLA_2 (IC_{50}= 0.02 μM) and significantly reduces induced mouse ear inflammation [25]. 12-Epi-scalaradial (**5**) is also an inhibitor of epidermal growth factor receptor (EGFR), which is implicated in many cancers [33]. Semisynthetic 12-epi-scalaradial (**5**) has displayed both antitubercular (MIC= 58 μM) and cytotoxic activity (human oral fibroblasts, IC_{50}= 1.26 μM; ovarian cancer SKOV3, IC_{50}= 23.3 μM; melanoma SK-MEL, IC_{50}> 42.7 μM; breast cancer BT549, IC_{50}= 21.0 μM; Vero, IC_{50}= 22.2 μM), as well as potent antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} value of 6.3 μM [31,32].



13, R_1= H; R_2= β-CHO
14, R_1= H; R_2= α-CHO
15, R_1= OAc; R_2= β-CHO

Fig. (3). Mooloolabenes A, B and C (**13-15**).

12-Deacetyl-12-epi-scalaradial (**6**) was first isolated in 1986 from the nudibranch *Chromodoris youngbleuthi* (currently known as *Glossodoris rufomarginata*)[20], collected at Hawai [15], and the Tongan sponge *Hyrtios erecta* [28b]. 12-Deacetyl-12-epi-scalaradial (**6**) has also been isolated from the Great Barrier Reef sponge *Collospongia auris* [29]. Recently, 12-deacetyl-12-epi-scalaradial (**6**) has been prepared by semisynthesis from natural pentacyclic scalaranes [31,32]. Semisynthetic 12-deacetyl-12-epi-scalaradial (**6**) has displayed both antitubercular (MIC= 64 μM) and cytotoxic activity (ovarian cancer SKOV3, IC_{50}= 31.0 μM; melanoma SK-MEL, IC_{50}= 26.4 μM; breast cancer BT549, IC_{50}= 19.4 μM; Vero, IC_{50}= 19.4 μM), as well as antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} value of 22 μM [31,32].

25-Dihydroscalaradial (**7**) and 18-epi-scalaradial (**8**) were isolated from the sponge *Cacospongia scalaris* collected at Tarifa Island (Spain)[14]. Both compounds showed significant cytotoxicity towards five tumour cell lines (mouse lymphoma P388 and Schabel, ED_{50}= 2 and 0.2 μg/mL; human lung carcinoma A549, ED_{50}= 2 and 0.2 μg/mL; human colon carcinoma HT29, ED_{50}= 2 and 0.2 μg/mL; human melanoma MEL28 ED_{50}= 2.5 and 0.5 μg/mL, respectively).

12,18-Diepi-scalaradial (**9**) was first isolated in 1979 from the Mediterranean sponge *Spongia nitens* [27]. Later, it has been found in the Great Barrier Reef sponge *Collospongia auris* [29], and the sponge *Spongia agaricina* collected near Tarifa Island (Spain)[30]. Compound **9** showed antimicrobial activity using the standard disk assay against *Staphylococcus aureus* (10 μg/disk), *Bacillus subtilis* (10 μg/disk), and *Candida albicans* (50 μg/disk)[29].

12-Deacetyl-12,18-diepi-scalaradial (**10**) was found in the Californian sponge *Spongia idia* [34]. This compound has been prepared by pyrolytic cleavage of natural pentacyclic scalaranes [31] and epimerization at C-18 from semisynthetic 12-deacetyl-12-epi-scalaradial (**6**) and its structure was confirmed by X-ray crystallography [32]. Natural 12-deacetyl-12,18-diepi-scalaradial (**10**) has displayed antifeedant properties [34,35]. Semisynthetic 12-deacetyl-12,18-diepi-scalaradial (**10**) has displayed both antitubercular (MIC= 8 μM) and cytotoxic activities (ovarian cancer SKOV3, IC_{50}= 19.4 μM; melanoma SK-MEL, IC_{50}= 18.6 μM; breast cancer BT549, IC_{50}= 12.9 μM; Vero, IC_{50}= 20.7 μM), as well as potent antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} value of 3.8 μM [31,32].

12-Deacetyl-18-epi-12-oxoscalaradial (**11**) was isolated in 1986 from the nudibranch *Chromodoris youngbleuthi* (currently known as *Glossodoris rufomarginata*)[20], collected at Hawai. This compound was not present in the sponge *Spongia oceania* on which the nudibranch feeds [15]. 12-Deacetyl-18-epi-12-oxoscalaradial (**11**) is also a semisynthetic compound, which has been prepared from other semisynthetic pentacyclic scalaranes [32]. It has displayed cytotoxic activity (ovarian cancer SKOV3, IC_{50}= 31.2 μM; melanoma SK-MEL, IC_{50}= 14.3 μM; breast cancer BT549, IC_{50}= 15.6 μM; Vero, IC_{50}= 15.6 μM), as well as antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} value of 30.1 μM [32].

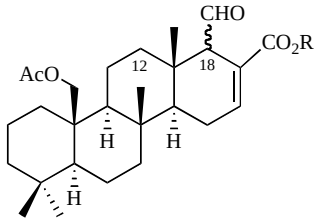
12-Deacetyl-12-oxoscalaradial (**12**) has been isolated recently from the nudibranch *Glossodoris rufomarginata* collected at the South China Sea [19]. Other *Glossodoris* nudibranchs, such as *G. pallida* from the South China Sea, and *G. vespa* and *G. averni* from Eastern Australia, also contain compound **12** as main metabolite [20].[20] The finding of scalaranes exhibiting the keto function at C-12 is particularly interesting. This structural feature is quite common in the homoscalarane and bishomoscalarane series but unusual in the scalaranes isolated from sponges. In fact, this feature has been found only in nudibranch metabolites, indicating the ability of these mollusks to oxidise the hydroxyl/acetoxyl function at C-12 of dietary scalaranes [19,20]. Recently, 12-deacetyl-12-oxoscalaradial (**12**) has been prepared by semisynthesis from natural pentacyclic scalaranes [31,32]. Natural 12-deacetyl-12-oxoscalaradial (**12**) is very toxic at 10 ppm when evaluated for its ichthyotoxicity in the mosquito fish *Gambusia affinis* test [19]. Semisynthetic 12-deacetyl-12-oxoscalaradial (**12**) has displayed both antitubercular (MIC= 130 μM) and cytotoxic activities (ovarian cancer SKOV3, IC_{50}= 41.6 μM; melanoma SK-MEL, IC_{50}= 14.6 μM; breast cancer BT549, IC_{50}= 15.6 μM; Vero, IC_{50}= 18.2 μM), as well as antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} value of 27.8 μM [31,32].

Other metabolites related to scalaradial (**2**) that possess a 1,4-dialdehyde moiety are mooloolabenes A (**13**), B (**14**) and C (**15**) (Fig. **3**), which were isolated from the Australian sponge *Hyattella intestinalis* [36]. These metabolites, however, are characterised by the lack of functionality at C-12 and lack of a methyl substituent at C-8 (norscalaranes). All were cytotoxic toward the P388 mouse leukemia cell line with IC_{50} values of 0.8, 1.2 and 3-10 μg/mL, respectively.

Also, compounds (**16**-**18**) (Fig. **4**) are similar to scalaradial (**2**), They were isolated from the Korean sponge *Smenospongia* sp. [37], and differ from scalaradial in the lack of functionality at C-12 and the oxidation degree at C-24, presenting either a carboxylic acid or a methyl ester. These compounds showed significant cytotoxicity against human chronic myelogenous leukemia K562 cell line (LC_{50} 3.7-8.6 μg/mL). In addition, compound **18** exhibited antibacterial activity against both Gram-positive and -negative bacteria [37].

Another subgroup of tetracyclic scalaranes is composed of rare 25-norscalarane compounds such as metabolites **19**-**26** (Fig. **5**). Hyrtial (**19**) was the first reported 25-norscalarane. It was isolated from the Tongan sponge *Hyrtios erecta*, and it showed anti-inflammatory activity at 50 μg/mL and 43% decrease in ear weight of phorbolmyrstic-acetate-induced inflammation of mouse ear ca. 50 μg/ear [28]. From the Great Barrier Reef sponge *Collospongia auris* was isolated 12-deacetylhyrtial (**20**) and methyl 18-hydroxy-25-norscalar-16-en-24-carboxylate (**21**) [29]. Both compounds showed antimicrobial activity using the standard disk assay against *Staphylococcus aureus* (25 μg/disk) and *Bacillus subtilis* (50 μg/disk) [29]. 12-Deacetylhyrtial (**20**) has also been isolated from the

Okinawan sponge *Hyrtios erectus* (also called *H. erecta*) along with its Δ^{17} isomer (12-deacetyl- Δ^{17}-hyrtial, **22**) and both compounds showed cytotoxic activity against KB cells with IC_{50} values of 10.0 and 2.82 μg/mL, respectively [38]. Norscalarals A-C (**23-25**) were isolated from the sponge *Cacospongia scalaris* collected at Tarifa Island (Spain). This new compound showed significant cytotoxicity towards five tumour cell lines (mouse lymphoma P388, ED_{50}= 1-2 μg/mL; Schabel, ED_{50}= 1-2 μg/mL; human lung carcinoma A549, ED_{50}= 1-2.5 μg/mL; human colon carcinoma HT29, ED_{50}= 1-5 μg/mL; human melanoma MEL28 ED_{50}= 2-2.5 μg/mL)[14]. Norscalaral B (**24**) has also been found in the Californian sponge *Hyatella intestinalis* along with its deacetyl derivative (12-deacetyl-norscalaral B, **26**), which showed mild cytotoxic activity against three tumour cell lines (breast carcinoma MDA-MB-231, GI_{50}= 4.9 μg/mL; lung carcinoma A549, GI_{50}= 4.5 μg/mL; colon carcinoma HT29, GI_{50}= 4.2 μg/mL)[39].



16, R= H; α-CHO
17, R= Me; α-CHO
18, R= Me; β-CHO

Fig. (4). Scalaradial-related compounds **16**-**18**.

The group of tetracyclic scalaranes also includes a number of homoscalaranes and bishomoscalaranes such as keto-aldehydes **27**-**61** (Fig. **6** and **7**). Within this subgroup of tetracyclic scalaranes, we can distinguish members with an α,β-unsaturated methyl ketone (compounds **27**-**44**, Fig. **6**) and members without unsaturation (compounds **45**-**61**, Fig. **7**).

For example, several 24-methylscalaranes (**27**-**30**) were obtained from Australian sponges of the genus *Carteriospongia* (syn. *Phyllospongia*), among them, 24-methyl-24,25-dioxoscalar-16-en-12β-yl 3-hydroxybutanoate (**27**) showed antifungal and antiinflammatory activity [8]. The structure of compound **30** was confirmed by X-ray crystallography [8]. From another Australian sponge (*Lendenfeldia* sp.) were isolated two additional 24-methylscalaranes (**31** and **32**)[40], which were also found in Palauan sponges (*Dictyoceratida* sp. and *Halichondria* sp.) along with two additional 24-homoscalaranes **33** and **34** [41]. 12α-Acetoxy-24-methyl-24-oxoscalar-16-en-22,25-dial (**33**) displayed significant inhibitory activity (IC_{50}= 0.5 μg/mL) on the

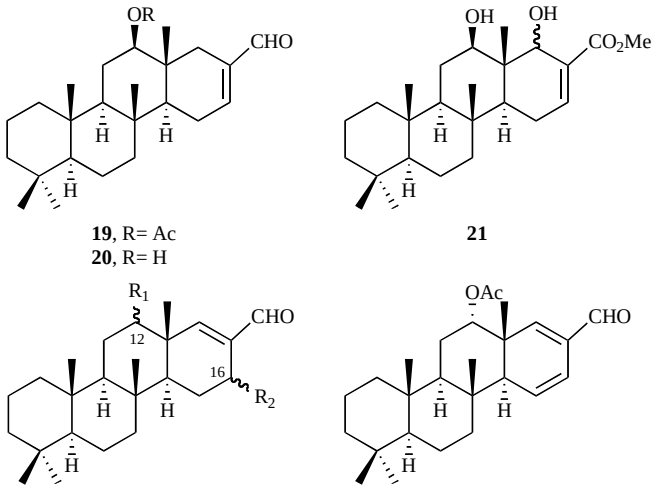
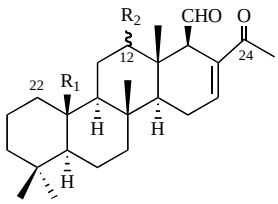
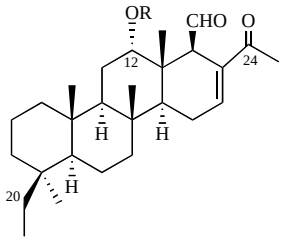


Fig. (5). 25-Norscalaranes.

platelet aggregations caused by adenosine 5'-diphosphate, collagen, or arachidonic acid [41]. Homoscalaranes **32** and **33** have also been isolated from other Palauan sponges of the order Dyctyoceratida such as *Lendenfeldia chondrodes* [42]. 24-Methyl-12,24,25-trioxoscalar-16-en-22-oic acid (**32**) has also been found in other *Lendenfeldia* sponges collected at Indonesia [43], and Madagascar [44]. In the Madagascan specimen, compound **32** was isolated as its methyl ester (24-methyl-12,24,25-trioxoscalar-16-en-22-oate, **35**), which was found as a natural constituent in another *Lendenfeldia* sponge collected at Saipan (Mariana Islands)[45]. This sponge also contained compounds **29** and **36**. Compound **32** was found to inhibit tumour cell growth in the National Cancer Institute´s 60-cell line panel with some cell line selectivity (mean GI_{50}= 1.17 μM; range 0.26 to 3.55 μM)[43]. Compound **35** exhibited cytotoxic activity against three tumour cell lines (breast carcinoma MDA-MB-231, GI_{50}= 2.0 μg/mL; lung carcinoma A549, GI_{50}= 0.1 μg/mL; colon carcinoma HT29, GI_{50}= 1.0 μg/mL)[44]. Compounds **29**, **35** and **36** were cytotoxic to four tumour cell lines (breast carcinoma MCF-7, MDA-MB-231, and T47D and prostate tumour PC-3 cells)[45]. 24-Methyl-12,24,25-trioxoscalar-16-en-22-oic acid (**32**) is also the major constituent of Japanese *Phyllospongia chondrodes*, which, in addition, contained the known homoscalaranes **29**, **31** and **33** together with the new homoscalaranes **37** and **38** [46]. Scalaranes **29**, **31**-**33**, **37** and **38** increased hemoglobin production in human chronic myelogenous leukemia cell line K562 at the concentration of 0.1-5.0 μg/mL, and induced erythroid differen-



27, R_1= Me; R_2= β-$OCOCH_2CH(OH)Me$
28, R_1= Me; R_2= α-OAc
29, R_1= CH_2OH; R_2= =O
30, R_1= CH_2OAc; R_2= =O
31, R_1= CH_2OH; R_2= α-OAc
32, R_1= CO_2H; R_2= =O
33, R_1= CHO; R_2= α-OAc
34, R_1= CO_2H; R_2= α-OH
35, R_1= CO_2Me; R_2= =O
36, R_1= CH_2OH; R_2= α-OH
37, R_1= CHO; R_2= =O
38, R_1=CO_2H; R_2= α-OAc
39, R_1= CH_2OAc; R_2= β-OH



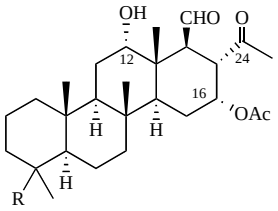
40, R= $EtCH(OH)CH_2CO$-
41, R= $EtCH(OAc)CH_2CO$-
42, R= $EtCH(OCOEt)CH_2CO$-
43, R= $MeCH(OAc)CH_2CO$-
44, R= $MeCH(OCOEt)CH_2CO$-

Fig. (6). Unsaturated 24-homoscalarane and 20,24-bishomoscalaranes.

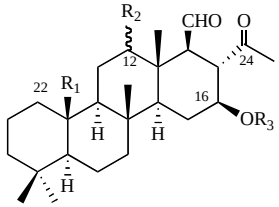
tiation in K562 cells [46]. From the Pacific nudibranch *Glossodoris sedna* was isolated from the 24-homoscalarane **39** (22-acetoxy-24-methyl-12β-hydroxy-24-oxoscalar-16-en-25-al), which was ichthyotoxic at 0.1 ppm against *Gambusia affinis* and inhibited mammalian phospholipase PLA_2 (IC_{50}= 18.0 μM)[47].

Within the subgroup of tetracyclic scalaranes possessing an α,β-unsaturated methyl ketone, there are various 20,24-bishomoscalarane members (compounds **40-44**, Fig. **6**). These metabolites have been isolated from the Australian sponge *Strepsichordaia lendenfeldi* [48,49]. Compounds **41-43** exhibited potent cytotoxicity against two tumour cell lines (mouse lymphoma P388, IC_{50}= 0.12, 0.12 and 0.2 μg/mL; human lung carcinoma A549, IC_{50}= 0.25, 0.21 and 0.2 μg/mL; respectively). Compounds **41** and **42** were also active against *Bacillus subtilis* [48].

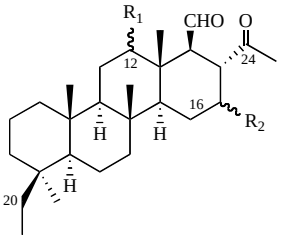
The other subgroup of keto-aldehydes posseses a saturated methyl ketone, and we can also distinguish 24-homoscalarane and 20,24-bishomoscalaranes (compounds **45-61**, Fig. **7**). The first isolated members of this subgroup are scalarherbacin A (**45**) and scalarherbacin B (**46**), which were found in the sponge *Dysidea herbacea* collected at the Red Sea [50]. Several similar 24-methylscalaranes (**47-49**) were obtained from an unclassified Australian sponge of the genus *Carteriospongia* (syn. *Phyllospongia*)[8]. Another Australian sponge of the genus *Carteriospongia*, *C. flabellifera*, contained the homoscalarane **50** [51], whose structure was later confirmed by X-ray diffraction analysis [52]. From an Indonesian sponge, *Phyllospongia* sp., were isolated the homoscalaranes **51** and **52**, whose structu-



45, R= Me
46, R= Et



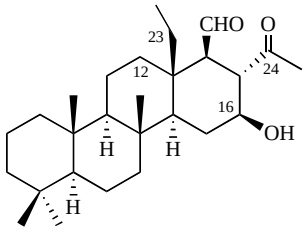
47, R_1= Me; R_2= β-OH; R_3= Ac
48, R_1= Me; R_2= β-OH; R_3= H
49, R_1= CH_2OAc; R_2= =O; R_3= Ac
50, R_1= Me; R_2= =O; R_3= Ac
51, R_1= Me; R_2= α-OAc; R_3= H
52, R_1= Me; R_2= α-OAc; R_3= Ac
53, R_1= Me; R_2= =O; R_3= H



54, R_1= β-OH; R_2= α-$EtCHOHCH_2CO_2$-
55, R_1= α-OAc; R_2= β-OH
56, R_1= =O; R_2= a-$EtCHOHCH_2CO_2$-
57, R_1= =O; R_2= a-$(Me)_2CHOHCH_2CO_2$-
58, R_1= α-OAc; R_2= β-$MeCHOHCH_2CO_2$-
59, R_1= α-OAc; R_2= β-$EtCHOHCH_2CO_2$-
60, R_1= α-OAc; R_2= β-OCOEt
61, R_1= α-OAc; R_2= β-OAc

Fig. (7). Saturated 24-homoscalarane and 20,24-bishomoscalaranes.

res were confirmed by X-ray analysis. Both compounds exhibited 30-95% inhibition of the growth of KB cells at 10 μg/mL [53]. 12α-Acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25-al (**51**) was also found, together with 16β-hydroxy-24-methyl-12,24-dioxoscalaran-25-al (**53**), in *Lendenfeldia* sponges collected at Madagascar. Both compounds (**51** and **53**) were shown to be cytotoxic against fourteen human tumour cell lines (IC_{50}= 1.45-3.86 μg/mL)[44].

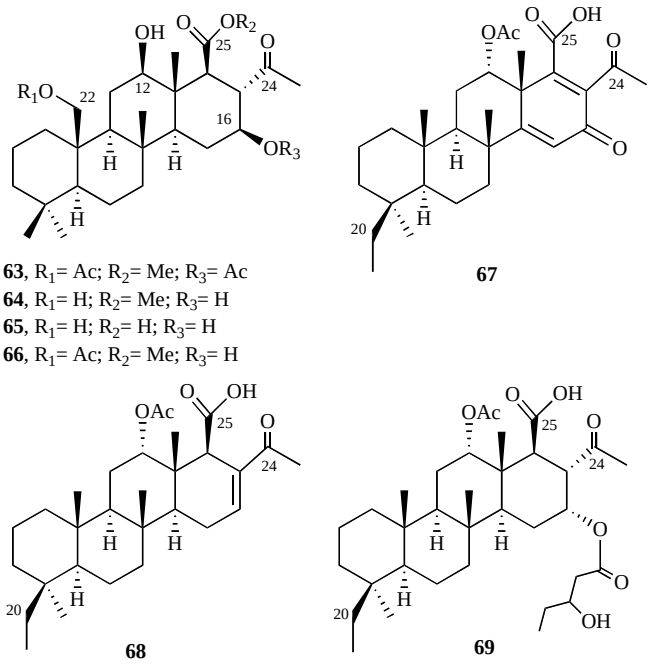


62

Fig. (8). 23,24-Bishomoscalarane **62**.

Within the subgroup of tetracyclic scalaranes possessing a saturated methyl ketone, there are various 20,24-bishomoscalarane members (compounds **54-61**, Fig. **7**). The first isolated member of this subgroup is foliaspongin (**54**), which has been found in the Okinawan sponge *Phyllospongia foliascens* and showed antiinflammatory properties [54]. From the Neo Guinean sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* was isolated 12α-acetoxy-16β-hydroxy-20,24-

dimethyl-24-oxoscalaran-25-al (**55**), which was ichthyotoxic to the fish *Lebistes reticulatus* (LD= 5 mg/L)[55]. Compound **55** has also been found in *Lendenfeldia* sponges collected at Madagascar [44], in the Australian sponge *Strepsichordaia lendenfeldi* [48], and an Indonesian sponge, *Phyllospongia* sp. [53]. This compound (**55**) exhibited potent cytotoxicity against thirteen human tumour cell lines (IC_{50}= 1.13-1.99 μg/mL)[44], two additional tumour cell lines (mouse lymphoma P388 and human lung carcinoma A549, IC_{50}= 0.1 μg/mL)[48], and exhibited 30-95% inhibition of the growth of KB cells at 10 μg/mL [53]. Later, re-examination of Okinawan sponges *Phyllospongia foliascens* yielded dehydrofoliaspongin (**56**) and phyllofoliaspongin (**57**) together with known foliaspongin (**54**), whose structure was revised based on chemical and physical evidence (ethyl group at C-4 is axial, β)[56]. Phyllofoliaspongin (**57**) showed cytotoxic, anti-trhrombocyte and vasodilative activities [56]. Similar 20,24-dimethylscalaranes (compounds **58-61**) were isolated from Australian sponges *Strepsichordaia lendenfeldi* [48,49]. Compounds **58-60** exhibited potent cytotoxicity against two tumour cell lines (mouse lymphoma P388, IC_{50}= 0.23, 0.5 and 0.67 μg/mL; human lung carcinoma A549, IC_{50}= 0.66, 0.5 and 0.67 μg/mL; respectively). Furthermore, compound **58** was active against *Bacillus subtilis* and *Staphylococcus aureus* and compound **60** was also active against *Bacillus subtilis* [48].



63, R_1= Ac; R_2= Me; R_3= Ac
64, R_1= H; R_2= Me; R_3= H
65, R_1= H; R_2= H; R_3= H
66, R_1= Ac; R_2= Me; R_3= H

67 **68** **69**

Fig. (9). 25-Oxidised 24-homoscalarane and 20,24-bishomoscalaranes.

Within the subgroup of tetracyclic scalaranes possessing a saturated methyl ketone, there is a rare 23,24-bishomoscalarane member (compound **62**, Fig. **8**), which was isolated from the Northern Adriatic sponge *Cacospongia scalaris* [57]. This compound is characterised by the lack of functionality at C-12 and methylation at C-23.

Finally, we describe several tetracyclic scalaranes that are metabolites related to 24-homoscalarane and 20,24-bishomoscalaranes. They are characterised by the oxidation state at C-25 as well as the lack of this carbon (25-norscalaranes). The first subgroup is composed of scalaranes possessing a carboxylic acid or derivative at C-25 (compounds **63-69**, Fig. **9**). For example, 24-homoscalarane **63** was found in the sponge *Lendenfeldia frondosa* collected at Solomon Islands [58]. 24-Homoscalaranes **64-66** were isolated from two different species of Madagascan sponges of the genus *Lendenfeldia* [44]. Methyl 12β,16β,22-trihydroxy-24-methyl-24-oxoscalaran-25-carboxylate (**64**) exhibited cytotoxicity against the human lung carcinoma A549 cell line (IC_{50}= 3.7 μg/mL)[44]. 20,24-Dimethylscalarane **67** has been isolated, as its methyl ester, from the Neo Guinean sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* [55], and its structure was confirmed by single-crystal X-ray diffraction [59]. From another sponge also collected at Papua New Guinea, *Phyllospongia papyracea*, were isolated the 20,24-bishomoscalaranes **68** and **69** [60].

The last group of tetracyclic scalaranes is composed of 24-homo-25-norscalarane and 20,24-bishomo-25-norscalaranes (compounds **70-84**, Fig. **10**). For example, 25-nor-24-methyl-12,24-dioxoscalar-16-en-22-oic acid (**70**) was isolated from Palauan sponges (*Dictyoceratida* sp. and *Halichondria* sp.)[41]. 12β, 16β,22-Trihydroxy-24-methyl-24-oxo-25-norscalarane (**71**) was found in the sponge *Phyllospongia dendyi* collected at the Indian Ocean [61]. 24-Methylscalaranes **72** and **73** have been isolated from an Indonesian sponge, *Phyllospongia* sp., and both compounds exhibited 30-95% inhibition of the growth of KB cells at 10 μg/mL [53]. 20,24-Dimethylscalarane **74** (phyllofenone A) was isolated from the South China Sea sponge, *Phyllospongia foliascens*, and showed weak antifungal activity against *Candida pseudotropicalis* [62]. Another specimen of the same Chinese sponge, *Phyllospongia foliascens*, contained a related 20,24-dimethylscalarane, phyllofenone E (**75**)[63]. From the same sponge, *Carteriospongia* (syn. *Phyllospongia*) *foliascens*, collected at Great Barrier Reef, compounds **76** and **77** on isolated [64]. Another specimen of the sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* collected at Papua New Guinea contained the related 20,24-dimethylscalarane **78**, which was moderately ichthyotoxic to the fish *Lebistes reticulatus* (LD= 20 mg/L)[55]. Compound **78** has also been found in an

Indonesian sponge, *Phyllospongia* sp., and exhibited 30-95% inhibition of the growth of KB cells at 10 μg/mL [53]. 25-Nor-12α-acetoxy-16β-(3'-hydroxy-butanoyloxy)-20,24-dimethyl-24-oxoscalarane (**79**) has been isolated from the Australian sponge *Strepsichordaia lendenfeldi* [49]. The related 20,24-dimethyl-25-norscalarane **80** was isolated from the Madagascaran sponge *Phyllospongia madagascarensis* [65]. Finally, there are several uncommon compounds that lack the C-25 and possess a double bond instead. For example, phyllofenone C (**81**), which was isolated from the Indonesian sponge, *Strepsichordaia aliena* [66]. Compound **82** is a chemical constituent of the sponge *Phyllospongia papyracea* collected from Hainan Island in the South China Sea. 12α-Acetoxy-16β-hydroxy-20,24-dimethyl-25-norscalar-17-en-24-one (**82**) was cytotoxic against the leukemia P388 cancer cell line, with an IC_{50} value of 5.0 μg/mL [67]. Recently, two new 20,24-bishomo-25-norscalaranes, compounds **83** and **84**, have been isolated from the Indonesian sponge *Carteriospongia* (syn. *Phyllos-pongia*) *foliascens*. Bishomonorscalarane **84** is an inhibitor of Ras proteolytic enzyme (IC_{50} = 38 μg/mL) and also inhibits the growth of four tumour cell lines (prostate PC3, IC_{50}= 3.8 μg/mL; colon LoVo, IC_{50}= 7.6 μg/mL; colon CACO2, IC_{50}= 3.4 μg/mL; breast MDA 468, IC_{50}= 9.5 μg/mL)[68].

2.2. Pentacyclic Scalaranes

The first subgroup of pentacyclic scalaranes contains compounds derived formally from scalarin (**1**), and therefore characterised by the functionalisation present in ring E, either a γ-lactol or a γ-lactone ring E (Fig. **11**). Scalarin (**1**) was first isolated in 1972 by Fattorusso *et al*. from the sponge *Cacospongia scalaris* collected in the gulf of Naples (Italy)[9]. Later, it has been found in other sponges *Cacospongia scalaris* collected at the Southern Coast of Spain [14] and collected at the gulf of Astakos (Greece)[69], as well as other different marine sponges. For example, scalarin (**1**) was found among the constituents of an undescribed sponge species of *Cacospongia* collected at Apra Harbor, Guam (Micronesia)[16,17], the sponges *Dysidea villosa* and *Dysidea marshalla* collected at the South China sea [18], the sponge *Hyatella intestinalis* collected at the gulf of California [39], the sponge *Hyrtios* sp. collected off Okinawa Island [70], the sponge *Spongia matamata* collected at Palau [71], the sponge *Hyrtios erecta* collected at Hainan (China)[72], and an unnamed sponge of the genus *Ircinia* [73]. During these studies, the structure and relative stereochemistry of scalarin (**1**) was verified by X-ray crystallography [73], however, the potential biological activity of this molecule has not yet been studied.

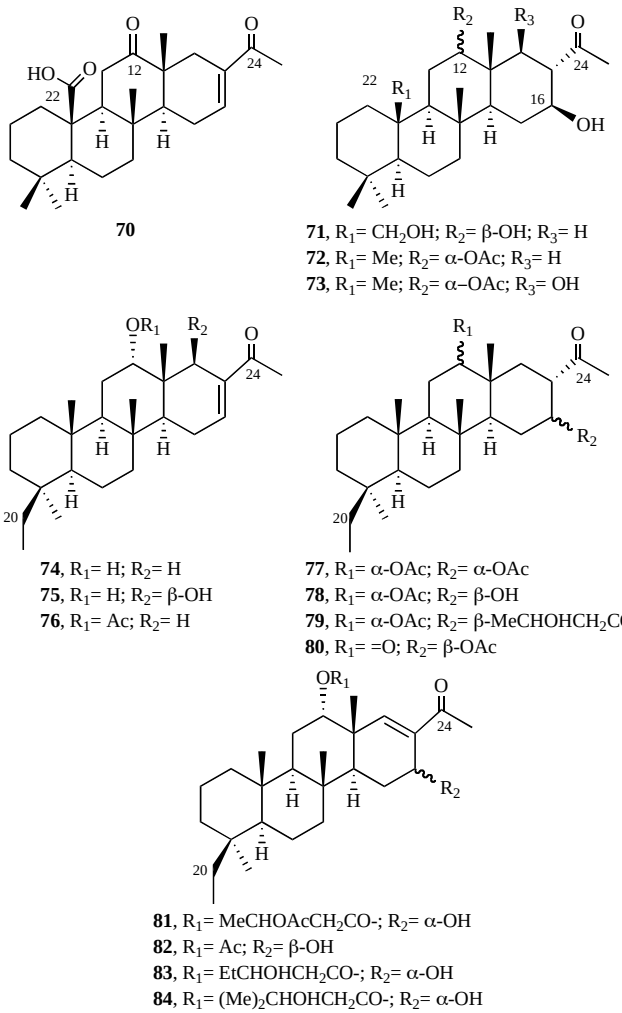


Fig. 10. 24-Homo-25-norscalaranes **70**-**73** and 20,24-bishomo-25-norscalaranes **74**-**84**.

A number of scalarin-related metabolites have been isolated, They differ mainly in the functionalisation at C-12 and C-25 (compounds **85-103**, Fig. **11** and **12**). For example, 12-epi-scalarin (**85**) was first isolated in 1977 from the Mediterranean sponge *Spongia nitens* [74]. Later, it has been found in the Tongan sponge *Hyrtios erecta* [28], in the sponge *Spongia agaricina* collected near Tarifa Island (Spain)[30], in a sponge *Hyrtios* sp. collected at American Samoa [32], in the sponges *Hyrtios erecta* collected at Setouchi (Japan)[75] and collected from Hainan Island in the South China Sea [76], in sponges of the genus *Spongia* collected at the Japan Sea [77,78] and collected at the South Sea of Korea [79], and in the nudibranch *Chromodoris funerea* collected at Kaibakku Lake, Palau [80]. 12-Epi-scalarin (**85**) exhibited moderate cytotoxicity towards four tumour cell lines (murine leukemia L1210, IC_{50}= 13.2 μg/mL; human cervix epithelioid carcinoma HeLa, IC_{50}= 26.0 μg/mL; human lung carcinoma A549, IC_{50}= 23.7 μg/mL; and human oral

Table 1. Biological Activity Found in Compounds 2-84

Compound	Biological activity
Scalaradial, **2**	Cytotoxic [12b]
Scalaradial, **2**	Antifeedant [16,17]
Scalaradial, **2**	Antitumour [18]
Scalaradial, **2**	Ichthyotoxic [19]
Scalaradial, **2**	Phospholipase A_2 (PLA_2) inhibition [24,25]
Desacetylscalaradial, **3**	Cytotoxic [13]
Desacetylscalaradial, **3**	Ichthyotoxic [19]
12-Deacetoxyscalaradial, **4**	Cytotoxic and antifeedant [12b]
12-Epi-scalaradial, **5**	PLA_2 inhibition and antiinflammarory [25]
12-Epi-scalaradial, **5**	Antimicrobial [29]
12-Epi-scalaradial, **5**	Antitubercular, antimicrobial and cytotoxic [31,32]
12-Epi-scalaradial, **5**	Epidermal growth factor receptor (EGFR) inhibition [33]
12-Deacetyl-12-epi-scalaradial, **6**	Antitubercular [31]
12-Deacetyl-12-epi-scalaradial, **6**	Antimicrobial and cytotoxic [32]
25-Dihydroscalaradial, **7**	Cytotoxic [14]
18-epi-scalaradial, **8**	Cytotoxic[14]
12,18-Diepi-scalaradial, **9**	Antimicrobial [29]
12-Deacetyl-12,18-diepi-scalaradial, **10**	Antitubercular, antimicrobial and cytotoxic [31,32]
12-Deacetyl-12,18-diepi-scalaradial, **10**	Antifeedant [34,35]
12-Deacetyl-18-epi-12-oxoscalaradial, **11**	Antimicrobial and cytotoxic [32]
12-Deacetyl-12-oxoscalaradial, **12**	Ichthyotoxic [19] and antitubercular [31]
12-Deacetyl-12-oxoscalaradial, **12**	Antimicrobial and cytotoxic [32]
Mooloolabenes A (**13**), B (**14**) and C (**15**)	Cytotoxic [36]
Compounds **16**-**18**	Cytotoxic [37]
Compound **18**	Antimicrobial [37]
Hyrtial, **19**	Antiinflammatory [28]
12-Deacetylhyrtial, **20**	Antimicrobial [29]
12-Deacetylhyrtial, **20**	Cytotoxic [38]
Compound **21**	Antimicrobial [29]
12-Deacetyl- Δ^{17}-hyrtial, **22**	Cytotoxic [38]
Norscalarals A-C, **23**-**25**	Cytotoxic [14]
12-Deacetylnorscalaral B, **26**	Cytotoxic [39]
24-Methyl-24,25-dioxoscalar-16-en-12β-yl 3-hydroxybutanoate, **27**	Antifungal and antiinflammatory [8]
22-Hydroxy-24-methyl-12,24-dioxoscalar-16-en-25-al, **29**	Cytotoxic [45] and antitumour [46]
12α-Acetoxy-22-Hydroxy-24-methyl-24-oxoscalar-16-en-25-al, **31**	Antitumour [46]
24-Methyl-12,24,25-trioxoscalar-16-en-22-oic acid, **32**	Antitumour [43,46]

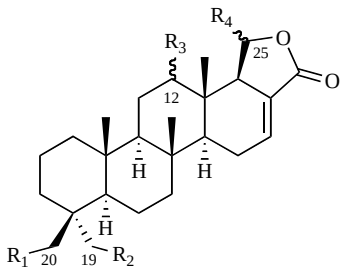
(Table 1) Contd.…

Compound	Biological activity
12α-Acetoxy-24-methyl-24-oxoscalar-16-en-22,25-dial, **33**	Platelet aggregation inhibition [41] and antitumour [46]
24-Methyl-12,24,25-trioxoscalar-16-en-22-oate, **35**	Cytotoxic [44,45]
22-Hydroxy-24-methyl-12α-hydroxy-24-oxoscalar-16-en-25-al, **36**	Cytotoxic [45]
24-Methyl-12,24-dioxoscalar-16-en-22,25-dial, **37**	Antitumour [46]
12α-Acetoxy-24-Methyl-24,25-dioxoscalar-16-en-22-oic acid, **38**	Antitumour [46]
22-Acetoxy-24-methyl-12β-hydroxy-24-oxoscalar-16-en-25-al, **39**	Ichthyotoxic and PLA_2 inhibition [47]
12α-(3'-Acetoxypentanoyloxy)-20,24-dimethyl-24-oxoscalar-16-en-25-al, **41**	Antimicrobial and cytotoxic [48]
12α-(3'-Propanoyloxypentanoyloxy)-20,24-dimethyl-24-oxoscalar-16-en-25-al, **42**	Antimicrobial and cytotoxic [48]
12α-(3'-Acetoxybutanoyloxy)-20,24-dimethyl-24-oxoscalar-16-en-25-al, **43**	Cytotoxic [48]
12α-Acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25-al, **51**	Cytotoxic [44,53]
12α,16β-Diacetoxy-24-methyl-24-oxoscalaran-25-al, **52**	Cytotoxic [53]
16β-Hydroxy-24-methyl-12,24-dioxoscalaran-25-al, **53**	Cytotoxic [44]
Foliaspongin, **54**	Antiinflammatory [54]
12α-Acetoxy-16β-hydroxy-20,24-dimethyl-24-oxoscalaran-25-al, **55**	Cytotoxic [44,48,53] and ichthyotoxic [55]
Phyllofoliaspongin, **57**	Cytotoxic, anti-thrombocyte and vasodilative [56]
12α-Acetoxy-16β-(3'-hydroxybutanoyloxy)-20,24-dimethyl-24-oxoscalaran-25-al, **58**	Antimicrobial and cytotoxic [48]
12α-Acetoxy-16β-(3'-hydroxypentanoyloxy)-20,24-dimethyl-24-oxoscalaran-25-al, **59**	Cytotoxic [48]
12α-Acetoxy-16β-propanoyloxy-20,24-dimethyl-24-oxoscalaran-25-al, **60**	Antimicrobial and cytotoxic [48]
Methyl 12β,16β,22-trihydroxy-24-methyl-24-oxoscalaran-25-carboxylate, **64**	Cytotoxic [44]
12α-Acetoxy-16β-hydroxy-24-methyl-24-oxo-25-norscalarane, **72**	Cytotoxic [53]
12α-Acetoxy-16β,18β-dihydroxy-24-methyl-24-oxo-25-norscalarane, **73**	Cytotoxic [53]
Phyllofenone A, **74**	Antifungal [62]
12α-Acetoxy-16β-hydroxy-20,24-dimethyl-24-oxo-25-norscalarane, **78**	Cytotoxic [53] and ichthyotoxic [55]
12α-Acetoxy-16β-hydroxy-20,24-dimethyl-25-norscalar-17-en-24-one, **82**	Cytotoxic [67]
12α-(3'-Hydroxy-4'-methylpentanoyloxy)-16α-hydroxy-20,24-dimethyl-25-norscalar-17-en-24-one, **84**	RCE-protease inhibition and antitumour [68]

epidermoid carcinoma KB, IC_{50}= 18.5 μg/mL)[77], as well as neurotrophic activity in pheochromocytoma (PC-12) cells at the concentration of 50 μg/mL [78]. Compound **85** also showed inhibition of farnesoid X-activated receptor (FXR) transactivation, which is related to potential drugs for hypercholesterolemia in humans, with IC_{50} value of 60.4 μM [79].

12-*O*-Deacetyl-scalarin (**86**) has been isolated from the sponge *Dysidea villosa* collected at the South China sea [18], and a sponge *Hyrtios* sp. collected off Okinawa Island [70]. Compound **86** exhibited nerve growth factor (NGF) synthesis-stimulating activity in cultured astroglial cells at 30 μg/mL, 4.8-fold of normal control, which has led to a patent for the treatment of Alzheimer's disease [70,81].

12-*O*-Deacetyl-12-epi-scalarin (**87**) has been isolated from sponges of the genus *Spongia* collected at the Japan Sea [77,78] and collected at the South Sea of Korea [79], and sponges *Hyrtios erecta* collected at the Red Sea (Egypt)[82], and collected near Kavieng, Papua New Guinea [83]. 12-*O*-Deacetyl-12-epi-scalarin (**87**) exhibited moderate cytotoxicity towards four tumour cell lines (murine leukemia L1210, IC_{50}= 2.3 μg/mL; human cervix epithelioid carcinoma HeLa, IC_{50}= 15.0 μg/mL; human lung carcinoma A549, IC_{50}= 14.8 μg/mL; human oral epidermoid carcinoma KB,



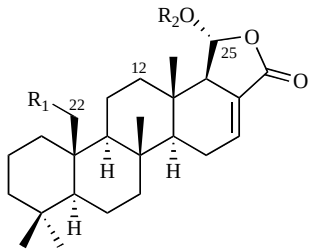
1, R_1= R_2= H; R_3= α-OAc; R_4= α-OH
85, R_1= R_2= H; R_3= β-OAc; R_4= α-OH
86, R_1= R_2= H; R_3= α-OH; R_4= α-OH
87, R_1= R_2= H; R_3= β-OH; R_4= α-OH
88, R_1= R_2= H; R_3= α-OH; R_4= β-OH
89, R_1= R_2= H; R_3= α–OAc; R_4= H
90, R_1= R_2= H; R_3= β-OAc; R_4= H
91, R_1= R_2= H; R_3= β-OH; R_4= H
92, R_1= R_3= H; R_2= OAc; R_4= α-OH
93, R_1= OAc; R_2= R_4= H; R_3= β-OAc
94, R_1= R_4= H; R_2= OAc; R_3= β-OAc
95, R_1= R_3= H; R_2= OAc; R_4= α-OAc
96, R_1= R_2= H; R_3= β-OH; R_4= α-OMe
97, R_1= R_4= H; R_2= OH; R_3= β-OH
98, R_1= OH; R_2= R_4= H; R_3= β-OH

Fig. (11). Scalarin (**1**) and related metabolites.

IC_{50}= 14.3 μg/mL)[77], as well as neurotrophic activity in pheochromocytoma (PC-12) cells at the concentration of 50 μg/mL [78]. Compound **87** also showed inhibition of farnesoid X-activated receptor (FXR) transactivation with IC_{50} value of 75.0 μM [79]. The chemical study of the sponge *Hyatella intestinalis*, collected at the gulf of California, has yielded the new sesterterpene 12-*O*-deacetyl-25-epi-scalarin (**88**)[39].

25-Dehydroxy-scalarin (**89**) has been found in the sponge *Cacospongia scalaris* collected at the Southern Coast of Spain [14], Meanwhile its epimer at C-12, 25-dehydroxy-12-epi-scalarin (**90**), was isolated from the Pacific nudibranch *Glossodoris dalli* extract, after acetylation [47], and also from the sponges *Hyrtios erecta* collected at the South China Sea [76] and *Brachiaster* sp. collected near Koh-Tao (Thailand)[84]. Both compounds (**89** and **90**) have been prepared by semisynthesis from scalarin (**1**) and 12-epi-scalarin (**85**), respectively [74]. Compound **90** has displayed both antitubercular (MIC= 117 μM) and cytotoxic activities (human breast adenocarcinoma MCF-7, IC_{50}= 5.2 μM; colorectal carcinoma HT-29, IC_{50}= 2.3 μM; human cervical carcinoma HeLa, IC_{50}= 5.5 μM; and human oral epidermoid carcinoma KB, IC_{50}= 3.0 μM)[84].

25-Dehydroxy-12-epi-deacetylscalarin (**91**) was first isolated in 1995 from the sponge *Heteronema* (syn. *Hyrtios*) *erecta* [85]. Later, it has been found in other sponges *Hyrtios erecta* collected at Hainan Island



99, R_1= OH; R_2= Ac
100, R_1= H; R_2= H
101, R_1= H; R_2= Ac
102, R_1= OAc; R_2= Ac
103, R_1= OAc; R_2= H

Fig. (12). Scalarin-related metabolites **99**-**103**.

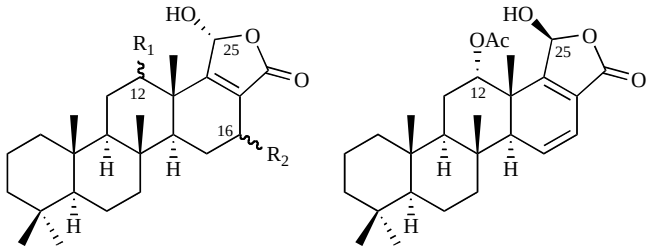
in the South China Sea [72], collected at the Indian Ocean, which included the X-ray structure determination [86], and collected at the Red Sea (Egypt)[87], as well as other different marine sponges. For example, compound **91** was found among the constituents of three undescribed sponge species of the genus *Spongia* collected at the Japan Sea [77,78] and collected at the South Sea of Korea [79], the sponge *Brachiaster* sp. collected near Koh-Tao (Thailand)[84], the sponge *Hyatella cribriformis* collected at the Indian Ocean [88], and the Thai sponge *Hyrtios gumminae* [89]. Recently, compound **91** has been prepared by semisynthesis from other natural pentacyclic scalaranes [32]. The biological activity of compound **91** is wide, for example, it has been described as a neurotrophic agent in pheochromocytoma (PC-12) cells at 50 μg/mL [78], as a farnesoid X-activated receptor (FXR) transactivation inhibitor (IC_{50}= 31.6 μM)[79], as a murine lymphocytic leukemia P388 cell line inhibitor (ED_{50}= 2.9 μg/mL)[86], and as a weak antitubercular agent (MIC= 16 μM [84]; 16% inhibition against *Mycobacterium tuberculosis* ($H_{37}Rv$) at 6.25 μg/mL)[87]. In addition, compound **91** has displayed cytotoxicity against a number of cancer cell lines (murine leukemia L1210, IC_{50}= 1.6 μg/mL; human cervix epithelioid carcinoma HeLa, IC_{50}= 16.5 μg/mL; human lung carcinoma A549, IC_{50}= 16.5 μg/mL; and human oral epidermoid carcinoma KB, IC_{50}= 17.1 μg/mL)[77]; human breast adenocarcinoma MCF-7, IC_{50}= 0.3 μM; colorectal carcinoma HT-29, IC_{50}= 0.9 μM; human cervical carcinoma HeLa, IC_{50}= 2.0 μM; and human oral epidermoid carcinoma KB, IC_{50}= 0.7 μM [84]; and human cholangiocarcinoma HuCCA-1, IC_{50}= 42 μM; human oral epidermoid carcinoma KB, IC_{50}= 7.0 μM; human cervical carcinoma HeLa, IC_{50}= 23 μM; hormone-independent breast cancer MDA-MB-231, IC_{50}= 5.9 μM; hormone-dependent breast cancer T47D, IC_{50}= 5.2 μM; and multidrug-resistant small-cell lung cancer H69AR, IC_{50}= 57 μM [89]. However, semisynthetic **91** lacks cytotoxicity at doses up to 45 μM against three human cancer cell lines (ovarian cancer SKOV3; melanoma SK-MEL; and

breast cancer BT549) and was not active against *Mycobacterium intracellulare* and methicillin-resistant *Staphylococcus aureus* [32].

12-Deacetoxy-19-acetoxyscalarin (**92**) was isolated from the sponge *Hyrtios erectus* (also called *H. erecta*) collected from Southern Japan and exhibited cytotoxicity against P388 murine leukemia cells (IC_{50}= 0.9 μg/mL)[90]. From the sponge *Hyrtios erecta*, collected from Hainan Island in the South China Sea, hyrtiosins A-C (**93-95**) were isolated [76]. We must say at this point that the names hyrtiosin A and B had been used previously for two indole alkaloids [91]. A sponge specimen of the genus *Spongia* collected at the South Sea of Korea contained the scalarin-related compounds **96-98** and exhibited inhibition of farnesoid X-activated receptor (FXR) transactivation with IC_{50} values of 24.0, >100, and 2.4 μM, respectively [79]. Compound **96** has been also isolated from a sample of the sponge *Hyrtios erecta* collected near Kavieng, Papua New Guinea, though this compound might be an isolation artifact [83].

The group of scalarin-related metabolites also includes a number of compounds which are characterised by the lack of functionality at C-12 (compounds **99-103**, Fig. **12**). For example, 12-deacetoxy-22-hydroxy-25-acetoxyscalarin (**99**) was found in the Korean sponge *Smenospongia* sp., and showed moderate cytotoxicity against human chronic myelogenous leukemia K562 cell line (LC_{50} 22.5 μg/mL)[37]. In addition, compound **99** exhibited antibacterial activity against both Gram-positive and -negative bacteria [37]. Deacetoxyscalarin (**100**) has been isolated from a sponge of the genus *Spongia* collected at the Japan Sea [78]. 12-Deacetoxy-25-acetoxy-scalarin (**101**) was isolated from the Thai sponge *Brachiaster* sp. and showed potent antitubercular activity (MIC= 4 μM)[84]. 12-Deacetoxy-22,25-diacetoxy-scalarin (**102**) and 12-deacetoxy-22-acetoxyscalarin (**103**) were isolated from the sponge *Smenospongia* sp. collected at Gagu-Do Island (Korea) and displayed moderate cytotoxicity toward the human leukemia cell line K562 (LC_{50} 4.9 and 11.2 μg/mL, respectively)[92].

Other scalarin-related metabolites are characterised by a γ-lactol ring E possessing a double bond between C-17 and C-18 (compounds **104-108**, Fig. **13**), instead of the typical double bond between C-16 and C-17. Hyrtiolide (**104**) has been isolated from an Okinawan specimen of *Hyrtios erectus* (also called *H. erecta*)[38] and the Thai sponge *Hyrtios gumminae* [89]. Hyrtiolide (**104**) showed weak cytotoxic activity against several cancer cell lines (human cholangiocarcinoma HuCCA-1, IC_{50}= 57 μM; human oral epidermoid carcinoma KB, IC_{50}= 12 μM; human cervical carcinoma HeLa, IC_{50}= 22 μM; hormone-independent breast cancer MDA-MB-231, IC_{50}= 26 μM; and hormone-dependent breast cancer T47D, IC_{50}= 34 μM)[89]. 12α-*O*-Acetylhyrtiolide (**105**) was found in a Chinese specimen of *Hyrtios erectus* (also called *H. erecta*)[72]. The related 12-*O*-acetyl-16-*O*-methylhyrtiolide (**106**), however, was isolated in a sponge of the genus *Spongia* collected at the Japan Sea and exhibited cytotoxicity against four tumour cell lines (murine leukemia L1210, IC_{50}= 2.2 μg/mL; human cervix epithelioid carcinoma HeLa, IC_{50}= 5.3 μg/mL; human lung carcinoma A549, IC_{50}= 5.3 μg/mL; and human oral epidermoid carcinoma KB, IC_{50}= 15.6 μg/mL)[77]. Sesterstatin 6 (**107**) was isolated from an Indian Ocean specimen of the sponge *Hyrtios erecta*, and showed significant cancer cell growth inhibition against murine P388 lymphocytic leukemia (ED_{50}= 0.17 μg/mL) and a series of human tumour cell lines (human pancreas carcinoma BXPC-3, GI_{50}= 0.44 μg/mL; thyroid KAT-4, GI_{50}= 0.4 μg/mL; thyroid SW1736, GI_{50}= 0.87 μg/mL; lung-NSC NCI-H460, GI_{50}= 0.18 μg/mL; pharynx-sq FADU, GI_{50}= 0.89 μg/mL; prostate DU-145, GI_{50}= 0.37 μg/mL)[93]. Another compound belonging to this subgroup is 12α-acetoxy-19β-hydroxyscalara-15,17-dien-24,25-olide (**108**) which is characterised by an additional double bond, probably formed by elimination of an oxygenated-precursor at C-16. This compound was found in the sponge *Spongia matamata* collected at Risong marine lake, Republic of Palau [71].



104, R_1= β-OH; R_2= α-OH
105, R_1=α-OAc; R_2= α-OH
106, R_1= β-OAc; R_2= α-OMe
107, R_1= β-OH; R_2= β-OH

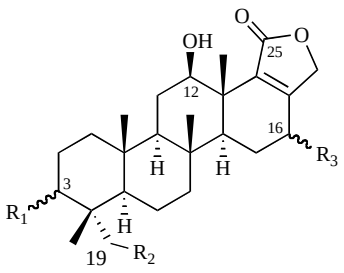
108

Fig. (13). Hyrtiolide-related metabolites **104-108**.

Another subgroup of scalarane metabolites which also contains a double bond between C-17 and C-18 are compounds **109-116** (Fig. **14**). These compounds are also characterised by a γ-lactone ring E having the carbonyl group located at C-25. There is a variety of oxygenation pattern at C-3, C-12, C-16 and C-19. For example, scalarolide (**109**) was isolated from the sponge *Spongia idia* [34] and *Leiosella idia* [35] collected at Point Loma, San Diego, California, USA. Also, compound **109** was isolated from the Okinawan sponge *Hyrtios erectus* (also called *H. erecta*)[38], from a sponge *Cacospongia* sp. collected at Little Barrier Island, New Zealand [94], from the Red Sea sponge *Hyr-*

tios erecta [82,95], from the sponge *Hyatella cribriformis* of the Indian Ocean [88], and the Thai sponge *Hyrtios gumminae* [89]. The X-ray structure of scalarolide (**109**) has been reported [73] as well as its semisynthesis [96]. Sesterstatins 1-3 (**110-112**) were isolated from The Republic of Maldives´ sponge *Hyrtios erecta* and showed cytotoxic activity against P-388 leukemia (ED_{50}= 0.46, 4.2 and 4.3 μg/mL, respectively)[97].

16β-Hydroxyscalarolide (**113**) was found in the sponges *Hyrtios erectus* (also called *H. erecta*) collected at Okinawa [38] and Red Sea [82]. 19-Acetylsesterstatin 3 (**114**) and 3-acetylsesterstatin 1 (**115**) and sesterstatin 7 or 16β-acetoxyscalarolide (**116**) were found in the Red Sea sponge *Hyrtios erecta* [87,89,95]. Sesterstatin 7 (**116**) has been previously reported as a semisynthetic intermediate from the compound 16β-hydroxyscalarolide [38]. Compounds **115** and **116** showed inhibition of *Mycobacterium tuberculosis* ($H_{37}Rv$)[87].



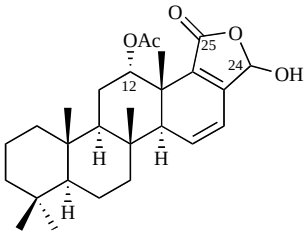
109, R_1= R_2= R_3= H
110, R_1= β-OH; R_2= R_3= H
111, R_1= H; R_2= C-20,OH; R_3= H
112, R_1= H; R_2= C-19,OH; R_3= H
113, R_1= H; R_2= H; R_3= β-OH
114, R_1= H; R_2= C-19,OAc; R_3= H
115, R_1= β-OAc; R_2= H; R_3= H
116, R_1= R_2= H; R_3= β-OAc

Fig. (14). Scalarolide-related metabolites **109-116**.

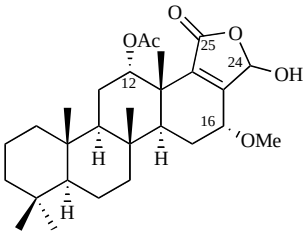
Another subgroup of scalarane metabolites, which also contains a double bond between C-17 and C-18 and a γ- lactol/lactone ring E (butenolide/hydroxybutenolide, having the carbonyl group located at C-25), are compounds **117-154** (Fig. **15** and **16**). Some of these compounds are characterised by a γ-hydroxybutenolide ring E (compounds **117-129**, Fig. **15**). For example, hyatolide E (**117**) and the related γ-lactols hyatolide C (**118**, OH-24β) and hyatolide D (**119**, OH-24α), both isolated as a 2.5:1 mixture of epimers, respectively, have been found during the chemical study of *Hyatella intestinalis* from the Gulf of California [39]. 24-Hydroxy-scalarolide (**120**) was found in the Great Barrier Reef sponge *Collospongia auris* and showed antimicrobial activity using the standard disk assay against *Staphylo-coccus aureus* (25 μg/disk), *Bacillus subtilis* (25 μg/disk), and *Candida albicans* (50 μg/disk)[29]. The related γ-hydroxybutenolides 12β-acetoxy-26-hydroxy-17-scalaren-25,24-olide (**121**) and 12β,16α,24-trihy-droxy-17-scalaren-25,24-olide (**122**) were obtained as mixtures of epimers from the Thai sponge *Hyrtios gumminae* [89]. Compound **122** showed weak cytoto-xic activity against several cancer cell lines (human cholangiocarcinoma HuCCA-1, IC_{50}= 65 μM; human oral epidermoid carcinoma KB, IC_{50}= 14.0 μM; human cervical carcinoma HeLa, IC_{50}= 26.0 μM; hormone-independent breast cancer MDA-MB-231, IC_{50}= 29.0 μM; and hormone-dependent breast cancer T47D, IC_{50}= 48.0 μM)[89]. 24β-methoxyscalarolide (**123**) was isolated from the sponge *Hyatella cribriformis* of the Indian Ocean [88].

The six additional γ-hydroxybutenolides (compounds **124-129**) belong to the bishomoscalarane-type of sesterterpenes. For example, phyllolactone E (**124**) was isolated from the marine sponge *Phyllospongia lamellosa* collected at the Indo-West Pacific [98]. Phyllactone D (**125**, Me-24α) and E (**125**, Me-24β) were isolated as a 1:1 mixture of epimers at C-24 from the sponge *Phyllospongia foliascens* collected at the South China Sea [99,100], and the sponge *Phyllospongia papyracea* collected also from the South China Sea [67]. Phyllactone F (**126**, Me-24α) and G (**126**, Me-24β) were also isolated as a 1:1 mixture of epimers at C-24 from the sponge *Phyllospongia foliascens* collected at the South China Sea [101,102]. The corresponding C-12 epimers of phyllactone D (**127**, Me-24α) and E (**127**, Me-24β) were isolated as a 1:4 mixture from the sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* collected at Indonesia [68]. The same sponge also contained the related epimeric 20,24-bishomoscalaranes **128** as a 1:1 mixture at C-24 [68]. The last metabolite having a γ-hydroxybutenolide group is compound **129**, which was isolated as a 1:1 mixture of epimers at C-24 from the sponge *Phyllospongia papyracea* collected at Papua New Guinea [60].

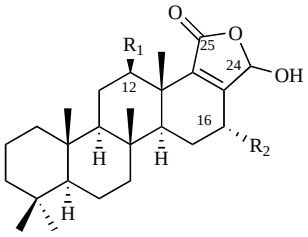
Within this subgroup of scalarane metabolites, possessing a double bond between C-17 and C-18, a γ-lactone ring E (butenolide, having the carbonyl group located at C-25), and a methyl group at C-24, are compounds **130-154** (Fig. **16**). Among these compounds, we can distinguish both homoscalaranes and mainly bishomoscalaranes. For example, 12β,22-dihydroxy-24-methylscalar-17-en-25,24-olide (**130**) has been isolated from the Dorid nudibranch *Chromodoris sedna* [103], and the Indo-Pacific sponge *Lendenfeldia frondosa* [104]. Phyllofolactone D (**131**) was isolated, accompanied by its homologue phyllofolactone C (**132**), from the sponge *Phyllospongia foliascens* collected at the South China Sea [105]. Phyllofolactone B (**133**) was found in a Pacific specimen of the sponge



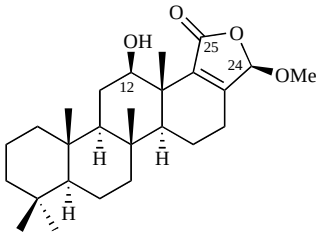
117



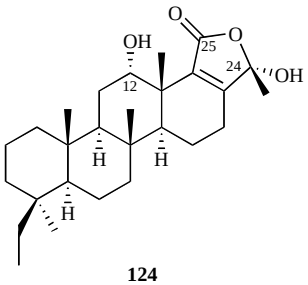
118 OH-24β
119 OH-24α



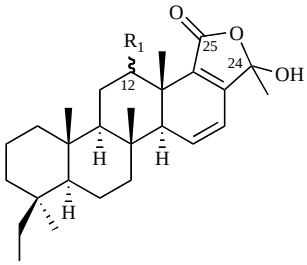
120, R_1= OH; R_2= H
121, R_1= OAc; R_2= H
122, R_1= OH; R_2= OH



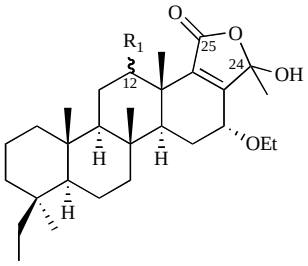
123



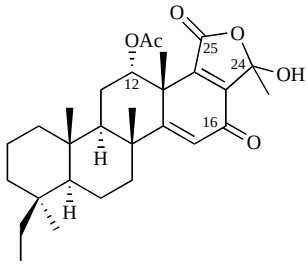
124



125, R_1= β-EtCHOHCH$_2$CO$_2$-
126, R_1= β-iPrCHOHCH$_2$CO$_2$-
127, R_1= α-EtCHOHCH$_2$CO$_2$-



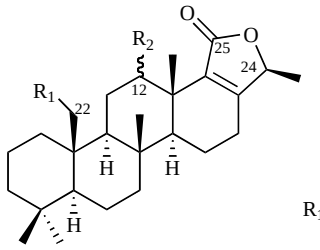
128, R_1= α-iPrCHOHCH$_2$CO$_2$-



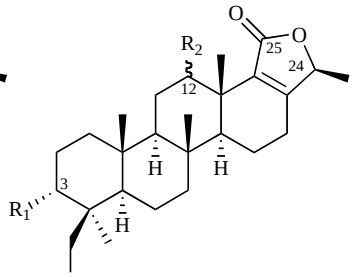
129

Fig. (15). γ-Hydroxybutenolide-based metabolites **117-129**.

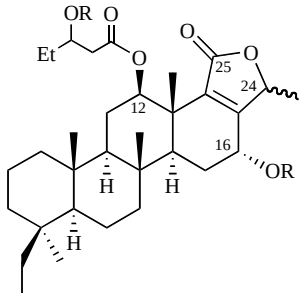
Phyllospongia foliascens [106], while in another sample of the same sponge was found the corresponding C-12 epimer, 12-epi-phyllofolactone B (**134**)[107]. This compound was renamed as phyllofolactone G (**134**) and was also found in another specimen of the sponge *Phyllospongia foliascens* collected at the South China Sea [100], accompanied by the related C24-epimer phyllofolactone F (**134**, Me-24α). Both phyllofolactones F and G (**134**) were also isolated from the sponge *Phyllospongia madagascarensis* and the assignment of the NMR signals were corrected [65]. Phyllolactones A-D (**135-138**) were isolated from the marine sponge



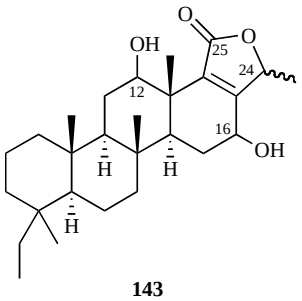
130, R_1= OH; R_2= β-OH
131, R_1= H; R_2= =O



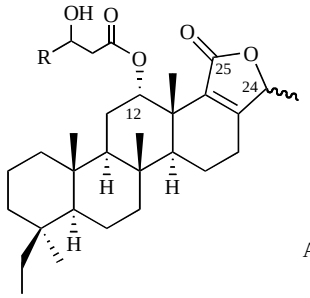
132, R_1= H; R_2= =O
133, R_1= H; R_2= α-OH
134, R_1= H; R_2= β-OH
135, R_1= PrOCO-; R_2= α-OH
136, R_1= EtOCO-; R_2= α-OH
137, R_1= MeOCO-; R_2= α-OH
138, R_1= EtOCO-; R_2= α-OAc
139, R_1= H; R_2= α–OAc



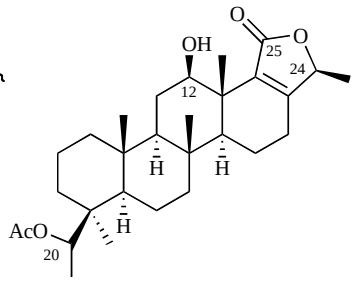
140, R= H, Me-24α
141, R= H, Me-24β
142, R= Ac, Me-24β



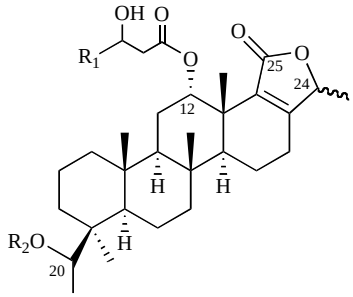
143



144, R= Me, Me-24β
145, R= Me, Me-24α
146, R= Et, Me-24β
147, R= Et, Me-24α



148

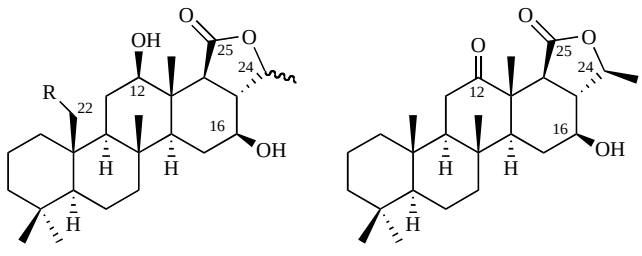


149, R_1= Me; R_2= Ac, Me-24β
150, R_1= Me; R_2= Ac, Me-24α
151, R_1= Et; R_2= Ac, Me-24β
152, R_1= Et; R_2= Ac, Me-24α
153, R_1= Me; R_2= EtCO, Me-24β
154, R_1= Me; R_2= EtCO, Me-24α

Fig. (16). γ-Butenolide-based metabolites **130-154**.

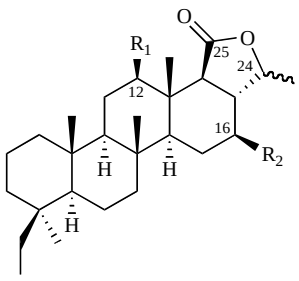
Phyllospongia lamellosa collected at the Indo-West Pacific, and were found to inhibit HIV-1 envelope-mediated fusion with IC_{50} of ~2 μM [98]. From the sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens*, collected at Great Barrier Reef, was isolated 12α-acetoxy-20,24β-dimethylscalar-17-en-25,24-olide (**139**)[64], which was also found in the sponge *Phyllospongia papyracea* collected at Papua New Guinea [60]. Phyllactones A-C (**140-142**) were isolated from the sponge *Phyllospongia foliascens* collected at the South China Sea, and showed moderate cytotoxicity against KB cells (IC_{50}= 20 μg/mL)[99]. Phyllactones H and I (**143**) were isolated from the sponge *Phyllospongia* sp. collected at the South China Sea [108]. Phyllofolactones H-K (**144-147**) were isolated from the Indonesian sponge, *Strepsichordaia aliena* [66]. The first isolated bishomoscalarane, which possess an oxygenated function at C-20 was 20-acetoxy-12β-hydroxy-20,24-dimethylscalar-17-en-25,24-olide (**148**) found in a specimen of *Carteriospongia* sp. collected at the Fiji Islands [109]. The structure of this compound was determined by single-crystal X-ray diffraction analysis. Other C20-functionalised bishomoscalaranes are honulactones C-D (**149-150**) and I-L (**151-154**), which were isolated from the Indonesian sponge, *Strepsichordaia aliena* [110]. Honulactones C (**149**) and D (**150**) exhibited cytotoxicity against P-388, A-549, HT-29, and MEL-28 cancer cells (IC_{50}= 1 μg/mL)[110].

Another subgroup of scalarane metabolites are compounds **155-162** that lack the double bond between C-17 and C-18 but possess the γ-lactone ring E with the carbonyl group located at C-25 (Fig. **17**). We can also distinguish both homoscalaranes and bishomoscalaranes. For example, 22-acetoxy-12β,16β-dihydroxy-24-methylscalaran-25,24-olide (**155**) was isolated from an Australian sponge (*Lendenfeldia* sp.)[40]. The related 12β,16β,22-trihydroxy-24-methylscalaran-25,24-olide (**156**, Me-24β) was found, along with compound **157** (12β,16β-dihydroxy-24-methylscalaran-25,24-olide), in the sponge *Phyllospongia dendyi* collected at the Indian Ocean [61]. Soon after, compound **156** was also isolated from the sponge *Lendenfeldia frondosa* collected at the Solomon Islands, and the signals assignments were revised [58]. Compound **157** has also been isolated from the sponge *Lendenfeldia* sp. collected at Indonesia [43]. The C-24 epimer of **156**, 12β,16β,22-trihydroxy-24α-methylscalar-25β,24α-olide (**158**), was isolated from the Indo-Pacific sponge *Lendenfeldia frondosa* [104]. From a Chinese specimen of the sponge *Phyllospongia foliascens* was isolated phyllofolactone L (**159**)[63]. Within this subgroup of scalaranes there are three known bishomoscalaranes, compounds (**160-162**). For example, 12α-acetoxy-16β-hydroxy-20,24-dimethylscalar-25β,24α-olide (**160**) was isolated from the Neo Guinean sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* [55]. Phyllofolactone A (**161**) was found in a Pacific specimen of the sponge *Phyllospongia foliascens* [106], while in another sample of the same sponge collected at the South China Sea was found the corresponding C-16 acetate, acetoxy-phyllofolactone A (**162**)[111].



155, R= OAc
156, R= OH, Me-24β
157, R= H
158, R= OH, Me-24α

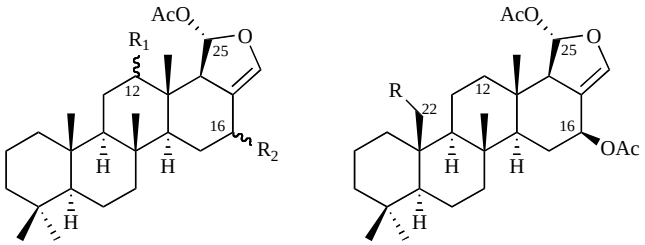
159



160, R_1= α-OAc; R_2= β-OH
161, R_1= =O; R_2= β-OH, Me-24β
162, R_1= =O; R_2= β-OAc, Me-24β

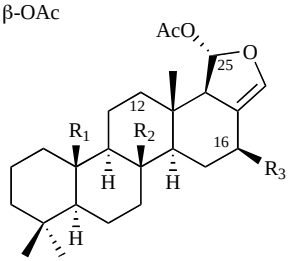
Fig. (17). γ-Lactone-based metabolites **155-162**.

Another subgroup of scalarane metabolites is composed of bioactive heteronemin (**163**) and its analogues, compounds **164-174** (Fig. **18**). These compounds are characterised by an unsaturated and acetylated γ-lactol ring E having the acetoxy group located at C-25. There is a variety of oxygenation pattern at C-12, C-16, C-21, and C-22. For example, heteronemin (**163**) has been isolated many times, and the first isolation was reported from an Australian sample of the sponge *Heteronema erecta* in 1976, in which the stereochemistry assignment of the oxygenated groups was wrong [112]. Heteronemin (**163**) was also found in the same sponge collected at the Red Sea, and the ^{13}C-NMR data of this molecule were reported along with a study of the stereochemistry at C-12, C-16 and C-25, remaining the latter ambiguous [113]. The correct stereostructure was not described until 1981 [13]. The controversy about the stereochemistry at C-25 ended after structure confirmation by X-ray analysis [114]. Other sources of heteronemin (**163**) are the following: sponge *Cacospongia scalaris* collected at Wakayama (Japan)[13]; sponge *Hyrtios erecta* and its nudibranch predators *Glossodoris hikeurensis* and *Glossodoris cincta* collected at Cocos Lagoon, Guam [16b]; sponge *Hyrtios erecta* collected at the Kingdom of Tonga [28]; sponge *Collospongia auris* collected at the Great Barrier Reef



163, R_1= β-OH; R_2= β-OAc
164, R_1= β-OAc; R_2= β-OAc
165, R_1= α-OH; R_2= β-OAc
166, R_1= α–OAc; R_2= β-OAc
167, R_1= =O; R_2= β-OAc
168, R_1= β–OH; R_2= β-OH
169, R_1= H; R_2= β-OAc

170, R= OH
171, R= OAc



172, R_1= Me; R_2= Me; R_3= OH
173, R_1= CHO; R_2= Me; R_3= OAc
174, R_1= Me; R_2= CHO; R_3= H

Fig. (18). Heteronemin-like metabolites **163-174**.

[29]; sponge *Hyrtios* sp. collected at Koh-Tao, Thailand [31]; sponge *Hyrtios* sp. collected at American Samoa [32]; sponge *Spongia idia* (syn. *Leiosella idia*) collected at San Diego, California [34,35]; sponge *Hyrtios* sp. collected at Okinawa Island (Japan)[70]; sponge *Hyrtios erecta* collected at the South China Sea [76]; sponge *Brachiaster* sp. collected at Thailand [84]; sponge *Hyrtios* cf. *erectus* (also called *H. erecta*) collected at Yakushima Island, Japan [90]; sponge *Hyatella intestinalis* collected at Darwin Harbor, Northern Australia [115]; sponge *Hyrtios erecta* collected at New Caledonia [116]; sponge *Hyrtios erecta* collected at Amami Island, Japan [117]; stony coral *Tubastraea micrantha* [118]; nudibranch *Glossodoris atromarginata* collected at Mandapam, India [119]; and sponge *Hyrtios reticulata* collected at New Caledonia [120]. Heteronemin (**163**) has resulted to be biologically active in various bioassay models, including antifeedant, antimicrobial, ichthyotoxicity, cytotoxicity, protein function inhibition, and antitubercular activity. For example, heteronemin (**163**) deterred feeding on sponges and nudibranches by several fishes [16b], and showed antimicrobial activity using the standard disk assay against *Staphylococcus aureus* (25 μg/disk), *Bacillus subtilis* (25 μg/disk), and *Candida albicans* (50 μg/disk) [29], as well as antimicrobial activity against *Mycobacterium intracellulare* (IC_{50}= 2.04 μM)[32]. Compound **163** immobilises the larvae of the red abalone *Haliotis rufescens* at 1mg/L in seawater, as well as bieng toxic to brine shrimp *Artemia* sp. at 10 mg/L and to the gametes of the giant kelp *Macrocystis pyrifera* at the same concentration [34]. Heteronemin (**163**) also showed cytotoxicity against human oral fibroblasts (IC_{50}= 5.25 μM)[31], ovarian cancer SKOV3 cells (IC_{50}= 3.4 μM)[32], melanoma SK-MEL cells (IC_{50}= 15.3 μM)[32], breast cancer BT549 cells (IC_{50}= 11.2 μM)[32], non-cancerous Vero cells (IC_{50}= 8.2 μM) [32], human epidermoid carcinoma KB cells (IC_{50}= 1.2 μg/mL [70], IC_{50}= 0.37 μM [84], IC_{50}= 0.23 μg/mL [117]), human breast adenocarcinoma MCF-7 cells (IC_{50}= 0.3 μM)[84], colorectal carcinoma HT-29 cells (IC_{50}= 0.4 μM)[84], human cervical carcinoma HeLa cells (IC_{50}= 0.45 μM)[84], murine leukemia L1210 cells (IC_{50}= 0.058 μg/mL)[117], and human thyroid carcinoma cells [119]. Also, heteronemin (**163**) is a known antitubercular agent (MIC= 3.0 μM [31,84]; 99% inhibition of *Mycobacterium tuberculosis*, H37Rv, MIC= 6.25 μg/mL and IC_{50}= 1.3 μg/mL)[121]. Finally, heteronemin (**163**) has displayed protein farnesyl transferase inhibition (IC_{50}= 3 μM)[120].

Heteronemin acetate (**164**) was isolated from the sponge *Hyrtios erecta* collected at the Kingdom of Tonga [28], and the Thai sponge *Brachiaster* sp. [84]. Recently, heteronemin acetate (**164**) has been prepared by semisynthesis from natural heteronemin (**163**) isolated from the sponge *Hyrtios* sp. [31,32]. Natural heteronemin acetate (**164**) showed cytotoxicity against human breast adenocarcinoma MCF-7 cells (IC_{50}= 6.45 μM), and antitubercular activity (MIC= 6.0 μM)[84]. Semisynthetic heteronemin acetate (**164**) has displayed both antitubercular (MIC= 3.0 μM) and cytotoxic activity (human oral fibroblasts, IC_{50}= 16.09 μM; ovarian cancer SKOV3, IC_{50}= 18.8 μM; melanoma SK-MEL, IC_{50}= 16.7 μM; breast cancer BT549, IC_{50}= 18.8 μM; Vero, IC_{50}= 9.0 μM), as well as antimicrobial activity against *Mycobacterium intracellulare* with an IC_{50} value of 18.8 μM [31,32]. 12-Epi-heteronemin (**165**) was isolated from the sponge *Hyrtios erecta* collected at New Caledonia [116,120]. 12-Epi-heteronemin acetate (**166**) was isolated from the sponge *Hyrtios erecta* collected at the Kingdom of Tonga [28], the sponge *Hyrtios* sp. collected at Okinawa Island (Japan)[70], and the sponge *Hyrtios erecta* collected at New Caledonia [116]. Compound **166** showed cytotoxicity against human epidermoid carcinoma KB cells (IC_{50}= 2.7 μg/mL)[70]. 12-Oxoheteronemin (**167**) has been prepared semisynthetically by oxidation from natural heteronemin (**163**)[31,32]. Semisynthetic 12-oxoheteronemin (**167**) has displayed both antitubercular (MIC= 0.23 μM) and cytotoxic activity (human oral fibroblasts, IC_{50}= 0.91 μM; ovarian cancer SKOV3, IC_{50}> 37.6 μM; breast cancer BT549, IC_{50}> 37.6 μM; Vero, IC_{50}> 37.6 μM), as well as antimicrobial activity against *Mycobacterium intracellulare* with an IC_{50} value of 5.1 μM [31,32]. Hyrtiosin D (16-O-deacetylheteronemin,

168) and hyrtiosin E (12-dehydroxy-heteronemin, **169**) were isolated from the sponge *Hyrtios erecta* collected at the South China Sea [76]. There exist five heteronemin-like compounds (**170-174**, Fig. **18**) that lack the functionalisation at C-12 typically seen among the scalarane metabolites. For example, 12-deacetoxy-22-hydroxyheteronemin (**170**) has been isolated from the sponge *Smenospongia* sp. collected at Gagu-Do Island (Korea) and displayed significant cytotoxicity toward the human leukemia cell line K562 (LC_{50} 0.02 μg/mL, respectively)[92]. Compound **170** has also been found in another sample of *Smenospongia* sp. collected at Soheuksan Island (Korea), along with 12-deacetoxy-22-acetoxyheteronemin (**171**), 12-deacetoxy-16-O-deacetylheteronemin (**172**) and 12-deacetoxy-22-formylheteronemin (**173**)[37]. These compounds (**170-173**) showed moderate cytotoxicity toward the human leukemia cell line K562 (LC_{50} 0.13, 6.8, 5.8 and 17.5 μg/mL, respectively) and some of them displayed antimicrobial activity (**170**: *Bacillus subtilis* MIC= 0.78 μg/mL, *Salmonella typhimurium* MIC= 6.25 μg/mL; **172**: *Bacillus subtilis* MIC= 3.12 μg/mL, *Salmonella typhimurium* MIC= 12.5 μg/mL)[37]. Finally, mooloolaldehyde (**174**) was isolated from the Australian sponge *Hyattella intestinalis* and resulted to be cytotoxic toward the P388 mouse leukemia cell line with IC_{50} value in the range 3-10 μg/mL [36].

Another subgroup of scalarane metabolites is composed of deoxoscalarin (**175**) and its analogues, compounds **175-213** (Fig. **19** and Fig. **20**). These compounds are characterised by a cyclic hemiacetal as ring E having normally a double bond in the neighbouring ring D and the hemiacetalic hydroxy group at C-25. There is a variety of oxygenation pattern at C-3, C-6, C-12, C-16, and C-21. For example, deoxoscalarin (**175**) has been isolated many times, and the first isolation was reported from a Mediterranean sample of the sponge *Spongia officinalis* collected at the Bay of Naples in 1973 [122]. Other sources of deoxoscalarin (**175**) are the following: nudibranch *Hypselodoris orsini* collected at the Gulf of Naples [12a]; sponge *Cacospongia mollior* collected at the Gulf of Naples [16a]; sponge *Cacospongia* sp. and its predatory nudibranch *Glossodoris pallida* collected at Apra Harbor, Guam and collected at Hainan Island, China [16b, 17,20]; nudibranch *Glossodoris rufomarginata* collected at the South China Sea [19]; nudibranch *Glossodoris averni* collected at Eastern Australia [20]; nudibranch *Glossodoris sedna* collected at Osa Ballena, Costa Rica [47]; sponge *Cacospongia scalaris* collected at the Gulf of Astakos, Greece [69]; nudibranch *Chromodoris funerea* collected at Kaibakku Lake, Palau [80]; and nudibranch *Chromodoris inornata* collected at Fukuoka, Japan [123]. Deoxoscalarin (**175**) showed cytotoxic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines (IC_{50}= 1.4 and 6.4 μg/mL, respectively)[123].

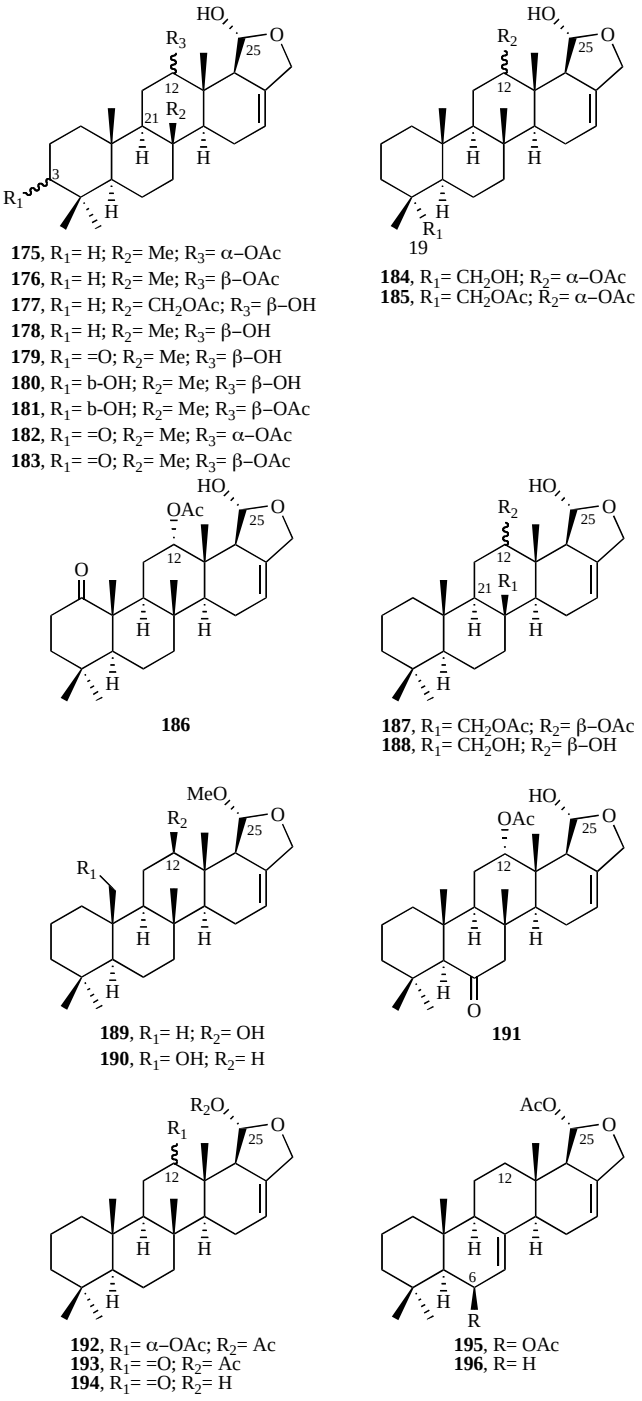


Fig. (19). Deoxoscalarin-like metabolites **175-196**.

12-Epi-deoxoscalarin (**176**) has been found in several marine sources. For example, it was isolated from the sponge *Collospongia auris* [29], the sponge *Spongia agaricina* [30], the sponge *Spongia idia* [34,35], the nudibranch *Glossodoris dalli* [47], the sponge *Hyrtios erectus* [72], the sponge *Spongia nitens* [74], the

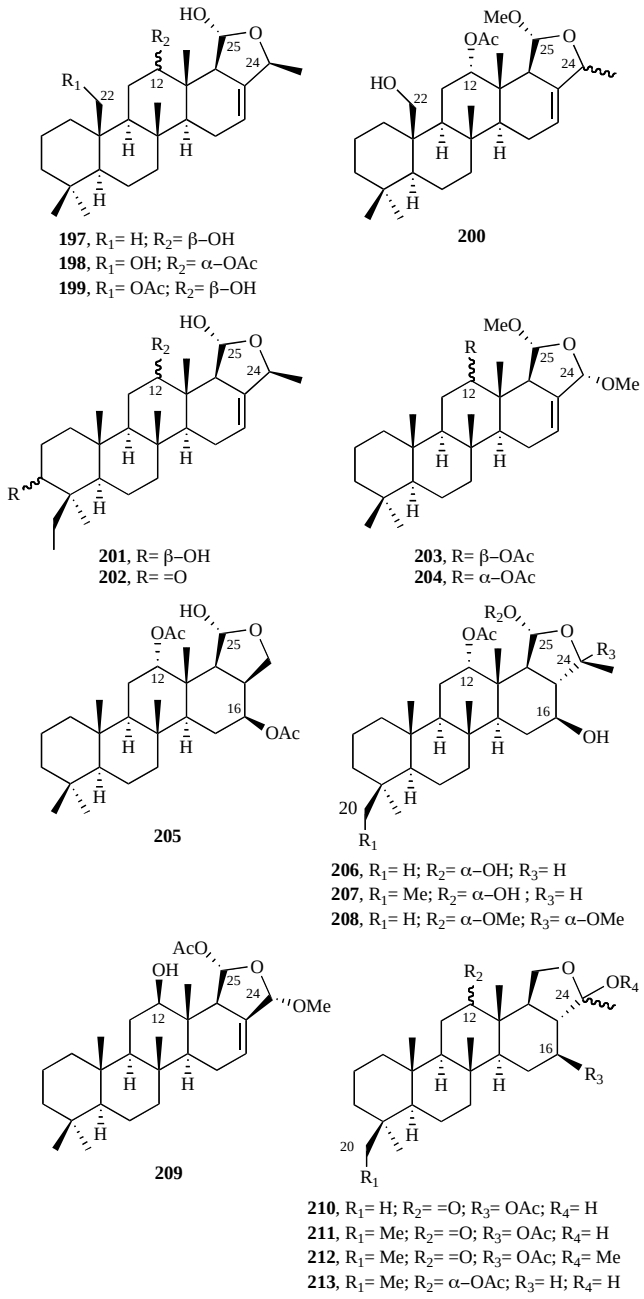


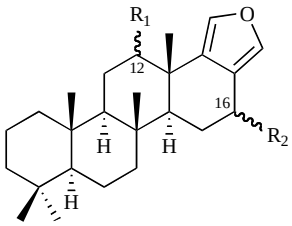
Fig. (20). Deoxoscalarin-like metabolites **197-213**.

sponge *Hyatella cribriformis* [88], the sponge *Hyatella intestinalis* [115], the nudibranch *Chromodoris inornata* [123], the sponge *Spongia officinalis* [124], and the sponge *Spongia* sp. [125]. 12-Epi-deoxoscalarin (**176**) showed cytotoxic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines (IC_{50}= 8.2 and >30.0 μg/mL, respectively)[123], as well as inhibition of transactivation for the nuclear hormone receptor FXR (farnesoid X-activated receptor, IC_{50}= 81.1 μM), a promising target to treat hypercholesterolemia in humans [125]. 21-Acetoxy-12-deacetyl-12-epi-deoxoscalarin (**177**) was isolated from the sponge *Hyatella intestinalis* collected at Darwin Harbor (Australia)[115], and from a Korean sample of a sponge of the genus *Spongia* [125]. Compound **177** showed inhibition of transactivation for the nuclear hormone receptor (IC_{50}= 25.3 μM), FXR (farnesoid X-activated receptor)[125]. 12-Deacetyl-12-epi-deoxoscalarin (**178**) has been found in several sources including: the nudibranch *Glossodoris pallida* from Hainan Island (China)[20], the sponge *Hyrtios erecta* [75], a sample of sponge *Spongia* sp. collected at the Japan Sea [78], the sponge *Hyatella cribriformis* [88], and the nudibranch *Glossodoris atromarginata* and its sponge prey probably belonging to the genus *Spongia* [119]. Recently, 12-deacetyl-12-epi-deoxoscalarin (**178**) has been prepared by semisynthesis from natural heteronemin (**163**) isolated from the sponge *Hyrtios* sp. [31,32]. A semisynthetic sample of compound (**178**) displayed weak antitubercular activity (MIC= 257 μM)[31]. Natural 12-deacetyl-12-epi-deoxoscalarin (**178**) induced neurite outgrowth in pheochromocytoma (PC-12) cells at the concentration of 50 μg/mL, which is a model system to study the mechanisms of neuronal differentiation [78]. 3-Oxo-12-deacetyl-12-epi-deoxoscalarin (**179**) was isolated, along with 3β-hydroxy-12-deacetyl-12-epi-deoxoscalarin (**180**) and 3β-hydroxy-12-epi-deoxoscalarin (**181**), from the sponge *Hyrtios erecta* collected at Setouchi (Japan)[75]. Compound **179** was also found in the same sponge collected at the Red Sea and was renamed as salmahyrtisol C [95]. Compounds **179-181** displayed cytotoxic activities against mouse leukemia P388 cell line, with compound **179** being the most potent (IC_{50}= 14.5 ng/mL) and also showing potent activity against several human gastric cancer cell lines (MKN-1, IC_{50}= 57.7 ng/mL; MKN-7, IC_{50}= 56.0 ng/mL; MKN-74, IC_{50}= 36.8 ng/mL), including *in vivo* increased mean survival times (up to 15 days) and life spans (up to 75%) in P388 lymphatic leukemia-implanted mice in a dose dependent manner [75]. The related 3-keto-scalarane metabolites deoxoscalarin-3-one (**182**) and 12-epi-deoxoscalarin-3-one (**183**) were isolated, along with 19-hydroxydeoxoscalarin (**184**) and 19-acetoxydeoxoscalarin (**185**), from the nudibranch *Chromodoris inornata* collected at Fukuoka (Japan)[123]. Deoxoscalarins **182-185** showed cytotoxic activity against murine lymphoma L1210 (IC_{50}= 0.95, 6.6, 4.1 and 0.35 μg/mL, respectively) and human epidermoid carcinoma KB cell lines (IC_{50}= 5.2, 22.8, 21.0 and 3.1 μg/mL, respectively)[123]. Deoxoscalarin-3-one (**182**) or the corresponding 1-keto analogue **186** was found in the nudibranch *Chromodoris funerea*, though the complete structure was not defined [80]. 19-Acetoxydeoxoscalarin (**185**) was also isolated from the Red Sea sponge *Hyrtios erecta* [87]. 21-Acetoxy-12-epi-deoxoscalarin (**187**) was isolated, along with 21-hydroxy-12-deacetyl-12-epi-deoxoscalarin (**188**) and 25α-methoxy-12-deacetyl-12-epi-deoxoscalarin (**189**), from a Korean sample of a sponge

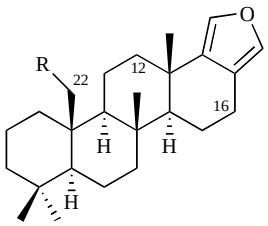
of the genus *Spongia* [125]. Compounds **187-189** showed inhibition of transactivation for the nuclear hormone receptor FXR (farnesoid X-activated receptor, IC_{50}= 8.1, 64.5, and 24.8 μM, respectively)[125]. 25α-Methoxy-12-deacetoxy-22-hydroxydeoxoscalarin (**190**) was isolated from a Korean sample of a sponge of the genus *Smenospongia*, and displayed antimicrobial activity against *Bacillus subtilis* (MIC= 50.0 μg/mL) and *Salmonella typhimurium* (MIC= 6.25 μg/mL), as well as potent cytotoxicity against human chronic myelogenous leukemia K562 cell line (LC_{50} 0.11 μg/mL)[37]. 6-Keto-deoxoscalarin (**191**) was isolated from the nudibranch *Hypselodoris orsini* collected at the Gulf of Naples [12a]. Deoxoscalarin acetate (**192**) was found in the North Adriatic sponge *Spongia officinalis* [124], and in the nudibranch *Glossodoris rufomarginata*, in which were also found two 12-keto deoxoscalarins, 25α-acetoxy-12-deacetoxy-12-oxo-deoxoscalarin (**193**) and 12-deacetoxy-12-oxo-deoxoscalarin (**194**)[19]. 12-Keto deoxoscalarins **193** and **194** were also isolated from the nudibranch *Glossodoris pallida* [20]. Compound **194** was also found in the nudibranch *Glossodoris atromarginata* and showed specific cytotoxicity against human thyroid carcinoma [119]. Mooloolabene D (**195**) and E (**196**), which are two norscalaranes that lack the methyl group attached to C-8 and functionalisation at C-12, were isolated from the Australian sponge *Hyattella intestinalis*, and were cytotoxic toward the P388 mouse leukemia cell line with IC_{50} values in the range 3-10 μg/mL [36].

Within the subgroup of scalarane metabolites composed of deoxoscalarin-based compounds, there are compounds characterised by a cyclic hemiacetal as ring E having normally a double bond in the neighbouring ring D and the hemiacetalic hydroxy group at either C-24 or C-25 (compounds **197-213**, Fig. **20**). There is a variety of oxygenation pattern at C-3, C-12, C-16, and C-22. There are included in this subgroup several homoscalarane and bishomoscalarane members. For example, 12-deacetyl-24-methyl-12-epideoxoscalarin (**197**) was isolated, together with 22-hydroxy-24-methyldeoxoscalarin (**198**), from the nudibranch *Chromodoris sedna* and displayed growth inhibition of the marine bacterium *Vibrio anguillarum* (100 μg/disk) [103]. Compound **197** was also found in the nudibranch *Glossodoris sedna* together with 12-deacetyl-22-acetoxy-24-methyl-12-epideoxoscalarin (**199**)[47]. 22-Hydroxy-25α-methoxy-24-methyldeoxoscalarin (**200**) was isolated from the sponge *Phyllospongia dendyi* of the Indian Ocean [126]. 3-Hydroxy-20,24-dimethyldeoxoscalarin (**201**) was isolated from the sponge *Dysidea vermicularis* and showed cytotoxicity against T-47D breast cancer cells (GI_{50}= 3.5 μM), while the related 3-oxo-20,24-dimethyl-deoxoscalarin (**202**) was found in a specimen of a sponge belonging to the genus *Carteriospongia* [127]. 24α,25α-dimethoxydeoxoscalarin (**203**) was found in the sponge *Dysidea villosa* [18], while the C-12 epimer 12-epi-24α,25α-dimethoxydeoxoscalarin (**204**) was isolated from the sponge *Collospongia auris* [29]. 16β-Acetoxy-dihydrodeoxoscalarin (**205**) was isolated from the Mediterranean sponge *Cacospongia scalaris* [69]. Dihydrodeoxoscalarins **206-208** were isolated from an Indonesian sponge of the genus *Phyllospongia* and exhibited 30-95% inhibition of the growth of KB cells at 10 μg/mL [53]. 12-Epideacetyl-24α-methoxy-25α-acetoxy-deoxoscalarin (**209**) was found in the Thai sponge *Hyrtios* sp. collected at Koh-Tao and showed antitubercular activity (MIC= 54 μM)[31]. Finally, there a few metabolites having the hemiacetalic hydroxy group at C-24. For example, scalardysin A (**210**) and B (**211**) were isolated from the sponge *Dysidea herbacea* [50], and scalardysin B (**211**) has also been found in sponges *Phyllospongia foliascens* collected at Okinawa and the South China Sea (named as phyllohemiketal A)[56,128,129]. Phylloketal (**212**) was isolated also from the South China Sea sponge *Phyllospongia foliascens* [130]. 12α-Acetoxy-24,25-epoxy-24-hydroxy-20,24-dimethylscalarane (**213**) was isolated from the Neo Guinean sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* and was moderately ichthyotoxic against the fresh water fish *Lebistes reticulatus* (LD= 40 mg/L)[55].

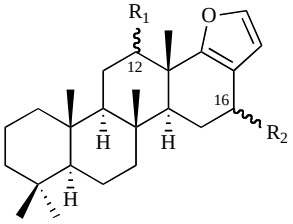
Another subgroup of scalarane metabolites includes a number of furanoscalaranes, which present a furan ring E together with oxygenation at C-12 and C-16 (compounds **214-229**, Fig. **21**). We are going to admit in this subgroup several furanoscalaranes with a rearranged furan ring E, whose skeleton could be named as isoscalarane (compounds **225-229**, Fig. **21**). Scalarafuran (**214**) has been isolated several times, and the first isolation was reported from a Californian sample of the sponge *Spongia idia* collected at Pt. Loma, San Diego in 1979 [34,35], though the molecule was known as a semisynthetic compound obtained by pyrolysis from heteronemin (**163**)[112,113]. Other sources of scalarafuran (**214**) are the following: sponge *Hyrtios erecta* collected at the Kingdom of Tonga [28b]; sponge *Hyrtios* sp. collected at Okinawa Island, Japan [70]; sponge *Hyrtios gumminae* collected at Similan Island, Thailand [89]; sponge *Hyrtios erecta* collected at Amami Island, Japan [117]. Recently, scalarafuran (**214**) has been prepared by semisynthesis from heteronemin (**163**), and showed antitubercular activity (MIC= 14.0 μM)[31,32]. Compound **214** displayed cytotoxicity against several cancer cell lines (human epidermoid carcinoma KB, IC_{50}= 7.2 μg/mL [70], IC_{50}= 58.0 μM [89], and 4.0 μg/mL [117]; murine leukemia L1210, IC_{50}= 2.9 μg/mL [117]; human cholangiocarcinoma HuCCA-1, IC_{50}= 49.0 μM [89]; human cervical carcinoma HeLa, IC_{50}= 63.0 μM [89]; hormone-independent



214, R_1= β–OH; R_2= β–OAc
215, R_1= α–OAc; R_2= H
216, R_1= =O; R_2= H
217, R_1= β–OH; R_2= H
218, R_1= β–OH; R_2= =O
219, R_1= α–OAc; R_2= β–OH
220, R_1= α–OAc; R_2= α–OH
221, R_1= β–OH; R_2= α–OH
222, R_1= β–OH; R_2= β–OH



223, R= OH
224, R= OAc



225, R_1= α–OAc; R_2= β–OH
226, R_1= α–OH; R_2= β–OH
227, R_1= α–OAc; R_2= β–OAc
228, R_1= β–OH; R_2= α–OAc
229, R_1= α–OH; R_2= =O

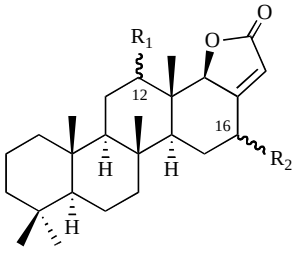
Fig. (21). Furoscalaran-like metabolites **214-229**.

breast cancer MDA-MB-231, IC_{50}= 14.0 μM [89]; hormone-dependent breast cancer T47D, IC_{50}= 28.0 μM [89]; and multidrug-resistant small-cell lung cancer H69AR, IC_{50}= 51.0 μM [89]). Scalarafuran (**214**) has been patented as an anti-HIV agent, since it inhibits the binding between HIV-1 integrase and its substrates (IC_{50}= 120.0 μM)[131]. 16-Deacetoxy-12-epi-scalarafuran acetate (**215**) was isolated from the nudibranch *Glossodoris averni* from Australia [20], the sponge *Hyrtios erectus* (also called *H. erecta*) from Hainan Island (China)[72], and the North Adriatic sponge *Spongia officinalis* [124]. From the nudibranch *Glossodoris pallida* from Hainan Island (China) was isolated 12,16-deacetoxy-12-oxoscalarafuran (**216**), while from the nudibranch *Glossodoris vespa* from Australia was isolated the related 16-deacetoxyscalara-furan (**217**)[20]. Compound **217** has also been found in a sponge of the genus *Spongia* collected at the Japan Sea, and exhibited cytotoxicity against human cervix epitheloid carcinoma HeLa cells, IC_{50}= 19.5 μg/mL [77]. Salmahyrtisol B (16-deacetoxy-16-oxoscalara-furan, **218**) was isolated from the Red Sea sponge *Hyrtios erecta*, and displayed cytotoxic activity against three types of cancer cells including murine leukemia P388, human lung carcinoma A549, and human colon carcinoma HT-29 with $IC_{50} \geq 1$ μg/mL [95]. Isoscalarafuran A (16-deacetyl-12-epi-scalarafuran acetate, **219**) and its C-16 epimer isoscalarafuran B (16-deacetyl-12,16-diepi-scalarafuran acetate, **220**) were isolated from a Southern Australian sponge, *Spongia hispida* [132]. Compound **219** was also found in the sponge *Hyrtios erectus* from Hainan Island (China)[72]. Sesterstatin 4 (16-deacetyl-16-epi-scalarafuran, **221**) and sesterstatin 5 (16-deacetyl-scalarafuran, **222**) were isolated from a sample of the sponge *Hyrtios erecta* collected at the Republic of Maldives, and their structures were confirmed by independent single crystal X-ray crystallographic analyses [133]. Both sesterstatins 4 (**221**) and 5 (**222**) inhibited the growth of a number of cancer cell lines (sesterstatin 4: murine leukemia P388, GI_{50}= 4.9 μg/mL; pancreas BXPC-3, GI_{50}= 1.6 μg/mL; thyroid KAT-4, GI_{50}= 2.0 μg/mL; thyroid SW1736, GI_{50}= 2.1 μg/mL; lung NSC NCI-H460, GI_{50}= 1.8 μg/mL; pharynx FADU, GI_{50}= 2.0 μg/mL; prostate DU-145, GI_{50}= 1.6 μg/mL; sesterstatin 5: murine leukemia P388, GI_{50}> 10 μg/mL; pancreas BXPC-3, GI_{50}= 2.2 μg/mL; melanoma RPMI-7951, GI_{50}= 2.1 μg/mL; CNS U251, GI_{50}= 1.9 μg/mL; lung NSC NCI-H460, GI_{50}= 2.5 μg/mL; pharynx FADU, GI_{50}= 1.9 μg/mL; prostate DU-145, GI_{50}= 1.9 μg/mL), and sesterstatin 5 (**222**) also inhibited the growth of the Gram-positive bacterium *Micrococcus luteus* (MIC= 25-50 μg/disk) [133]. 12-Dehydroxy-16-deacetoxy-22-hydroxy-scalarafuran (**223**) and the corresponding acetate 12-dehydroxy-16-deacetoxy-22-acetoxy-scalarafuran (**224**) were isolated from the sponge *Smenospongia* sp. collected at Soheuksan Island (Korea), and exhibited antimicrobial activity (**223**: *Bacillus subtilis* MIC= 1.56 μg/mL, *Micrococcus luteus* MIC= 6.25 μg/mL, *Salmonella typhimurium* MIC= 12.5 μg/mL; **224**: *Bacillus subtilis* MIC= 3.12 μg/mL, *Micrococcus luteus* MIC= 25.0 μg/mL), as well as cytotoxicity against human chronic myelogenous leukemia K562 cell line (LC_{50} 0.97 and 2.3 μg/mL, respectively)[37].

We will comment now an several furanoscalaranes with a rearranged furan ring E, whose skeleton could be named as an isoscalarane (compounds **225-229**, Fig. **21**). For example, furoscalarol (**225**) has been isolated several times, and the first isolation was reported from a sample of the sponge *Cacospongia mollior* [134]. Other sources of furoscalarol (**225**) are the following: nudibranch *Hypselodoris orsini* collected at the Gulf of Naples [12a]; sponge *Cacospongia mollior* collected near Naples [12b]; sponge *Hyatella intestinalis* collected at the Gulf of California [39], as well as the sponges *Hyrtios* sp. collected at Okinawa Island (Japan)[70], and *Hyrtios erectus* (also called *H. erecta*) collected at Hainan Island (China)[72], which also contained the corresponding deacetyl derivative 12-deacetylfuroscalarol (**226**)[70,72]. Compound **226** inhibited rabbit platelet aggregation induced by adenosine diphosphate with the IC_{50} values of 50-100 μg/mL

[70]. Furoscalarol (**225**) has also been found in the Mediterranean sponge *Cacospongia scalaris*, which also contained the corresponding acetate, acetylfuroscalarol (**227**)[14,69]. Acetylfuroscalarol (**227**) showed significant cytotoxicity toward five cancer cell lines (mouse lymphoma P388 and Schabel, ED_{50}= 2.5 μg/mL; human lung carcinoma A549, ED_{50}= 5.0 μg/mL; human colon carcinoma HT29, ED_{50}= 2.5 μg/mL; human melanoma MEL28 ED_{50}= 10.0 μg/mL)[14]. From the sponge *Spongia agaricina*, collected near Tarifa Island (Spain), was isolated 12,16-di-epi-12-deacetyl-16-acetylfuroscalarol (**228**), which showed significant cytotoxicity against four cancer cell lines (mouse lymphoma P388, human lung carcinoma A549, human colon carcinoma HT-29, and human melanoma MEL-28 with IC_{50} values of 1.0 μg/mL in all cases)[30]. The last furanoscalarane is 12-deacetylfuroscalar-16-one (**229**), which was found in a sample of the sponge *Cacospongia* sp. collected at Little Barrier Island, New Zealand [135].

The last subgroup of scalarane metabolites is composed of compounds (**230-236**, Fig. **22**) with an isoscalarane skeleton typified by scalarolbutenolide (**230**), which was isolated for the first time from the sponge *Spongia nitens* in 1981 [136]. Scalarolbutenolide (**230**) has also been found, along with the corresponding C-16 epimer 16-epi-scalarolbutenolide (**231**), in the sponge *Spongia agaricina* [30]. 16-Epi-scalarolbutenolide (**231**) has also been isolated from the Red Sea sponge *Hyrtios erecta*, and displayed 40% inhibitory activity against *Mycobacterium tuberculosis* (H_{37}Rv)[87]. 16-Deacetyl-16-episcalarolbutenolide (**232**) and 12-acetyl-16-deacetyl-16-episcalarolbutenolide (**233**) were isolated from the sponge *Hyrtios erectus* (also called *H. erecta*) collected at Yakushima Island (Japan), and were cytotoxic against P388 leukemia cells with IC_{50} values of 0.4, and 2.1 μg/mL, respectively [90]. A sample of the sponge *Hyrtios erecta*, collected at Setouchi (Japan), also contained 16-deacetyl-16-episcalarolbutenolide (**232**) as constituent [75]. 12-Acetyl-12,16-diepi-16-deacetylscalarolbutenolide (**234**) and the corresponding acetate, 12-acetyl-12,16-diepi-scalarolbutenolide (**235**), were isolated from the sponge *Spongia matamata* collected at Palau [71]. Compound **234** has also been found in an Indo-Pacific sponge of the genus *Hyrtios* [104], as well as in the nudibranch *Chromodoris inornata*, whose sample of **234** showed cytotoxic activity against murine lymphoma L1210 (IC_{50}= 2.4 μg/mL) and human epidermoid carcinoma KB cells (IC_{50}= 7.6 μg/mL)[123]. Compound **235** has also been isolated from the nudibranch *Glossodoris pallida* collected at Hainan Island (China)[20]. Finally, 12-acetyl-16-epi-scalarolbutenolide (**236**) has been isolated from the sponge *Hyrtios erectus* (also called *H. erecta*) collected at Kavieng (Papua New Guinea), and showed weak cytotoxic activity against human breast cancer MCF-7 cells and was toxic at concentrations of 50.0 μg/mL [83].



230, R_1= β–OH; R_2= α–OAc
231, R_1= β–OH; R_2= β–OAc
232, R_1= β–OH; R_2= β–OH
233, R_1= β–OAc; R_2= β–OH
234, R_1= α–OAc; R_2= β–OH
235, R_1= α–OAc; R_2= β–OAc
236, R_1= β–OAc; R_2= β–OAc

Fig. (22). Scalarolbutenolide-like metabolites **230-236**.

1.3. Miscellaneous Scalaranes

The last group of scalarane metabolites is composed of a number of compounds (**237-265**, Fig. **23**) that differ in their structure in several aspects, including the presence of cyclopropane and cyclobutane rings, but have in common many structural features with the scalarane skeleton.

The first subgroup includes a number of pentacyclic pyrroloterpenes, named molliorins A-C (**237-239**), which possess a pyrrole ring E and were isolated from the sponge *Cacospongia mollior* [137-139]. It is thought that their mixed biosynthetic origin is scalaradial (**2**) that reacts with available amines to form the pyrrole ring. Another subgroup is composed pentacyclic scalaranes possessing a γ-lactone ring E, having the carbonyl group located at C-25 and the hydroxy group at C-12 (compounds **240-244**, Fig. **23**). They also belong to the homoscalarane series. 16β,22-Dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone (**240**) and 22-acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25,12β-olactone (**241**) were isolated from sponges of the genus *Lendenfeldia* collected at Western Australia and Madagascar [40,44]. Compound **240** has also been found in Palauan sponges *Dictyoceratida* sp. and *Halichondria* sp. [41], the Indonesian sponge *Lendenfeldia* sp. [43], the sponge *Lendenfeldia frondosa* collected at Solomon Islands [58], and the sponge *Phyllospongia dendyi* collected at the Indian Ocean [61]. Compound **240** was examined in the broad range of tumour cell lines represented by the National Cancer Institute´s 60-cell line panel, and was found to inhibit tumour cell growth with very little specificity for individual cell lines (average GI_{50} value 20.4 μM)[43], as well as it exhibited cytotoxicity against lung carcinoma A549

Table 2. Biological Activity Found in Compounds 85-236

Compound	Biological Activity
12-Epi-scalarin, **85**	Cytotoxic [77], neurotrophic activity [78], and FXR inhibition [79]
12-O-Deacetyl-scalarin, **86**	NGF synthesis-enhancer [81]
12-O-Deacetyl-12-epi-scalarin, **87**	Cytotoxic [77], neurotrophic activity [78], and FXR inhibition [79]
25-Dehydroxy-12-epi-scalarin, **90**	Antitubercular and cytotoxic [84]
25-Dehydroxy-12-epi-deacetylscalarin, **91**	Neurotrophic activity [78], and FXR inhibition [79]
25-Dehydroxy-12-epi-deacetylscalarin, **91**	Antitubercular [84,87] and cytotoxic [77,84,86,89]
12-Deacetoxy-19-acetoxyscalarin, **92**	Cytotoxic [90]
Compounds **96-98**	FXR inhibition [79]
12-Deacetoxy-22-hydroxy-25-acetoxyscalarin, **99**	Antimicrobial and cytotoxic [37]
12-Deacetoxy-25-acetoxyscalarin, **101**	Antitubercular [84]
12-Deacetoxy-22,25-diacetoxyscalarin, **102**	Cytotoxic [92]
12-Deacetoxy-22-acetoxyscalarin, **103**	Cytotoxic [92]
Hyrtiolide, **104**	Cytotoxic [89]
12-O-Acetyl-16-O-methylhyrtiolide, **106**	Cytotoxic [77]
Sesterstatin 6, **107**	Antitumour [93]
Sesterstatins 1-3, **110-112**	Cytotoxic [95]
3-Acetylsesterstatin 1, **115**	Antitubercular [87]
Sesterstatin 7, **116**	Antitubercular [87]
24-Hydroxyscalarolide, **120**	Antimicrobial [29]
12β,16α,24-Trihydroxy-17-scalaren-25,24-olide, **122**	Cytotoxic [89]
Phyllolactones A-D, **135-138**	Antiviral [98]
Phyllactones A-B,**140-141**	Cytotoxic [99]
Honulactones C-D, **149-150**	Cytotoxic [110]
Heteronemin, **163**	Antifeedant [16b], antimicrobial [29,32], ichthyotoxic [34], cytotoxic [31,32,70,84,117,119], antitubercular [31,84,121], and protein farnesyl transferase inhibition [120]
Heteronemin acetate, **164**	Antimicrobial [32], cytotoxic [31,32,84], and antitubercular [31,84]
12-Epi-heteronemin acetate, **166**	Cytotoxic [70]
12-Oxoheteronemin, **167**	Antimicrobial, cytotoxic, and antitubercular [31,32]
12-Deacetoxy-22-hydroxyheteronemin, **170**	Antimicrobial [37] and cytotoxic [37,92]
12-Deacetoxy-22-acetoxyheteronemin, **171**	Cytotoxic [37]
12-Deacetoxy-16-O-deacetylheteronemin, **172**	Antimicrobial and cytotoxic [37]
12-Deacetoxy-22-formylheteronemin, **173**	Cytotoxic [37]
Mooloolaldehyde, **174**	Cytotoxic [36]
Deoxoscalarin, **175**	Cytotoxic [123]
12-Epi-deoxoscalarin, **176**	Cytotoxic [123] and FXR inhibition [125]
21-Acetoxy-12-deacetyl-12-epi-deoxoscalarin, **177**	FXR inhibition [125]

(Table 2) Contd….

Compound	Biological Activity
12-Deacetyl-12-epi-deoxoscalarin, **178**	Antitubercular [31] and neurotrophic activity [78]
Deoxoscalarins **179**-**181**	Cytotoxic [75]
Deoxoscalarins **182**-**185**	Cytotoxic [123]
Deoxoscalarins **187**-**189**	FXR inhibition [125]
25α-Methoxy-12-deacetoxy-22-hydroxydeoxoscalarin, **190**	Antimicrobial and cytotoxic [37]
12-Deacetoxy-12-oxo-deoxoscalarin, **193**	Cytotoxic [119]
Mooloolabenes D-E, **194**-**195**	Cytotoxic [36]
12-Deacetyl-24-methyl-12-epideoxoscalarin, **197**	Antimicrobial [103]
3-Hydroxy-20,24-dimethyl-deoxoscalarin, **201**	Cytotoxic [127]
Dihydrodeoxoscalarins **206**-**208**	Cytotoxic [53]
12-Epideacetyl-24α-methoxy-25α-acetoxy-deoxoscalarin, **209**	Antitubercular [31]
12α-Acetoxy-24,25-epoxy-24-hydroxy-20,24-dimethylscalarane, **213**	Ichthyotoxic [55]
Scalarafuran, **214**	Antitubercular [31], cytotoxic [70,89,117], and anti-HIV [131]
16-Deacetoxyscalarafuran, **217**	Cytotoxic [77]
Salmahyrtisol B (16-deacetoxy-16-oxoscalarafuran, **218**)	Cytotoxic [95]
Sesterstatins 4 and 5, **221**-**222**	Cytotoxic [133]
Scalarafurans **223** and **224**	Antimicrobial and cytotoxic [37]
12-Deacetylfuroscalarol, **226**	Platelet-aggregation inhibition [70]
Acetylfuroscalarol, **227**	Cytotoxic [14]
12,16-di-epi-12-deacetyl-16-acetylfuroscalarol, **228**	Cytotoxic [30]
16-Epi-scalarolbutenolide, **231**	Antitubercular [87]
16-Deacetyl-16-episcalarolbutenolide, **232**	Cytotoxic [90]
12-Acetyl-16-deacetyl-16-episcalarolbutenolide, **233**	Cytotoxic [90]
12-Acetyl-12,16-diepi-16-deacetylscalarolbutenolide, **234**	Cytotoxic [123]
12-Acetyl-16-epi-scalarolbutenolide, **236**	Cytotoxic [83]

cells (GI_{50}= 0.5 μg/mL,1.27 μM)[44]. Compound **241** has also been isolated from the Palauan sponge *Lendenfeldia chondrodes* [42], and the sponge *Phyllospongia chondrodes* collected at Okinawa (Japan)[46]. Compound **241** showed repellent activity against the blue mussel *Mytilus edulis galloprovincialis* [42], cytotoxicity against lung carcinoma A549 cells (GI_{50}= 1.0 μg/mL,2.13 μM)[44], and induction of differentiation of K562 (myelogenous leukemia cell line) to hemoglobin producing erythroblast cells [46]. The C-16 epimer of compound **240**, 16α,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone (**242**), was isolated from the sponge *Lendenfeldia frondosa* collected at Solomon Islands [58]. Sednolide (**243**) and sednolide 22-acetate (**244**) were isolated from the nudibranch *Chromodoris sedna* collected at Baja California (Mexico), and sednolide (**243**) inhibited the growth of the marine bacterium *Vibrio anguillarum* at 100 μg/disk [103]. Hyatelones A-C (**245**-**247**), hyatolides A (**248**) and B **(249**), and hyatelactam (**250**) are all scalarane-related sesterterpenes with novel ring systems, and were isolated from the sponge *Hyatella intestinalis* collected at the Gulf of California [39]. Hyatelone A (**245**) showed mild cytotoxic activity against the tumour cell lines MDA-MB-231 (breast carcinoma, GI_{50}= 5.4 μg/mL), and HT-29 (colon adenocarcinoma, GI_{50}= 9.2 μg/mL) [39]. Hyatolide A (**248**) showed mild cytotoxic activity against the tumour cell lines MDA-MB-231 (breast carcinoma, GI_{50}= 4.8 μg/mL), A459 (lung adenocarcinoma, GI_{50}= 5.1 μg/mL), and HT-29 (colon adenocarcinoma, GI_{50}= 5.0 μg/mL), while hyatelactam (**250**) was only cytotoxic against the HT-29 (colon adenocar-

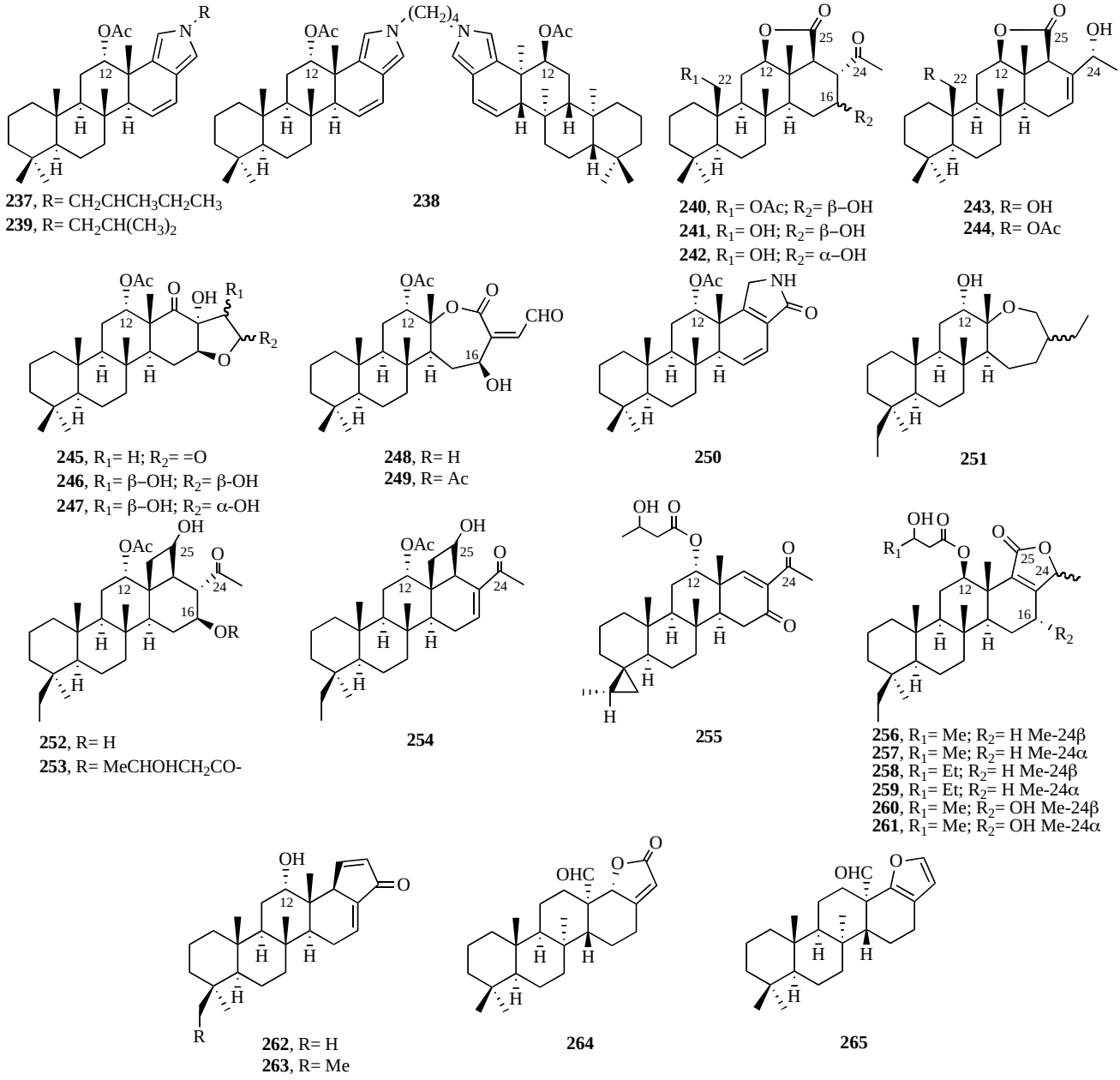


Fig. (23). Miscellaneous scalaranes **237-265**.

cinoma, GI_{50}= 8.1 μg/mL) cell line [39]. 12β-hydroxy-20,24-dimethyl-13,18-oxa-25-norscalarane (**251**) was isolated from the Madagascaran sponge *Phyllospongia madagascarensis* and is characterised by a seven-membered oxacycle that makes its skeletal system unique [65].

Within the group of miscellaneous scalaranes, there are several metabolites possessing either a cyclobutanol or a cyclopropane ring. They also belong to the bishomoscalarane series. For example, 12α-acetoxy-23,25-cyclo-16β,25-dihydroxy-20,24-dimethyl-24-oxoscalarane (**252**) was isolated from the Neo Guinean sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens*, and was tested against the fresh water fish *Lebistes reticulatus* for its ichthyotoxicity (LD 5 mg/L)[55]. Another cyclobutanol-containing metabolite is the related ester, 12α-acetoxy-16β-(3'-hydroxybutanoy-loxy)-13β,18β-cyclobutan-20,24-dimethyl-24-oxosca-laran-25β-ol (**253**), which was isolated from the Australian sponge *Strepsichordaia lendenfeldi* collected at the Great Barrier Reef [49]. The last cyclobutanol-containing metabolite is 12α-acetoxy-13β,18β-cyclobutan-20,24-dimethyl-24-oxoscalar-16-en-25-ol (**254**), which was found in the sponge *Phyllospongia papyracea* collected at Papua New Guinea [60]. With respect to the cyclopropane-containing metabolites, honu'enone (**255**)

Table 3. Biological Activity Found in Compounds 240-263

Compound	Biological Activity
16β,22-Dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone, **240**	Cytotoxic [43,44]
22-acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25,12β-olactone, **241**	Antifouling [42], cytotoxic [44], and antitumour [46]
Sednolide, **243**	Antimicrobial [103]
Hyatelone A, **245**	Cytotoxic [39]
Hyatolide A, **249**	Cytotoxic [39]
Hyatelactam, **250**	Cytotoxic [39]
12α-Acetoxy-23,25-cyclo-16β,25-dihydroxy-20,24-dimethyl-24-oxoscalarane, **252**	Ichthyotoxic [55]
Honulactone A, **256**	Cytotoxic [110]
Honulactone B, **257**	Cytotoxic [110]
Phyllofenone D, **262**	Cytotoxic [63]
Phyllofenone B, **263**	Cytotoxic [106]

was isolated from an Indonesian sponge *Strepsichordaia aliena* collected at Turtle Bay [66]. The same sponge also afforded honulactones A (**256**) and B (**257**), and E-H (**258-261**), which differ mainly in the orientation of the methyl group at C-24, the length of the ester chain, and the oxygenation grade at C-16 [110]. Honulactones A (**256**) and B (**257**) exhibited cytotoxicity against P-388, A-549, HT-29, and MEL-28 cancer cells (IC_{50}= 1.0 μg/mL)[110].

Other miscellaneous scalaranes are phyllofenone D (**262**) and the related bishomoscalarane homologue phyllofenone B (**263**), which were isolated from the sponge *Phyllospongia foliascens* collected at the South China Sea [63,106]. Phyllofenone D (**262**) was cytotoxic against the P388 leukemia cell line with an IC_{50} value of 6.5 μg/mL [63], while phyllofenone B (**263**) was cytotoxic against the same target with an IC_{50} value of 5.0 μg/mL [106]. Finally, two scalarane-related sesterterpenes, coscinalactone (**264**) and coscinafuran (**265**), were isolated from the sponge *Coscinoderma mathewsi* [140]. These compounds possess a different stereochemistry in the skeletal structure in comparison with known scalarane-type sesterterpenes. In particular, they are characterised by a *cis-fused* B/C ring juncture.

3. CONCLUSION

The scientific investigations of the scalarane family of sesterterpenoids have been an active field during the last two decades producing more than one hundred publications on isolation and structural characterisation of its members, including several preliminary biological studies. Until quite recently researchers had not initiated any structure/function studies, and therefore this area also remains largely unexplored. In particular, recent investigations on the structure-activity relationships of antitubercular scalaranes have been reported [31,32]. The work listed in this review justifies the potential for discovery of novel pharmaceutical agents and biological probes in this area of research.

4. REFERENCES

[1] Connolly J. D.; Hill R. A. Dictionary of Terpenoids. In: *Sesterterpenoids*. Chapman & Hall: London, **1991**; vol. *2*, p. 1110.

[2] (a) Hanson, J. R. Sesterterpenoids. *Nat. Prod. Rep.* **1986**, *3*, 123-132; (b) Hanson, J. R. The sesterterpenoids. *Nat. Prod. Rep.* **1992**, *9*, 481-489; (c) Hanson, J. R. The sesterterpenoids. *Nat. Prod. Rep.* **1996**, *13*, 529-535.

[3] Liu,Y.; Wang, L.; Jung, J. H.; Zhang, S. Sesterterpenoids. *Nat. Prod. Rep.* **2007**, *24*, 1401-1429.

[4] (a) Faulkner, D. J. Marine natural products. *Nat. Prod. Rep.* **2002**, *19*, 1-49 and previous reviews of this series; (b) Faulkner, D. J.; Newman, D. J.; Cragg, G. M. Investigations of the marine flora and fauna of the Islands of Palau. *Nat. Prod. Rep.* **2004**, *21*, 50-76.

[5] Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. Marine natural products. *Nat. Prod. Rep.* 2010, **27**, 165-237 and previous reviews of this series.

[6] De Rosa, S.; Mitova, M. In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, **2005**, vol. *32*, pp. 109-168.

[7] (a) Ungur, N.; Kulcitki, V. Synthesis of scalarane sesterterpenoids. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 241-258; (b) Ungur, N.; Kulcitki, V. Synthetic paths towards scalaranes: assembling the scalaranic skeleton and further transformations. *Phytochem. Rev.* **2005**, *3*, 401-415.

[8] Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J. Terpenoid constituents from two Phyllospongia spp. *Aust. J. Chem.*, **1980**, *33*, 1783-1797.

[9] Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. Scalarin, a new pentacyclic C-25 terpenoid from the sponge Cacospongia scalaris. *Tetrahedron* **1972**, *28*, 5993-5997.

[10] Cimino, G.; De Stefano, S.; Minale, L. Scalaradial, a third sesterterpene with the tetracarbocyclic skeleton of scalarin,

from the sponge *Cacospongia scalaris*. *Experientia* **1974**, *30*, 846-847.

[11] Puliti, R.; Mattia, C. A.; Mazzarella, L. Scalaradial, a sesterterpenoid metabolite from the marine sponge *Cacospongia mollior*. *Acta Crystallogr, Sect. C* **1995**, *51*, 1703-1707.

[12] (a) Cimino, G.; Fontana, A.; Giménez, F.; Marin, A.; Mollo, E.; Trivellone, E.; Zubia, E. Biotransformation of a dietary sesterterpenoid in the mediterranean nudibranch *Hypselodoris orsini*. *Experientia* **1993**, *49*, 582-586; (b) De Rosa, S.; Puliti, R.; Crispino, A.; De Giulio, A.; Mattia, C. A.; Mazzarella, L. A new scalarane sesterterpenoid from the marine sponge *Cacospongia mollior*. *J. Nat. Prod.* **1994**, *57*, 256-262.

[13] Yasuda, F.; Tada, H. Desacetylscalaradial, a cytotoxic metabolite from the sponge Cacospongia scalaris. *Experientia* **1981**, *37*, 110-111.

[14] Rueda, A.; Zubia, E.; Ortega, M. J.; Carballo, J. L.; Salvá, J. New cytotoxic metabolites from the sponge *Cacospongia scalaris*. *J. Org. Chem.* **1997**, *62*, 1481-1485.

[15] Terem, B.; Scheuer, P. J. Scalaradial derivatives from the nudibranch *Chromodoris youngbleuthi* and the sponge *Spongia oceania*. *Tetrahedron* **1986**, *42*, 4409-4412.

[16] (a) Cimino, G.; De Rosa, S.; De Stefano, S.; Sodano, G. The chemical defense of four mediterranean nudibranchs. *Comp. Biochem. Physiol.* **1982**, *73B*, 471-474; (b) Rogers, S. D.; Paul, V. J. Chemical defenses of three *Glossodoris nudibranchs* and their dietary Hyrtios sponges. *Mar. Ecol. Prog. Ser.* **1991**, *77*, 221-232.

[17] Avila, C.; Paul, V. J. Chemical ecology of the nudibranch *Glossodoris pallida*: is the location of diet-derived metabolites important for defense?. *Mar. Ecol. Prog. Ser.* **1997**, *150*, 171-180.

[18] Huang, X.-C.; Liu, H.-L.; Lou, L.-G.; Guo, Y.-W. Chemical constituents of two marine sponges *Dysidea villosa* and *Dysidea marshalla*. *Chinese J. Nat. Med.* **2008**, *6*, 425-429.

[19] Gavagnin, M.; Mollo, E.; Docimo, T.; Guo, Y.-W.; Cimino, G. Scalarane metabolites of the nudibranch *Glossodoris rufomarginata* and its dietary sponge from the south china sea. *J. Nat. Prod.* **2004**, *67*, 2104-2107.

[20] Manzo, E.; Gavagnin, M.; Somerville, M. J.; Mao, S.-C.; Ciavatta, M. L.; Mollo, E.; Schupp, P. J.; Garson, M. J.; Guo, Y.-W.; Cimino, G. Chemistry of *Glossodoris nudibranchs*: specific occurrence of 12-keto scalaranes. *J. Chem. Ecol.* **2007**, *33*, 2325-2336.

[21] Kubo, I.; Ganjian, I. Insect antifeedant terpenes, hot-tasting to humans. *Experientia* **1981**, *37*, 1063-1064.

[22] Caprioli, V.; Cimino, G.; Colle, R.; Gavagnin, M.; Sodano G.; Spinella, A. Insect antifeedant activity and hot taste for humans of selected natural and synthetic 1,4-dialdehydes. *J. Nat. Prod.* **1987**, *50*, 146-151.

[23] Szallasi, A.; Biró, T.; Modarres, S.; Garlaschelli, L.; Petersen, M.; Klusch, A.; Vidari, G.; Jonassohn, M.; De Rosa, S.; Sterner, O.; Blumberg, P. M.; Krause, J. E. Dialdehyde sesquiterpenes and other terpenoids as vanilloids. *Eur. J. Pharmacol.* **1998**, *356*, 81-89.

[24] (a) De Carvalho, M. S.; Jacobs, R. S. Two-step inactivation of bee venom phospholipase A_2 by scalaradial. *Biochem. Pharmacol.* **1991**, *42*, 1621-1626; (b) Potts, B. C. M.; Faulkner, D. J. Phospholipase A_2 inhibitors from marine organisms. *J. Nat. Prod.* **1992**, *55*, 1701-1717; (c) Potts, B. C. M.; Faulkner, D. J.; De Carvalho, M. S.; Jacobs, R. S. Chemical mechanism of inactivation of bee venom phospholipase A_2 by the marine natural products manoalide, luffariellolide, and scalaradial. *J. Am. Chem. Soc.* **1992**, *114*, 5093-5100; (d) Monti, M. C.; Casapullo, A.; Cavasotto, C. N.; Napolitano, A.; Riccio, R. Scalaradial, a dialdehyde-containing marine metabolite that causes an unexpected noncovalent PLA_2 inactivation. *ChemBioChem* **2007**, *8*, 1585-1591.

[25] Marshall, L. A.; Winkler, J. D.; Griswold, D. E.; Bolognese, B.; Roshak, A.; Sung, C.-M.; Webb, E. F.; Jacobs, R. Effects of scalaradial, a type II phospholipase A_2 inhibitor, on human neutrophil arachidonic acid mobilization and lipid mediator formation. *J. Pharm. Exp. Therap.* **1994**, *268*, 709-717.

[26] Corey, E. J.; Luo, G.; Lin, L. S. A simple enantioselective synthesis of the biologically active tetracyclic marine sesterterpene scalarenedial. *J. Am. Chem. Soc.* **1997**, *119*, 9927-9928.

[27] Cimino, G.; De Stefano, S.; Di Luccia, A. Further sesterterpenes from the sponge Spongia nitens: 12-epi-scalaradial and 12,18-diepi-scalaradial. *Experientia* **1979**, *35*, 1277-1278.

[28] (a) Crews, P.; Bescansa, P.; Bakus, G. J. A non-peroxide norsesterterpene from a marine sponge *Hyrtios erecta*. *Experientia* **1985**, *41*, 690-691; (b) Crews, P.; Bescansa, P. Sesterterpenes from a common marine sponge *Hyrtios erecta*. *J. Nat. Prod.* **1986**, *49*, 1041-1052.

[29] Bergquist, P. R.; Cambie, R. C.; Kernan, M. R. Scalarane sesterterpenes from *Collospongia auris*, a new thorectid sponge. *Biochem. System. Ecol.* **1990**, *18*, 349-357.

[30] Rueda, A.; Zubia, E.; Ortega, M. J.; Carballo, J. L.; Salvá, J. New metabolites from the sponge *Spongia agaricina*. *J. Nat. Prod.* **1998**, *61*, 258-261.

[31] Jaisamut, S.; Thengyai, S.; Yuenyongsawad, S.; Karalai, C.; Plubrukarn, A.; Suwanborirux, K. Structure-activity relationships of antitubercular scalaranes: Heteronemin revisited. *Pure Appl. Chem.* **2009**, *81*, 1019-1026.

[32] Kamel, H. N.; Kim, Y. B.; Rimoldi, J. M.; Fronczek, F. R.; Ferreira, D.; Slattery, M. Scalarane sesterterpenoids: semisynthesis and biological activity. *J. Nat. Prod.* **2009**, *72*, 1492-1496.

[33] Xie, Y.; Liu, L.; Huang, X.; Guo, Y.; Lou, L. Scalaradial inhibition of epidermal growth factor receptor-mediated Akt phosphorylation is independent of secretory phospholipase A_2. *J. Pharm. Exp. Therap.* **2005**, *314*, 1210-1217.

[34] Walker, R. P.; Thompson, J. E.; Faulkner, D. J. Sesterterpenes from *Spongia idia*. *J. Org. Chem.* **1980**, *45*, 4976-4979.

[35] Thompson, J. E.; Walker, R. P.; Faulkner, D. J. Screening and bioassays for biologically-active substances from forty marine sponge species from San Diego, California, USA. *Mar. Biol.* **1985**, *88*, 11-21.

[36] Somerville, M. J.; Hooper, J. N. A.; Garson, M. J. Mooloolabenes A-E, norsesterterpenes from the Australian sponge *Hyattella intestinalis*. *J. Nat. Prod.* **2006**, *69*, 1587-1590.

[37] Song, J.; Jeong, W.; Wang, N.; Lee, H.-S.; Sim, C. J.; Oh, K.-B.; Shin, J. Scalarane sesterterpenes from the sponge Smenospongia sp. *J. Nat. Prod.* **2008**, *71*, 1866-1871.

[38] Miyaoka, H.; Nishijima, S.; Mitome, H.; Yamada, Y. Three new scalarane sesterterpenoids from the Okinawan sponge *Hyrtios erectus*. *J. Nat. Prod.* **2000**, *63*, 1369-1372.

[39] Hernández-Guerrero, C. J.; Zubía, E.; Ortega, M. J.; Carballo, J. L. Sesterterpene metabolites from the sponge *Hyatella intestinalis*. *Tetrahedron* **2006**, *62*, 5392-5400.

[40] Kazlauskas, R.; Murphy, P. T.; Wells, R. J. Five new C_{26} tetracyclic terpenes from a sponge (Lendenfeldia sp.). *Aust. J. Chem.*, **1982**, *35*, 51-59.

[41] Nakagawa, M.; Hamamoto, Y.; Ishihama, M.; Hamasaki, S.; Endo, M. Pharmacologically active homosesterterpenes from Palauan sponges. *Tetrahedron Lett.* **1987**, *28*, 431-434.

[42] Sera, Y.; Adachi, K.; Shizuri, Y. A new epidioxy sterol as an antifouling substance from a Palauan marine sponge, *Lendenfeldia chondrodes*. *J. Nat. Prod.* **1999**, *62*, 152-154.

[43] Dai, J.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G. Cytotoxic metabolites from an Indonesian sponge Lendenfeldia sp. *J. Nat. Prod.* **2007**, *70*, 1824-1826.

[44] Chill, L.; Rudi, A.; Aknin, M.; Loya, S.; Hizi, A.; Kashman, Y. New sesterterpenes from *Madagascan Lendenfeldia* sponges. *Tetrahedron* **2004**, *60*, 10619-10626.

[45] Liu, Y.; Liu, R.; Mao, S.-C.; Morgan, J. B.; Jekabsons, M. B.; Zhou, Y.-D.; Nagle, D. G. Molecular-targeted antitumor agents. 19. Furospongolide from a marine Lendenfeldia sp. sponge inhibits hypoxia-inducible factor-1 activation in breast tumor cells. *J. Nat. Prod.* **2008**, *71*, 1854-1860.

[46] Aoki, S.; Higuchi, K.; Isozumi, N.; Matsui, K.; Miyamoto, Y.; Itoh, N.; Tanaka, K.; Kobayashi, M. Differentiation in chronic myelogenous leukemia cell K562 by spongean sesterterpene. *Biochem. Biophys. Res. Comm.* **2001**, *282*, 426-431.

[47] Fontana, A.; Mollo, E.; Ortea, J.; Gavagnin, M.; Cimino, G. Scalarane and homoscalarane compounds from the nudibranch *Glossodoris sedna* and *Glossodoris dalli*: Chemical and biological properties. *J. Nat. Prod.* **2000**, *63*, 527-530.

[48] Bowden, B. F.; Coll, J. C.; Li, H.: Cambie, R. C.; Kernan, M. R.; Bergquist, P. R. New cytotoxic scalarane sesterterpenes from the dictyoceratid sponge *Strepsichordaia lendenfeldi*. *J. Nat. Prod.* **1992**, *55*, 1234-1240.

[49] Jahn, T.; König, G. M.; Wright, A. D. Three new scalarane-based sesterterpenes from the tropical marine sponge *Strepsichordaia lendenfeldi*. *J. Nat. Prod.* **1999**, *62*, 375-377.

[50] Kashman, Y.; Zviely, M. New alkylated scalarins from the sponge *Dysidea herbacea*. *Tetrahedron Lett.* **1979**, *40*, 3879-3882.

[51] Schmitz, F. J.; Chang, J. C. Sesterterpenes from a pacific sponge, *Carteriospongia flabellifera*. *J. Nat. Prod.* **1988**, *51*, 745-748.

[52] Hossain, M. B.; Beatty, K.; Schmitz, F. J.; Van der Helm, D. X-ray structure of sesterterpene, 16β-acetoxy-24-methyl-12,24-dioxoscalaran-25-al. *J. Chem. Cryst.* **1995**, *25*, 765-767.

[53] Roy, M. C.; Tanaka, J.; De Voogd, N.; Higa, T. New scalarane class sesterterpenes from an Indonesian sponge, Phyllospongia sp. *J. Nat. Prod.* **2002**, *65*, 1838-1842.

[54] (a) Kikuchi, H.; Tsukitani, Y.; Shimizu, I.; Kobayashi, M.; Kitagawa, I. Foliaspongin, an antiinflammatory bishomosesterterpene from the marine sponge *Phyllospongia foliascens* (Pallas). *Chem. Pharm. Bull.* **1981**, *29*, 1492-1494; (b) Kikuchi, H.; Tsukitani, Y.; Shimizu, I.; Kobayashi, M.; Kitagawa, I. Marine natural products. XI. An antiinflammatory scalarane-type bishomosesterterpene, foliaspongin, from the Okinawan marine sponge *Phyllospongia foliascens* (Pallas). *Chem. Pharm. Bull.* **1983**, *31*, 552-556.

[55] (a) Braekman, J. C.; Daloze, D.; Kaisin, M.; Moussiaux, B. Ichthyotoxic sesterterpenoids from the neo guinean sponge *Carteriospongia foliascens*. *Tetrahedron* **1985**, *41*, 4603-4614; (b) Braekman, J. C.; Daloze, D.; Kaisin, M.; Moussiaux, B. Erratum: Ichthyotoxic sesterterpenoids from the neo guinean sponge *Carteriospongia foliascens*. *Tetrahedron* **1986**, *42*, 445; (c) Braekman, J. C.; Daloze, D. Chemical defence in sponges. *Pure Appl. Chem.* **1986**, *58*, 357-364.

[56] Kitagawa, I.; Kobayashi, M.; Lee, N.-K.; Oyama, Y.; Kyogoku, Y. Marine natural products. XX. Bioactive scalarane-type bishomosesterterpenes from the Okinawan marine sponge *Phyllospongia foliascens*. *Chem. Pharm. Bull.* **1989**, *37*, 2078-2082.

[57] De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Tommonaro, G.; Zavodnik, N. A new dimethylscalarane derivative from the sponge *Cacospongia scalaris*. *Tetrahedron* **1998**, *54*, 6185-6190.

[58] Alvi, K. A.; Crews, P. Homoscalarane sesterterpenes from *Lendenfeldia frondosa*. *J. Nat. Prod.* **1992**, *55*, 859-865.

[59] De Clercq, J. P.; Van Meerssche, M.; Braekman, J. C.; Daloze, D. A new 20,24-dimethylscalarane derivative isolated from the sponge *Carteriospongia foliascens*, $C_{30}H_{42}O_6$. *Acta Crystallogr., Sect. C* **1985**, *41*, 1222-1224.

[60] Li, H.-J.; Amagata, T.; Tenney, K.; Crews, P. Additional scalarane sesterterpenes from the sponge *Phyllospongia papyracea*. *J. Nat. Prod.* **2007**, *70*, 802-807.

[61] Rao, C. B.; Kalidindi, R. S. H. S. N.; Trimurtulu, G.; Rao, D. V. Metabolites of porifera, part III. New 24-methylscalaranes from *Phyllospongia dendyi* of the indian ocean. *J. Nat. Prod.* **1991**, *54*, 364-371.

[62] Zeng, L.-M.; Fu, X.; Su, J.-G.; Chen, S.; Snyder, J. K. Phyllofenone A, a new scalarane sesterterpene from the sponge *Phyllospongia foliascens* (Pallas). *Chem. Res. Chin. Univ.* **1991**, *7*, 100-106.

[63] Zhang, H.-J.; Tang, H.-F.; Yi Y.-H.; Lin, H.-W. Scalarane sesterterpenes from the chinese sponge *Phyllospongia foliascens*. *Helv. Chim. Acta* **2009**, *92*, 762-767.

[64] (a) Quinn R. J.; Tucker, D. J. Two novel bisalkylated norscalaranes from the sponge *Carteriospongia foliascens*. *Aust. J. Chem.* **1989**, *42*, 751-755; (b) Barron, P. F.; Quinn R. J.; Tucker, D. J. Structural elucidation of a novel scalarane derivative by using high-field (14.1 T) N.M.R. spectroscopy. *Aust. J. Chem.* **1991**, *44*, 995-999.

[65] Ponomarenko, L. P.; Kalinovsky, A. I.; Stonik, V. A. New scalarane-based sesterterpenes from the sponge *Phyllospongia madagascarensis*. *J. Nat. Prod.* **2004**, *67*, 1507-1510.

[66] Jiménez, J. I.; Yoshida, W. Y.; Scheuer, P. J.; Kelly, M. Scalarane-based sesterterpenes from an Indonesian sponge *Strepsichordaia aliena*. *J. Nat. Prod.* **2000**, *63*, 1388-1392.

[67] Lan, W.-J.; Li, H.-J. New sesterterpenoids from the marine sponge *Pyllospongia papyracea*. *Helv. Chim. Acta* **2007**, *90*, 1218-1222.

[68] Williams, D. E.; Hollander, I.; Feldberg, L.; Frommer, E.; Mallon, R.; Tahir, A.; Van Soest, R.; Andersen, R. J. Scalarane-based sesterterpenoid RCE-protease inhibitors isolated from the Indonesian marine sponge *Carteriospongia foliascens*. *J. Nat. Prod.* **2009**, *72*, 1106-1109.

[69] Tsoukatou, M.; Siapi, H.; Vagias, C.; Roussis, V. New sesterterpene metabolites from the Mediterranean sponge *Cacospongia scalaris*. *J. Nat. Prod.* **2003**, *66*, 444-446.

[70] Doi, Y.; Shigemori, H.; Ishibashi, M.; Mizobe, F.; Kawashima, A.; Nakaike, S.; Kobayashi, J. New sesterterpenes with nerve growth factor synthesis-stimulating activity from the Okinawan marine sponge Hyrtios sp. *Chem. Pharm. Bull.* **1993**, *41*, 2190-2191.

[71] Lu, Q.; Faulkner, D. J. Two new sesterterpenoids and a new 9,11-secosterol from spongia matamata. *J. Nat. Prod.* **1997**, *60*, 195-198.

[72] Qiu, Y.; Deng, Z.; Pei, Y.; Fu, H.; Li, J.; Proksch, P.; Lin, W. Sesterterpenoids from the marine sponge *Hyrtios erectus*. *J. Nat. Prod.* **2004**, *67*, 921-924.

[73] Cambie, R. C.; Rickard, C. E. F.; Rutledge, P. S.; Yang, X.-S. Scalarolide and scalarin, sesterterpenes from Cacospongia and Ircinia sponges. *Acta Crystallogr. Sect. C* **1999**, *55*, 112-114.

[74] Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. 12-Epi-scalarin and 12-epi-deoxoscalarin, sesterterpenes from the sponge *Spongia nitens*. *J. Chem. Soc., Perkin 1* **1977**, 1587-1593.

[75] Tsuchiya, N.; Sato, A.; Hata, T.; Sato, N.; Sasagawa, K.; Kobayashi, T. Cytotoxic scalarane sesterterpenes from a sponge, *Hyrtios erecta*. *J. Nat. Prod.* **1998**, *61*, 468-473.

[76] Yu, Z.-G.; Bi, K.-S.; Guo, Y.-W. Hyrtiosins A-E, five new scalarane sesterterpenes from the South china sea sponge *Hyrtios erecta*. *Helv. Chim. Acta* **2005**, *88*, 1004-1009.

[77] Tsukamoto, S.; Miura, S.; Van Soest, R. W. M.; Ohta, T. Three new cytotoxic sesterterpenes from a marine sponge Spongia sp. *J. Nat. Prod.* **2003**, *66*, 438-440.

[78] Tokue, T.; Miura, S.; Kato, H.; Hikaru, H.; Hirota, H.; Ohta, T.; Tsukamoto, S. Neurotrophic sesterterpenes isolated from a marine sponge, Spongia sp. *Heterocycles* **2006**, *69*, 521-526.

[79] Nam, S.-J.; Ko, H.; Ju, M. K.; Hwang, H.; Chin, J.; Ham, J.; Lee, B. J.; Won, D. H.; Choi, H.; Ko, J.; Shin, K.; Oh, T.; Kim, S.; Rho, J.-R.; Kang, H. Scalarane sesterterpenes from a marine sponge of the genus Spongia and their FXR antagonistic activity. *J. Nat. Prod.* **2007**, *70*, 1691-1695.

[80] Kernan, M. R.; Barrabee, E. B.; Faulkner, D. J. Variation of the metabolites of *Chromodoris funerea*: Comparison of specimens from a Palauan marine lake with those from adjacent waters. *Comp. Biochem. Physiol.* **1988**, *89B*, 275-278.

[81] Kobayashi, J.; Mizobe, F. JP Patent 06239741 A, **1994**.

[82] Ashour, M. A.; Elkhayat, E. S.; Ebel, R.; Edrada, R.; Proksch, P. Indole alkaloid from the Red sea sponge *Hyrtios erectus*. *Arkivoc* **2007**, *15*, 225-231.

[83] Díaz-Marrero, A. R.; Matainaho, T.; Van Soest, R.; Roberge, M.; Andersen, R. J. Scalarane-based metabolites isolated from the antimitotic extract of the marine sponge *Hyrtios erectus*. *Nat. Prod. Res.* **2008**, *22*, 1304-1309.

[84] Wonganuchitmeta, S.-N.; Yuenyongsawad, S.; Keawpradub, N.; Plubrukarn, A. Antitubercular sesterterpenes from the Thai sponge Brachiaster sp. *J. Nat. Prod.* **2004**, *67*, 1767-1770.

[85] Venkateswarlu, Y.; Biabani, M. A. F.; Rao, T. P. A new sesterterpene from the sponge *Heteronema erecta*. *Ind. J. Chem. B* **1995**, *34*, 563-564.

[86] Pettit, G. R.; Cichacz, Z. A.: Tan, R.: Herald, D. L.: Melody, N.; Hoard, M. S.; Doubek, D. L.; Hooper, J. N. A. Antineoplastic agents. 385. The isolation and structure of a scalarane-type sesterterpene from the Indian ocean porifera *Hyrtios erecta*. *Collect. Czech. Chem. Commun.* **1998**, *63*, 1671-1677.

[87] Youssef, D. T. A.; Shaala, L. A.; Emara, S. Antimycobacterial scalarane-based sesterterpenes from the Red sea sponge *Hyrtios erecta*. *J. Nat. Prod.* **2005**, *68*, 1782-1784.

[88] Kumar, M. M. K.; Krishna, N.; Muralidhar, P.; Sastry, B. S.; Rao, D. V. A new scalarane sesterterpene from a marine spnge Hyatella cribriformis Hyatt of the Indian ocean. *Ind. J. Chem. B* **2008**, *47*, 325-328.

[89] Mahidol, C.; Prawat, H.; Sangpetsiripan, S.; Ruchirawat, S. Bioactive scalaranes from the Thai sponge *Hyrtios gumminae*. *J. Nat. Prod.* **2009**, *72*, 1870-1874.

[90] Ryu, G.; Matsunaga, S.; Fusetani, N. Three new cytotoxic sesterterpenes from the marine sponge *Hyrtios cf. erectus*. *J. Nat. Prod.* **1996**, *59*, 515-517.

[91] Kobayashi, J.; Murayama, T.; Ishibashi, M.; Kosuge, S.; Takamatsu, M.; Ohizumi, Y.; Kobayashi, H.; Ohta, T.; Nozoe, S.; Sasaki, T. Hyrtiosins A and B, new indole alkaloids from the Okinawan marine sponge *Hyrtios erecta*. *Tetrahedron* **1990**, *46*, 7699-7702.

[92] Rho, J.-R.; Lee, H.-S.; Shin, H. J.; Ahn, J.-W.; Kim, J.-Y.; Sim, C. J.; Shin, J. New sesterterpenes from the sponge Smenospongia sp. *J. Nat. Prod.* **2004**, *67*, 1748-1751.

[93] Pettit, G. R.; Tan, R.; Cichacz, Z. A. Antineoplastic agents. 542. Isolation and structure of sesterstatin 6 from the Indian ocean sponge *Hyrtios erecta*. *J. Nat. Prod.* **2005**, *68*, 1253-1255.

[94] Cambie, R C.; Rutledge, P. S.; Yang, X.-S.; Bergquist, P. R. Chemistry of sponges. 18. 12-Desacetylfuroscalar-16-one, a new sesterterpene from a Cacospongia sp. *J. Nat. Prod.* **1998**, *61*, 1416-1417.

[95] Youssef, D. T. A.; Yamaki, R. K.; Kelly, M.; Scheuer, P. J. Salmahyrtisol A, a novel cytotoxic sesterterpene from the Red sea sponge *Hyrtios erecta*. *J. Nat. Prod.* **2002**, *65*, 2-6.

[96] Meng, X.-J.; Liu, Y.; Fan, W.-Y.; Hu, B.; Du, W.; Deng, W.-P. The first synthesis of marine sesterterpene (+)-scalarolide. *Tetrahedron Lett.* **2009**, *50*, 4983-4985.

[97] Pettit, G. R.; Cichacz, Z. A.; Tan, R.; Hoard, M. S.; Melody, N.; Pettit, R. K. Antineoplastic agents. 386. Isolation of sesterstatins 1-3 from the marine sponge *Hyrtios erecta*. *J. Nat. Prod.* **1998**, *61*, 13-16.

[98] Chang, L. C.; Otero-Quintero, S.; Nicholas, G. M.; Bewley, C. A. Phyllolactones A-E: new bishomoscalarane sesterterpenes from the marine sponge *Phyllospongia lamellosa*. *Tetrahedron* **2001**, *57*, 5731-5738.

[99] Fu, X.; Zeng, L. M.; Su, J. Y.; Pais, M.; Potier, P. Scalarane-type bishomosesterterpenes from the sponge *Phyllospongia foliascens*. *J. Nat. Prod.* **1992**, *55*, 1607-1613.

[100] Wan, Y.; Li, Q.; Zeng, L.; Su, J. Secondary metabolites of the marine sponge, *Phyllospongia foliascens*. *Acta Scientarium Naturalium* **1998**, *37*, 81-84.

[101] Fu, X.; Zeng, L.; Su, J.; Pais, M.; Potier, P. Two new sesterterpenes from a South china sea sponge. *J. Nat. Prod.* **1993**, *56*, 1985-1988.

[102] Zeng, L.; Fu, X.; Su, J.; Wang, Q. Phyllactones F and G, further bis-homoscalarane sesterterpenes from the sponge *Phyllospongia foliascens*. *Chem. Res. Chin. Univ.* **1993**, *9*, 161-164.

[103] Hochlowski, J. E.; Faulkner, D. J.; Bass, L. S.; Clardy, J. Metabolites of the dorid nudibranch *Chromodoris sedna*. *J. Nat. Prod.* **1983**, *48*, 1738-1740.

[104] Stessman, C. C.; Ebel, R.; Corvino, A. J.; Crews, P. Employing dereplication and gradient 1D NMR methods to rapidly characterize sponge-derived metabolites. *J. Nat. Prod.* **2002**, *65*, 1183-1186.

[105] Fu, X.; Zeng, L.; Su, J.; Schmitz, F. J. Phyllofolactones C and D, two new minor homoscalarane sesterterpenes from the chinese sponge *Phyllospongia foliascens*. *J. Nat. Prod.* **1999**, *62*, 644-646.

[106] Zeng, L.; Fu, X.; Su, J.; Pordesimo, E. O.; Traeger, S. C.; Schmitz, F. J. Novel bishomoscalarane sesterterpenes from the sponge *Phyllospongia foliascens*. *J. Nat. Prod.* **1991**, *54*, 421-427.

[107] Reddy, M. V. R.; Venkateswarlu, Y.; Rao, J. V. A new bishomoscalarane sesterterpene 12-epi-phyllofolactone-B from *Phyllospongia foliascens*. *Indian J. Chem. B* **1993**, *32*, 1196-1197.

[108] Wang, Y.-Q.; Su, J.-Y.; Zeng, L.-M.; Wang, M.-Y. Two new scalarane-type sesterterpenes phyllactone H and I from the sponge Phyllospongia sp. *Chem. J. Chin. Univ.* **1996**, *17*, 1747-1749.

[109] Croft, K. D.; Ghisalberti, E. L.; Skelton, B. W.; White, A. H. Structural study of a new dialkylated scalarane from a Carteriospongia sp. *J. Chem. Soc., Perkin 1* **1983**, 155-159.

[110] Jiménez, J. I.; Yoshida, W. Y.; Scheuer, P. J.; Lobkovsky, E.; Clardy, J.; Kelly, M. Honulactones: new bishomoscalarane sesterterpenes from the Indonesian sponge *Strepsichordaia aliena*. *J. Org. Chem.* **2000**, *65*, 6837-6840.

[111] Fu, X.; Zeng, L.; Su, J. Acetoxy phyllofolactone A – A new bishomoscalarane sesterterpene from the South china sea sponge *Phyllospongia foliascens*. *Chem. J. Chin. Univ.* **1992**, *13*, 628-629.

[112] Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. Heteronemin, a new scalarin type sesterterpene from the sponge *Heteronema erecta*. *Tetrahedron Lett.* **1976**, *17*, 2631-2634.

[113] Kashman, Y.; Rudi, A. The ^{13}C-NMR spectrum and stereochemistry of heteronemin. *Tetrahedron* **1977**, *33*, 2997-2998.

[114] Patil, A. D.; Westley, J. W.; Baures, P. W.; Eggleston, D. S. Structure of heteronemin. *Acta Crystallogr. Sect. C* **1991**, *47*, 1250-1253.

[115] Karuso, P.; Cambie, R. C.; Bowden, B. F.; Bergquist, P. R. Chemistry of sponges, VI. Scalarane sesterterpenes from *Hyatella intestinalis*. *J. Nat. Prod.* **1989**, *52*, 289-293.

[116] Bourguet-Kondracki, M. L.; Martin, M. T.; Debitus, C.; Guyot, M. 12-Epi-heteronemin: new sesterterpene from the marine sponge *Hyrtios erecta*. *Tetrahedron Lett.* **1994**, *35*, 109-110.

[117] Kobayashi, M.; Okamoto, T.; Hayashi, K.; Yokoyama, N.; Sasaki, T.; Kitagawa, I. Marine natural products. XXXII. Absolute configurations of C-4 of the manoalide family, biologically active sesterterpenes from the marine sponge *Hyrtios erecta*. *Chem. Pharm. Bull.* **1994**, *42*, 265-270.

[118] Alam, M.; Sanduja, R.; Wellington, G. M. Heteronemin from the stony coral *Tubastraea miccantha*. *Heterocycles* **1988**, *27*, 719.

[119] Fontana, A.; Cavaliere, P.; Ungur, N.; D'Souza, L.; Parameswaram, P. S.; Cimino, G. New scalaranes from the nudibranch *Glossodoris atromarginata* and its sponge prey. *J. Nat. Prod.* **1999**, *62*, 1367-1370.

[120] Ledroit, V.; Debitus, C.; Ausseil, F.; Raux, R.; Menou, J.-L.; Hill, B. Heteronemin as a protein farnesyl transferase inhibitor. *Pharm. Biol.* **2004**, *42*, 454-456.

[121] El Sayed, K. A.; Bartyzel, P.; Shen, X.; Perry, T. L.; Zjawiony, J. K.; Hamann, M. T. Marine natural products as antituberculosis agents. *Tetrahedron* **2000**, *56*, 949-953.

[122] Cimino, G.; De Stefano, S.; Minale, L. Deoxoscalarin, a further sesterterpene with the unusual tetracyclic carbon skeleton of scalarin, from *Spongia officinalis*. *Experientia* **1973**, *29*, 934-936.

[123] Miyamoto, T.; Sakamoto, K.; Amano, H.; Arakawa, Y.; Nagarekawa, Y.; Komori, T.; Higuchi, R.; Sasaki, T. New cytotoxic sesterterpenoids from the nudibranch *Chromodoris inornata*. *Tetrahedron* **1999**, *55*, 9133-9142.

[124] De Giulio, A.; De Rosa, S.; Di Vincenzo, G.; Zavodnik, N. Terpenoids from the North adriatic sponge *Spongia officinalis*. *J. Nat. Prod.* **1989**, *52*, 1258-1262.

[125] Nam, S.-J.; Ko, H.; Shin, M.; Ham, J.; Chin, J.; Kim, Y.; Kim, H.; Shin, K.; Choi, H.; Kang, H. Farnesoid X-activated receptor antagonists from a marine sponge Spongia sp. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5398-5402.

[126] Rao, C. B.; Kalidindi, R. S. H. S. N.; Rao, D. V.; Sreedhara, C. Metabolites of porifera. Part IV. A new sesterterpene from *Phyllospongia dendyi* of the Indian ocean. *Ind. J. Chem. B* **1993**, *32*, 288-290.

[127] Jaspars, M.; Jackson, E.; Lobkovsky, E.; Clardy, J.; Diaz, M. C.; Crews, P. Using scalarane sesterterpenes to examine a sponge taxonomic anomaly. *J. Nat. Prod.* **1997**, *60*, 556-561.

[128] Fu, X.; Zeng, L.; Su, J.; Chen, S.; Snyder, J. K. Bishomoscalarane sesterterpenes from the sponge *Phyllospongia foliascens*. *Chem. J. Chin. Univ.* **1991**, *12*, 1486-1487.

[129] Fu, X.; Zeng, L.; Su, J.; Snyder, J. K. Spectral study on a bishomosesterterpene, phyllohemiketal A. *J. Instrum. Anal.* **1993**, *12*, 29-33.

[130] Fu, X.; Zeng, L.; Su, J.; Schmitz, F. J. A new sesterterpene from the sponge *Phyllospongia foliascens*. *Chin. Chem. Lett.* **1991**, *2*, 543-544.

[131] Shen, X.; Guo, Y.; Jian, H.; Yu, Z.; Du, L. CN Patent 1864691 A, **2006**.

[132] Davis, R.; Capon, R. J. Two new scalarane sesterterpenes: isoscalarafuran-A and –B, epimeric alcohols from a southern Australian marine sponge, *Spongia hispida*. *Aust. J. Chem.* **1993**, *46*, 1295-1299.

[133] Pettit, G. R.; Tan, R.; Melody, N.; Cichacz, Z. A.; Herald, D. L.; Hoard, M. S.; Pettit, R. K.; Chapuis, J.-C. Antineoplastic agents 397: Isolation and structure of sesterstatins 4 and 5 from *Hyrtios erecta* (The republic of maldives). *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2093-2098.

[134] (a) Cafieri, F.; De Napoli, L.; Fattorusso, E.; Santacroce, C.; Sica, D. Furoscalarol, a scalarin-like furanosesterterpenoid from the marine sponge *Cacospongia mollior*. *Gazz. Chim. Ital.* **1977**, *107*, 71-74; (b) Cimino, G.; Cafieri, F.; De Napoli, L.; Fattorusso, E. Carbon-13 NMR spectrum and absolute stereochemistry of furoscalarol. *Tetrahedron Lett.* **1978**, 2041-2044.

[135] Cambie, R. C.; Rutledge, P. S.; Yang, X.-S.; Bergquist, P. R. Chemistry of sponges. 18. 12-Desacetylfuroscalar-16-one, a new sesterterpene from a Cacospongia sp. *J. Nat. Prod.* **1998**, *61*, 1416-1417.

[136] Cimino, G.; De Rosa, S.; De Stefano, S. Scalarolbutenolide, a new sesterterpenoid from the marine sponge *Spongia nitens*. *Experientia* **1981**, *37*, 214-216.

[137] Cafieri, F.; De Napoli, L.; Fattorusso, E.; Santacroce, C.; Sica, D. Molliorin-A: A unique scalarin-like pyrroloterpene from the sponge *Cacospongia mollior*. *Tetrahedron Lett.* **1977**, *18*, 477-480.

[138] Cafieri, F.; De Napoli, L.; Fattorusso, E.; Santacroce, C. Molliorin-B, a second scalarin-like pyrroloterpene from the sponge *Cacospongia mollior*. *Experientia* **1977**, *33*, 994-995.

[139] Cafieri, F.; De Napoli, L.; Iengo, A.; Santacroce, C. Molliorin-C, a further pyrroloterpene present in the sponge *Cacospongia mollior*. *Experientia* **1978**, *34*, 300-301.

[140] Kimura, J.; Hyosu, M. Two new sesterterpenes from the marine sponge, *Coscinoderma mathewsi*. *Chem. Lett.* **1999**, 61-62.

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