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Review Article

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Terpenes from soft corals of the genus *Lobophytum* (Alcyoniidae): Chemistry and biological activities

R. Y. Perry Burhan*, Endah Mutiara Marhaeni Putri, Yulfi Zetra, Ridho Herdhiansyah and Masteria Yunovilsa Putra*

Molecular Geochemistry Laboratory, Chemistry Department, Institut Teknologi Sepuluh Nopember, Kampus ITS Sukolilo, Surabaya

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ABSTRACT

Soft corals belonging to the genus Lobophytum (Alcyoniidae) have been proven to be rich sources of natural terpenes. Many of these terpenes show interesting biological activities. This review reports details of terpenes isolated from Lobophytum soft corals during the period 2004–2014, complete with their structures, names, literatures and biological activities.

Keywords: soft corals, *lobophytum*, terpenes

INTRODUCTION

Marine soft corals are known to be rich sources of structurally and biologically intriguing natural products[1,2].*Lobophytum* comprises a group of soft corals belonging to the phylum Cnidaria, class Anthozoa, order Alcyonacea and family Alcyoniidae. Soft corals of the genus *Lobophytum*are a family with more than 20 species present in tropical and subtropical waters. Various natural products, distributed mainly in marine soft corals of the genus of *Lobophytum*[3], have attracted much attention from chemists sepcializing in natural products due to their structural complexity and remarkable pharmacological activitiessuch as cytotoxicity[4–11], antibacterial activities[12], anti-inflammatory properties[12–14], and HIV-inhibitory activity[15].

Since 2004, more than 50 research papers have been published on investigation of the chemical consituents of the soft corals genus *Lobophytum*, the majority reporting new and novel terpenes. In this review, acoording to the numbers of C-atoms, terpenes were divided into two groups: diterpenes, and biscembranoids. From literature, we do not find sequiterpene isolated from the genus of Lobophytum. Most of isolated diterpenes are cembranoid compounds[16], which are often found in high concentrations (up to 5% dry weight) in soft corals and have possible chemical defense roles against predators such as fish as well as microorganisms and other corals[17,18]. The purpose of this review is to focus on the terpene constituents of *Lobophytum*, highlight their novel chemistry and pharmacological activities.

2. Diterpenes

Diterpenes are group of terpenes the structures of which are derivable from geranylfarnesyl diphosphate as their precursor, and cembranes form a large group of macrocyclic diterpenes[19]. Soft corals are well-known for their high content of diterpenes, of which particularly cembrane-type diterpenes are the characteristic constituents of this genus[20]. The folowing discussion is divided into four according to these structural characteristics.

2.1. Cembrane Diterpenes

2.1.1 Cembrane Diterpenes with a Furan Ring or a γ -Lactone

Seventeen cytotoxic cembranoidsmichaolides A—Q **(1-17)**, bearing theα-methylene-γ-lactone, were isolated from

the CH_2Cl_2 extract of the Formosan soft coral *Lobophytum michaelae* TIXIER-DURIVAULT (Alcyonidae) [21,22]. Compounds **2** and **6** showed potent cytotoxicity against HT-29 and P-388 cell lines. Compounds**8**and **9** showed moderate cytotoxity against HT-29 and P-388 cell lines. Hydroxylation at C-14 together with anα-exo-methylene-γ-lactone and a 3,4-trisubstituted epoxy may be important for potent cytotoxicity.

Chemical investigation of the Et_2O-soluble fraction from an acetone extract of the soft coral *Lobophytum sp*., collected at the Lingshui Bay, Hainan Province, China, led to the isolation of six cembranolide, lobophytolides A – F**(18-23)**, all containing an α -methylidene- γ -lactone moiety[23]. Their structures, including their relative configuration, were elucidated by extensive analyses of the spectroscopic data.

The soft coral *Lobophytum durum*, resulted seventeen cembranolide named durumolides A-L**(24-35)**with a *trans*-fused α-methylene-γ-lactone and durumolides M–Q**(36-40)**possessing an α-methoxymethyl-γ-lactone[3,12,13]. Compounds **24-35** were determined mainly through NMR techniques and HR-ESI-MS analysis. Moreover, the absolute configuration of **26**, **29**, and **33** were established by application of modified Mosher's method. The antibacterial activities, anti-inflammatory effects, and anti-HCMV (Human cytomegalovirus) endonuclease activity of durumolides A–L **(24-35)**were also evaluated in vitro. Anti-inflammatory activity of **24**, **26**, **29**, and **34**(10 μM) significantly reduced the levels of the iNOS protein to 34.7 ± 7.9%, 0.0 ± 0.0%, 0.8 ± 0.6% and 5.7 ± 2.2%, respectively, and COX-2 protein to 62.5±4.3%, 42.5±8.6%, 47.8 ± 9.0% and 71.6 ± 5.8%, respectively. Compounds **24-26** and **28** revealed greater antibacterial potential than the positive control (ampicilin) against *Salmonella enteritidis*. Compounds **25 and 26**exhibite significant antibacterial activity at a concentration of 100 μg/disk and compound **24** andcompound **28** at concentration of 200 μg/disk, and compound 27 at concentration of 250 μg/disk. The results for inhibition of HCMV endonuclease activity assay are all negative at a concentration of 1 mg/mL[12].

Durumolides M-Q **(36-40)**were evaluated in vitro for the cytotoxicity against A-459 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), and P-388 (mouse lymphocytic leukemia) cancer cell lines, and antiviral activity against human cytomegalovirus. Preliminary cytotoxic screening revealed that compound **39** exhibited cytotoxicity against P-388 (mouse lymphocytic leukemia) cell line with an ED_{50} of 3.8 μg/mL. Moreover, compound **40** showed significant antiviral activity against human cytomegalovirus with an IC_{50} of 5.2 μg/mL[13].

The soft coral *Lobophytum crassum*(Von Marenzeller, 1886) was collected atDongsha Island, Taiwan, at a depth of 6 m, has led to the isolation of lobocrasol**(41)**[11], possessing an unprecendented diterpenoid skeleton. Compound **41**exhibited cytotoxicity against the P-388 cell with ED_{50} of 3.2 μg/mL.

Lobocrassin A**(42)** isolated from *Lobophytum crassum*, collected at the coast of northeast Taiwan at a depth of 10 m. Compound **42**is the first cembranoid possessing an α-chloromethyl-α-hydroxy-γ-lactone functionality and is the first chlorinated cembranoid from soft corals belonging to the genus *Lobophytum*[25].

Chemical investigation of the Dongsha Atoll soft coral *Lobophyum crassum* has afforded four cembranoids crassumols B-C **(43-44)**and 13-acetoxysarcophytoxide **(45)**[27]. The cytotoxicity and anti-HCMV (Human cytomegalovirus) activities of compounds **43-44**and **56**were evaluated in vitro. Compound **45**exhibited cytotoxicity against A-549 (human lung carcinoma) cell line with an ED_{50} of 3.6 μg/mL.Crassumol G**(46)**, wasisolated from the methanol extract of the Vietnamese soft coral *Lobophytum crassum*[28]. The anti-inflammatory activity of compounds **46** were evaluated by the inhibitory effect on tumor necrosis factor-alpha (TNFα)-induced nuclear factor-kappa B (NF-κB) transcriptional activation in HepG2 cells.

Two new 7,8-epoxycembranoids, namely (2S*,7S*,8S*,12R*,1Z,3E,10E)-7,8:2,16-diepoxycembra-1(15),3,10-trien-12-ol **(47)** and (2S*,7S*,8S*,11R*,1Z,3E)-7,8:2,16-diepoxycembra-1(15),3,12(20)-trien-11-ol **(48)**were isolated from a Chinese soft coral *Lobophytum sp*., collected by hand on a coral reef off Ximao island (Sanya Bay, Hainan Province, China) at a depth of 8 m[33].Compounds **47-48**were tested for the inhibitory effect on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in mouse peritoneal macrophages (PEMΦ). The bioassay results revealed that compounds **47-48** showed weak activity (IC_{50}>10 μM). In addition, compounds **47-48**were weakly cytotoxic against mouse PEMΦ (IC_{50}>10 μM).

A new hydroperoxy-substituted cembranoid diterpene, 2-hydroperoxysarcophine **(49)**was isolated from the marine soft coral *Lobophytum crassum*collected in the sea waters of Hainan island. Also isolated were two other cembranoid diterpenes, obtained for the first time from a natural source, *i.e.*, 7*b*,8*b*-epoxy-4*a*-hydroxycembra-1(15),2,11-trien-16,2-olide**(50)** and 7*b*,8*b*-epoxy-4*b*-hydroxycembra-1(15),2,11-trien-16,2-olide**(51)**[36]. Their structures and relative configurations were elucidated on the basis of extensive spectroscopic analyses including 1D- and 2D-NMR, and HR-ESI-MS experiments.

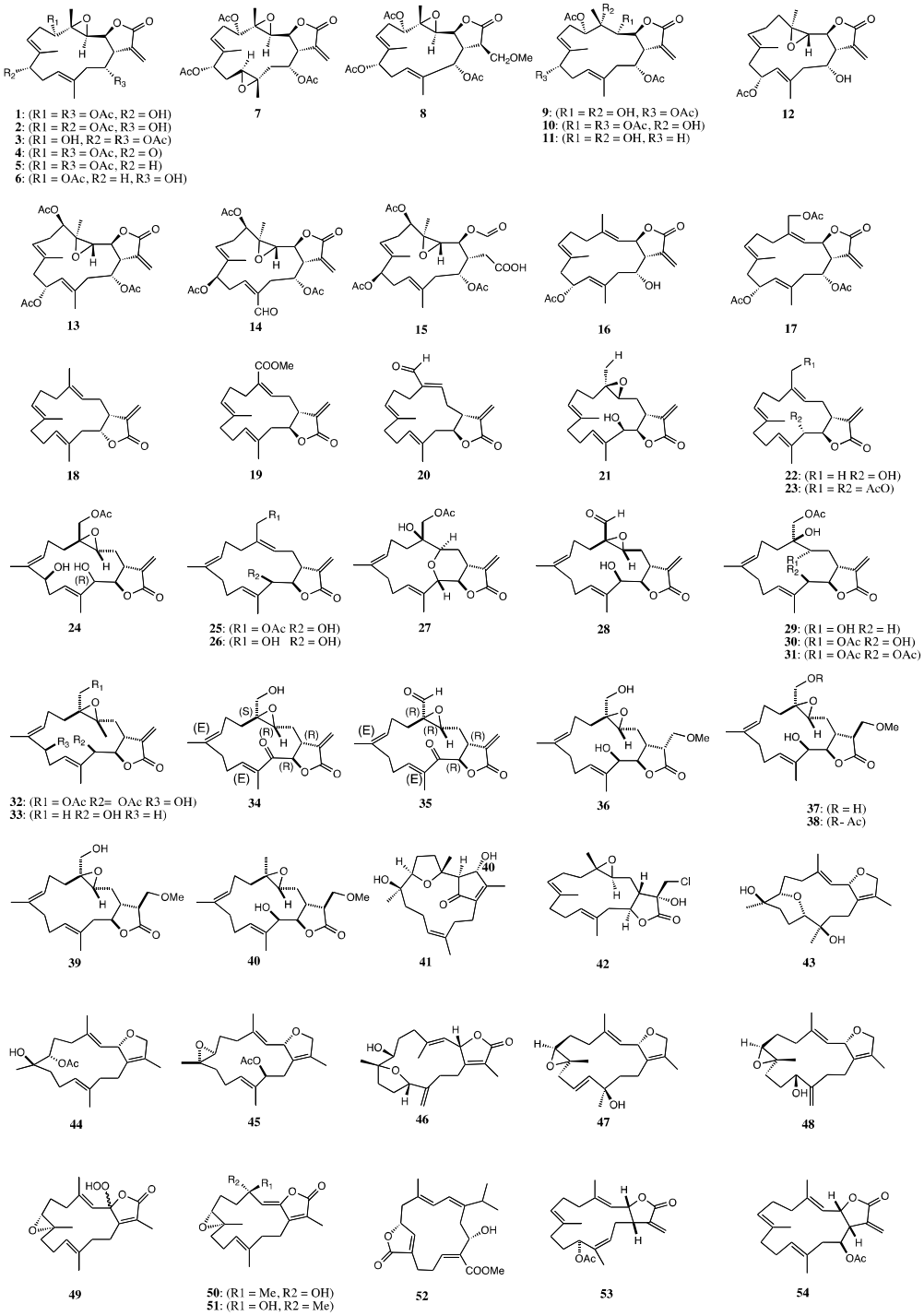


Figure 1. Compounds 1-54,Cembrane Diterpenes with a Furan Ring or γ-Lactone

Sarcophytolin D**(52)**have been isolated from the soft coral *Lobophytum sarcophytoides*[38]. The relative structures of **52**were elucidated on the basis of extensive spectroscopic and the absolute configurations of **52**were determined by Mosher's method and CD spectrum. The in vitro anti inflammatory effect of **52**was tested. In this assay, the up-regulation of the pro-inflammatory iNOS and COX-2 proteins of LPS-stimulated RAW264.7 macrophage cells was evaluated using immunoblot analysis. At a concentration of 10 μM, compound **52**was found to effectively reduce the levels of iNOS to 38.4±14.9%.

Two unnamed cembrane di terpenes, **53-54**were isolated from an Okinawan soft coral *Lobophytum crassum*[39]. The structures of these two new cembranoids were determined on the basis of spectroscopic evidence. In particular, the absolute stereochemistry of **53**and **54**were elucidated by the application of the modified Mosher's method and circular dichroism (CD) spectral data. The inhibitory effects of compounds **53-54**on LPS induced NO production against Raw 264.7 cells were evaluated. Compounds **53**and **54**showed significant inhibitory effect of NO

production, and their IC_{50} (3.8±0.97 and 4.0±0.91)values were less than 10 μM (107.3±5.5 and 100.0±6.6) without any cytotoxic effect. These data indicated that the α-methylene-γ-lactone moiety obviously plays a role for an inhibitory effect on NO production. The inhibitory mechanism of these cembranoids was confirmed by the inhibition of inducible NO synthase (iNOS) expression *via* suppression of a transcription factor nuclear factor k B (NF-k B).

2.1.2 δ-Lactone-type Cembrane Diterpenes

Durumhemiketalolides A-C **(55-57)** also isolated from the soft coral *Lobophytum durum*[14]. This compounds characterized as possessing a hemiketal tetrahydropyran ring and anα-methylene-δ-lactone ring *cis*-fused to a 14-membered ring. Compounds **55-57**were evaluated for anti-inflammatory activity using RAW 264.7 macrophages, anti-HCMV (human cytomegalovirus) endonuclease activity, and antibacterial activity against *Salmonella enteritidis* (ATCC13076).

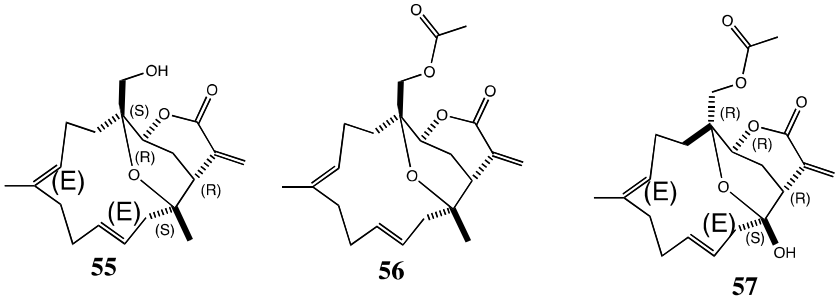


Figure 2. Compounds 55-57, Cembrane Diterpenes with anδ −Lactone

2.1.3The isopropyl(ene)-type Cembrane Diterpenes

Crassumol A**(58)** was isolated from the Dongsha Atoll soft coral *Lobophytum crassum.* The structures of **58**was isolated elucidated by extensive NMR and HR-ESI-MS experiments. The cytotoxicity and anti-HCMV (Human cytomegalovirus) activities of **58**were evaluated *in vitro* but do not show activity[27].

From the EtOAc extract of a Chinese soft coral *Lobophytum* sp., has affordedtwo new cembranes, namely (4*,7*S**,8*S**,1*Z*,2*E*,11*E*)-16-acetoxy-7,8-epoxycembra-1(15),2,11-trien-4-ol **(59)** and (7*S**,8*S**,15*S**,1*E*,3*E*,11*E*)-7,8-epoxycembra-1,3,11-trien-15,16-diol**(60)[33].**Compounds **61-62**were tested for their inhibitory effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in mouse peritoneal macrophages (PEM*Φ*). The bioassay results revealed that compounds **59**showed moderate inhibition with an inhibitory concentration 50% (IC50) of 5.6 μM.

Lobocrassins C-E **(61-63)**were isolated from the soft coral *Lobophytum crassum*, collected by hand using scuba equipment off the coast of northeast Taiwan at a depth of 10 m[25]. 16-hydroxy-sinulariol C**(64)[37] was isolated from the Hainan soft coral *Lobophytum sp***. Compound **64**was tested for cytotoxicity agains human lung adenocarcinoma A-549 and human promyelocytic leukemia HL-60 tumor cell lines, but did not show activity at a concentration of 20 μg/mL.The chemical investigation of soft coral *Lobophytum sarcophytoides* has led to the discovery of three cembranoids, sarcophytolins A-C**(65-67)[38]**. Sarcophytolin B**(66)** was shown to exhibit cytotoxicity toward a limited panel of cancer cell lines. The in vitro anti-inflammatory effect of **65-67**were tested. In this assay, the up-regulation of the pro-inflammatory iNOS and COX-2 proteins of LPS-stimulated RAW264.7 macrophage cells was evaluated using immunoblot analysis. At a concentration of 10 μM, Compounds**65-67**were found to effectively reduce the levels of iNOS to 39.0±14.1% and 24.4±11.3%[38].

Twounnamed cembrane diterpenes**68-69**were isolated from an Okinawan soft coral *Lobophytum crassum*. The structures of these two new cembranoids were determined on the basis of spectroscopic evidence[39].

2.1.4 **Cembrane Diterpenes with Furanidines Rings**

Four new cembranoid diterpenes lobocrasols A-D **(70-73)** were isolated from the methanol extract of the soft coral *Lobophytum crassum*[24]. The sample of *L. crassum* collected in Con Co, Quangtri, Vietnam. The anti-inflammatory effects of isolated compounds were evaluated using NF-κB luciferase and reverse transcription polymerase chain reaction (RT-PCR). Compounds **70** and **71** significantly inhibited TNFα induced NF-κB transcriptional activity in HepG2 cells in a dose-dependent manner, with IC_{50} values of 6.30 ± 0.42 and 6.63 ± 0.11 μM, respectively. Furthermore, the transcriptional inhibition of these compounds was confirmed by a decrease in cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) gene expression levels in HepG2 cells[24].The structure–activity relationships of compounds **70-73**indicated that the presence of an epoxy group at C-1/C-15 is necessary for the anti-inflammatory activity of these compounds.

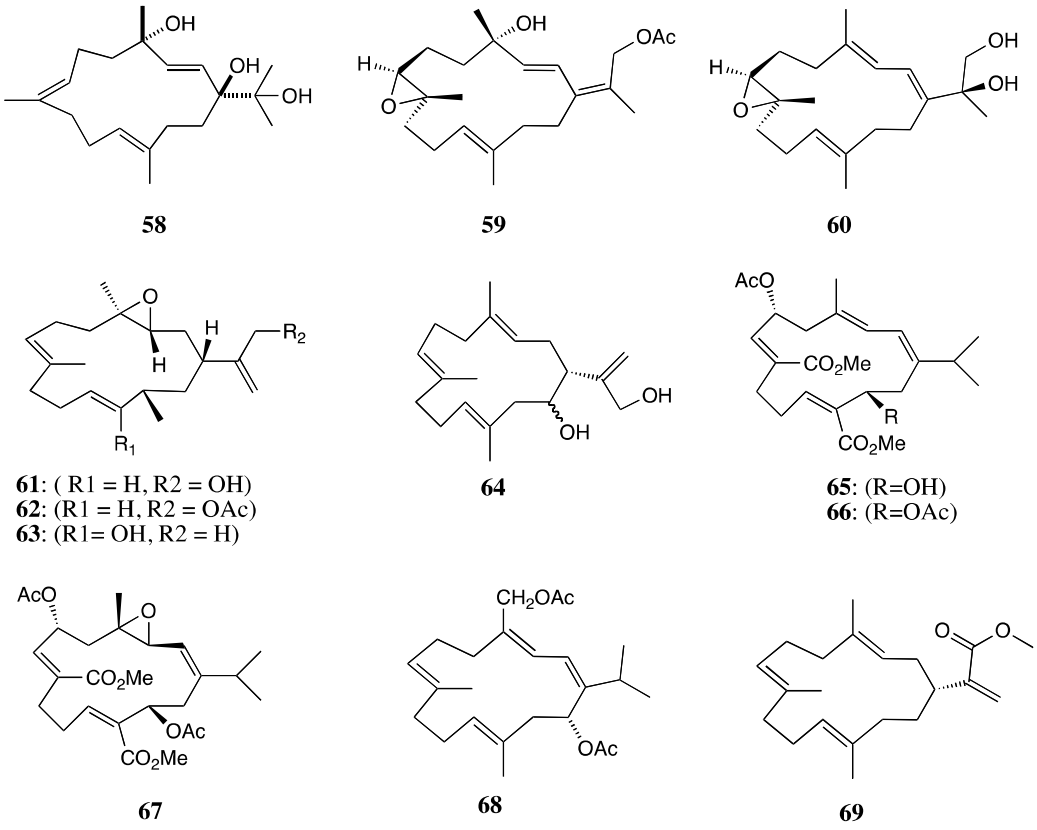


Figure 3. Compounds 58-69, The isoprpyl(ene)-type Cembrane Diterpenes

From a methanol extract of *L. laevigatum* collected at Khanh Hoa province, Viet Nam, four cembranoids with unusual tetrahydrofuran functionalities, namely laevigatol A–D **(74-77)** were isolated[26]. The structures of compounds **74-77** were elucidated by extensive spectroscopic analyses, and the absolute stereochemistry of **74** was determined using the modified Mosher's method. The anti-inflammatory activity of compounds compounds **74-77** were evaluated through the inhibition of TNFα-induced NF-κB luciferase reporter, and by attenuation of TNFα-induced pro-inflammatory protein (iNOS and COX-2) expression in Hep-G2 cells. Compounds **74-75** showed dose-dependent inhibitory effects on the TNFα-induced NF-κB transcriptional activity in Hep-G2 cells. Moreover, compounds **74-75** significantly inhibited the induction of COX-2 and iNOS mRNA dose-dependently, indicating that these compound attenuated the synthesis of these transcripts at the transcriptional level. These primary results suggested that compounds **74-75** might be useful anti-inflammatory agents for human[26].

Crassumols D–F**(78-80)**were isolated from the methanol extract of the Vietnamese soft coral *Lobophytum crassum*[28]. The anti-inflammatory activity of compounds **78-80**were evaluated by the inhibitory effect on tumor necrosis factor-alpha (TNFα)-induced nuclear factor-kappa B (NF-κB) transcriptional activation in HepG2 cells. Compound **79**(IC50=9.23± 1.66 μM) exhibited significant inhibitory effect, whereas the other compounds were inactive.

Five cembranoids, namely crassumolides A–F **(81-86)**[29], were isolated from the soft coral *Lobophytum crassum*, collected off the coast of Kenting. Compound **83** was isolated for the first time from a natural source. The structures of these compounds were elucidated by extennsive spectroscopic analysis. The absolute stereochemistry of **81**was determined by the modified Mosher's method. The cytotoxicity of Compounds **81-84** and **86** against human liver carcinoma (HepG2 and HepG3), human breast carcinoma (MCF-7 and MDA-MB-231), human lung carcinoma (A-549), and human oral cancer cells (Ca9-22) was studied, and the ability of Compounds **81-84**and **86**to inhibit up-regulation of the pro-inflammatory iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2) proteins in LPS (lipopolysaccharide)- stimulated RAW264.7 macrophage cells was also evaluated. Compounds **81**and **83** were cytotoxic toward Ca9-22 cancer cells with IC_{50} of 3.2 μg/mL and 1.7 μg/mL, respectively[29].

Specimens of the soft corals Lobophytum sp. was collected at the lagoon of Southern Mayotte, Comoros Islands, northwest of Madagascar, resulted crassumolide E_1 **(87)**. The cembranoid **87** was found to exhibit a moderate inhibitory effect on acetylcholinesterase[30].

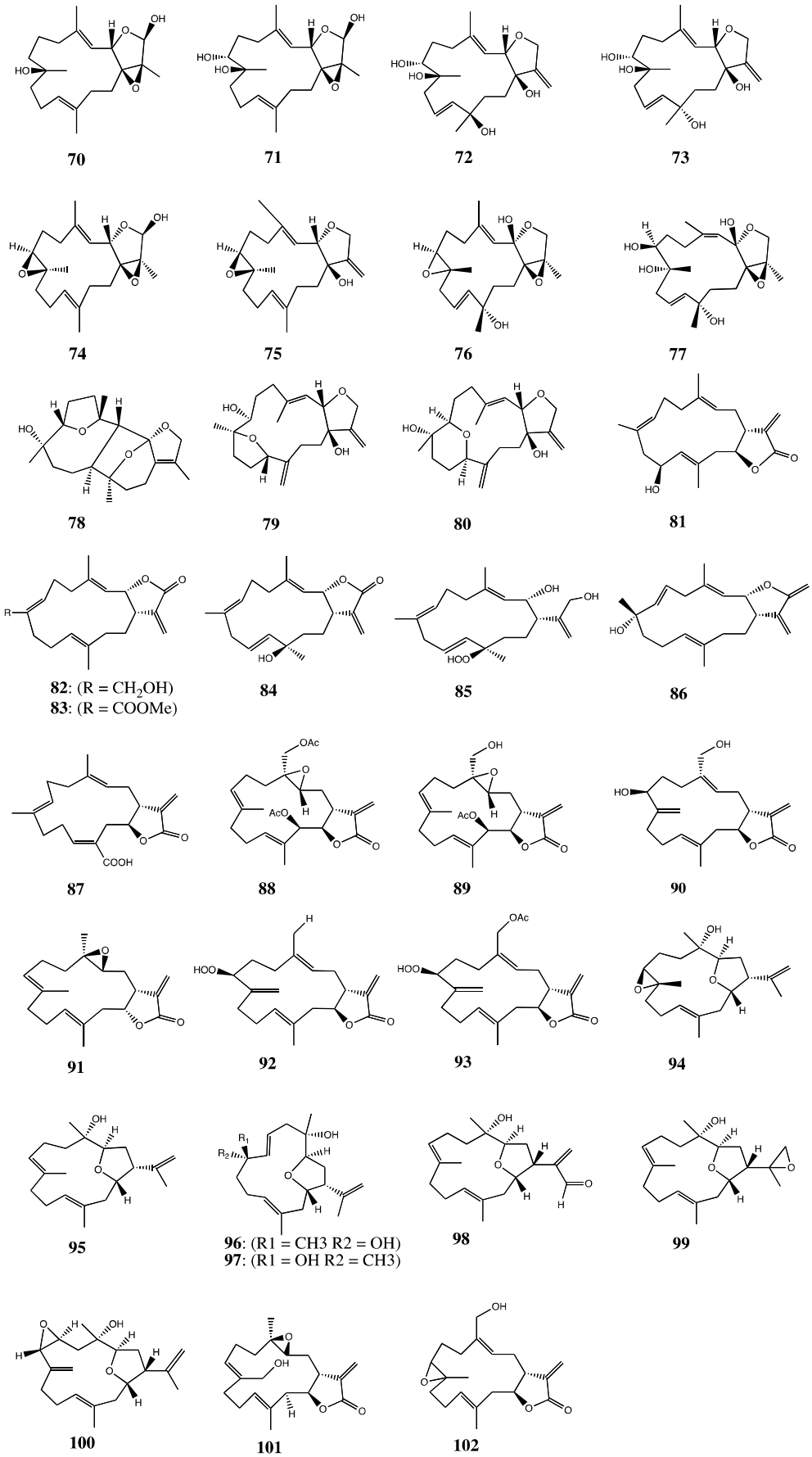


Figure 4. Compounds 70-102, Cembranes Diterpenes with Furanidine Rings

Three metabolites, crassumolides G-I **(88-90)** were isolated from the ethyl acetate extract of *Lobophytum crassum*, collected by hand via scuba at Dongsha Atoll, located in northeastern South China Sea[31]. Compound **88** was discovered for the first time from natural sources. The structures of these compounds have been established by extensive spectroscopic analysis. The ability of compounds **88-90**to inhibit the expression of proinflammatory proteins iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2) in LPS (lipopolysaccharide)-stimulated RAW 264.7 macrophage cells was evaluated in order to discover anti-inflammatory compounds. Compounds **88-90** were found to display significant in vitro anti-inflammatory activity in LPS-stimulated RAW264.7 macrophage cells by inhibiting the expression of the iNOS protein. Also, compounds **88-90**exhibited moderate activity to reduce the expression of COX-2.

Chemical examination of a South China Sea soft coral *Lobophytum sp*. led to the isolation of three new α-methylene-γ-lactone-containing cembranoids, (1R*,3R*, 4R*,14R*,7E,11E)-3,4-epoxycembra-7,11,15(17)-trien-16,14-olide **(91)**, (1R*,7S*,14S*,3E, 11E)-7-hydroperoxycembra-3,8(19),11,15(17)-tetraen-16,14-olide **(92)**, and (1R*,7S*,14S*,3E,11E)-18-acetoxy-7-hydroperoxycembra-3,8(19),11,15(17)-tetraen-16,14-olide **(93)**[32]. The structures of compounds **91-93** were elucidated through extensive spectroscopic analysis, including 1D and 2D NMR data. Compounds **92**and **93**contain a rare hydroperoxyl group at C-7. Compounds **91-93**were found to show moderate cytotoxic activity against the selected tumor cell lines including SGC7901 (human gastric carcinoma), A549 (human lung epithelial carcinoma), MCF7 (human breast carcinoma), HCT116 (human colonic carcinoma), and B16 (mouse melanoma) with IC_{50} values ranged from 1.2 to 8.6 μg/mL. Compounds **92**and **93**displayed moderate inhibition against the bacteria *S. aureus*and *S. pneumoniae*with inhibitory rates of around 90% at 20 μg/mL.

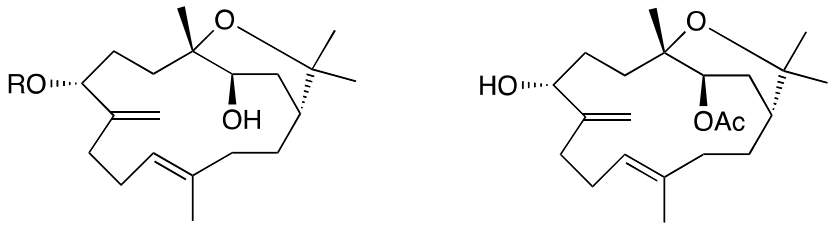
From Dongsha Atoll soft corals of the genus Lobophytum resulted four cembranoids, lobophylins A–D **(94-97)**[34]. The structures of compounds **94-97**were elucidated on the basis of extensive spectroscopic methods. Compounds **94-97**are rarely found cembranoids possessing a tetrahydrofuran moiety with a 3,14-ether linkage. The cytotoxicity of compounds **94-97**.against four human cancer cell lines was investigated, however, none of these was found to possess anti-cancer activity.

The chemical investigation of cultured octocoral *Lobophytum crassum* led to the discovery of three cembranoids, culobophylins A–C **(98-100)**[35]. The structures of compounds **98-100** were established by detailed spectroscopic analysis, including extensive examination of 2D NMR (1H–1H COSY, HMQC and HMBC) correlations. Compound **99**is rarely found in cembranoids possessing an isopropyl moiety with an epoxide group. The cytotoxicity of compounds **98-100**against human promyelocytic leukemia (HL60), human breast carcinoma (MDA-MB-231) and human colon adenocarcinoma (HCT-116 and DLD-1) cell lines was studied[35]. Compound **98**exhibited cytotoxicity against the HL60, MDA-MB-231, DLD-1 and HCT-116 cancer cell lines with IC_{50s} of 3.0, 16.8, 4.6 and 16.3 μg/mL, respectively. Furthermore, compound **98**exhibited moderate to weak cytotoxic activity against HL60, DLD-1 and HCT-116 cancer cell lines (the IC50 values were 6.8, 16.2 and 16.7 μg/mL for HL60, DLD-1 and HCT-116, respectively). The ability of compounds **98-100**to inhibit the expression of the pro-inflammatory iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2) proteins in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells was also evaluated[35]. At a concentration of 10 μM, compounds **98-100**did not inhibit COX-2 and iNOS proteins expression relative to the control cells stimulated with LPS only.

Two cembranoid named 19-hydroxy-sarcocrassolide **(101)** and 18-deacetyldeepoxy lobolide **(102)** also isolated from the Hainan Soft Coral *Lobophytum* sp[37]. The structures of 86-87, including relative stereochemistry, were elucidated by detailed analyses of spectroscopic data and by comparison with the data reported in literature. 19-hydroxy-sarcocrassolide **(101)** and 18-deacetyldeepoxy lobolide **(102)** were tested for cytotoxicity against human lung adenocarcinoma A-549 and human promyelocytic leukemia HL-60 tumor cell lines, but they were inactive at a concentration of 20 μg/mL.

2.1.5 Cembrane Diterpenes with Tetrahydropyrane Rings

Three novel cembrane diterpenoids, Decaryiols B–D **(103-105)**[40], characterized by a bicyclic skeleton of the decaryiol-type, have been isolated from the Indonesian soft coral *Lobophytum sp.* The stereostructures of **103-105**have been established through extensive NMR spectroscopic analysis, application of the modified Mosher method, and chemical conversion. **Compounds 103-105**have been evaluated for cell growth inhibitory activity against three different cell lines, H9c2 (cardiacmyoblasts), C6 (glioma), and HeLa (epithelial carcinoma). Compound **105**was significantly significantly active against the C6 glioma cell line with IC_{50} value 40 ± 3 μM.

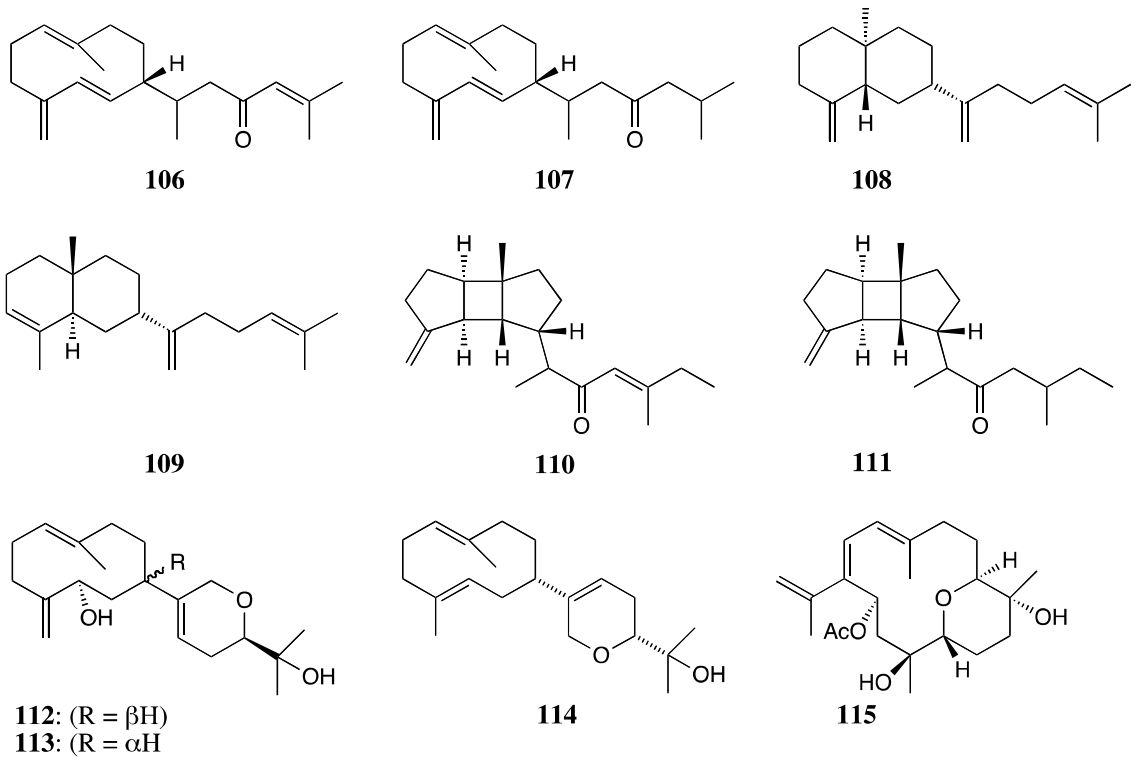


103: R = H
104: R = OH
105

Figure 5. Compounds 103-105, Cembrane Diterpenes with Tetrahydropyrane Rings

2.2. Non-Cembrane Diterpenes

Two new prenylgermacrane-type diterpenoids, lobophytumins A **(106)** and B **(107)**, two new prenyleudesmanetype diterpenoids, lobophytumins C **(108)** and D **(109)**, and two new spatane-type diterpenoids, lobophytumins E **(110)** and F **(111)**, were isolated from the Hainan soft coral *Lobophytum cristatum* Tixier-Durivault[41]. Prenylgermacrane-type[42,43] and prenyleudesmane-type[44,45-47] diterpenoids are quite rare in soft coral. While spatane-type diterpenes have been found only in brown algae previously[48], this is the first reported isolation of spatane-type diterpenes from a soft coral source. Compounds **108-109**were examined for growth-inhibition activities in vitro toward human lung adenocarcinoma A-549 cells and human colon carcinoma HCT-116 cells. Compounds **108-109**showed weak cytotoxicity against the A-549 cell line with IC_{50} values of 35.66±3.20 and 36.69± 5.11 μM, respectively. The IC_{50} values of 3 and 4 against the HCT-116 cell line were 37.10 ± 3.49 and 35.74±4.63 μM, respectively[41].



106 **107** **108**

109 **110** **111**

112: (R = βH)
113: (R = αH
114 **115**

Figure 6. Compounds 106-115, Non-Cembrane Diterpenes

Lobocompactols A **(112)** and B **(113)** were isolated from the methanol extract of the soft corals *Lobophytum compactum*, The antioxidant capacity of compounds **112-113**was measured using an oxygen radical absorbance capacity (ORAC) assay. Compounds **101-102** showed moderate peroxyl radical-scavenging activities of 1.4 and 1.3 μM Trolox equivalents, respectively, at a concentration of 5 μM[49].

A new 10-membered-ring diterpene, Cyclolobatriene **(114)** were isolated from the Okinawan soft coral *Lobophytum pauciflorum*. Cyclolobatriene **(114)** is an additional example of rare prenylated germacrenes. Their structures were established by extensive NMR spectroscopic analyses. Cyclolobatriene **(114)** showed cytotoxic effect with IC_{50} of 0.64 μM against human epidermoid carcinoma A431 cells[50].

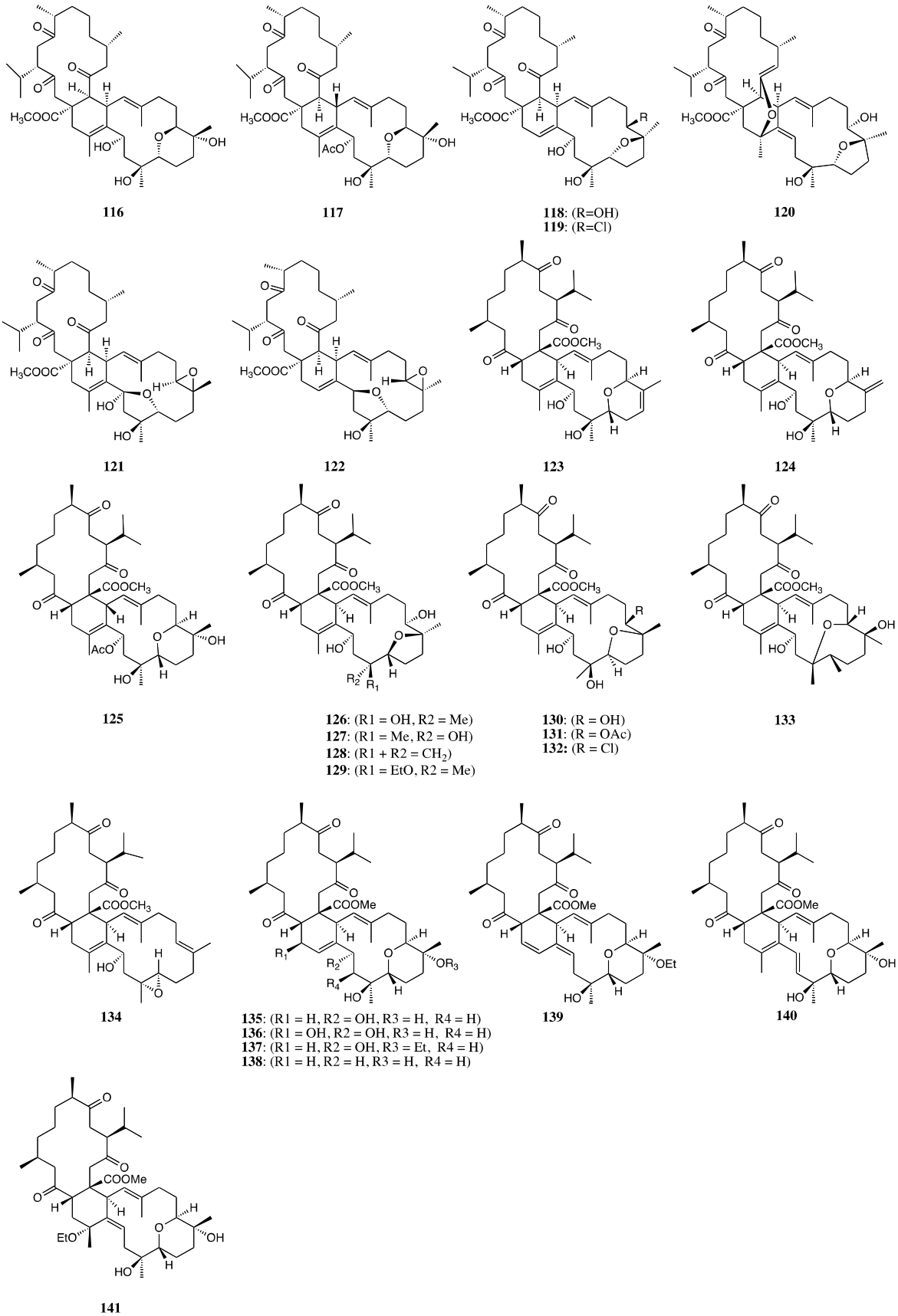


Figure 7.Compounds 116-141, Biscembranes

A new "monomeric" cembrane lobophytone T was isolated from from Soft Coral *Lobophytum pauciflorum.* The

antibiotic assay indicated that Compound **115**exhibited strong inhibition against *Staphylococcus aureus*, *S. pneumoniae*, and *Saccharomyces cerevisiae* with the inhibitory rates around 90% at 20 μg/mL.

3. Biscembranes

Biscembranoids are a family of marine natural products with anunusual structure pattern, which is featured by the tetraterpenoids with a 14–6–14-membered tricyclic backbone. The structural variation of biscembranes is frequentlyfound in ring C(mark ring C in the figure), where the high oxygenation, and tri-, penta-, and hexaepoxy cyclization occurred. The plausible biogenetic pathway is assumed to involve a Diels-Alder cycloaddition of two cembranes, cembranoid diene and cembranoid dienophile[52–59]. Most biscembranoids have been isolated from coral genus *Sarcophyton* (*S. tortuosum, S. glaucum, S. latum, and S. elegans*). The soft coral *Lobophytum pauciflorum* also contains a variety of biscembrane analogues, but they presented the structure pattern with antipodal Diels–Alder cycloaddition and were named isobiscembranoids. From 2010 to 2011,27 new biscembranoids were isolated from the chinese soft coras *Lobophytum pauciflorum*, named lobophytones A-S **(116-134)** and U-Z_1**(135 -141)**[51,60-62].All structures of the lobophytones were elucidated by interpretation of 1D and 2D NMR (COSY, HSQC, HMBC, and NOESY) spectroscopic data in association with MS and IR data.

Lobophytone A-S **(116-135)** and U-Z_1 **(136-141)**were tested against lipopolysaccharide (LPS)-induced nitric oxide (NO) release in mouse peritoneal macrophage. **Compounds 119**, **132**and **140**showed significant inhibition toward LPS-induced nitric oxide (NO) in mouse peritoneal macrophage with IC_{50} 4.70 μM, 2.8 μM and 2.6 μM, respectively.The antibiotic assay indicated that Compound **132** exhibited strong inhibition against *Staphylococcus aureus*, *S. pneumoniae*, and *Saccharomyces cerevisiae* with the inhibitory rates around 90% at 20 μg/mL. Compound **136**exhibited significant inhibition against *S. aureus* (IC_{50} = 18.7±0.6 mm) and *S. pneumoniae* (IC_{50} = 19.8 ± 0.8 mm).

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