

Review

Anti-Inflammatory Activities of Natural Products Isolated from Soft Corals of Taiwan between 2008 and 2012

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Received: 30 July 2013; in revised form: 12 September 2013 / Accepted: 13 September 2013 /

Published: 23 October 2013

Abstract: This review reports details on the natural products isolated from Taiwan soft corals during the period 2008–2012 focusing on their *in vitro* and/or *in vivo* anti-inflammatory activities. Chemical structures, names, and literature references are also reported. This review provides useful and specific information on potent anti-inflammatory marine metabolites for future development of immune-modulatory therapeutics.

Keywords: soft coral; anti-inflammatory activity; iNOS; COX-2; superoxide anion; elastase

1. Introduction

Marine natural products, especially those from stationary or slow moving marine organisms, are used naturally as a chemical defense to protect the organisms from dangerous predators, stressful local environments, and/or the encroachment of competitors. Due to the biological and chemical diversity of marine habitats, and the identification and greater understanding of marine secondary metabolites with unique chemical structures and biological activities, natural products from marine organisms are increasingly being considered as a major source of new therapeutics [1–3]. More than 20,000 novel compounds have been isolated and identified from marine organisms since the 1960s [4]. At least two current drugs and a series of anti-tumor drug candidates in preclinical or clinical trials have been developed from marine natural products [2–4]. The soft corals or Alcyonacea, an order of Anthozoa widely distributed in warm seawaters, have been a particular focus of attention. An abundance of unique secondary metabolites including sesquiterpenoids, diterpenoids, steroids and other chemical compounds have been isolated and identified from various species of soft corals [5–7]. It has been estimated that the percentage of new metabolites discovered from soft corals represents up to 22% of the total new marine natural products reported from 2010 to 2011 [5,6]. Importantly, many of the natural products discovered from soft corals have been demonstrated to exhibit a spectrum of biological activities such as anti-tumor, antiviral, antifouling and anti-inflammatory [5–8].

Inflammation processes often constitute an initial activation of the mammalian immune system, and the body's normal defense or protective mechanisms in response to microbial infection or irritation or injury of tissues/organs. Increasing evidence suggests a critical link between inflammation and the chronic promotion/progression of various human diseases, including atherosclerosis, diabetes, arthritis, inflammatory bowel disease, cancer and Alzheimer. Proinflammatory enzymes, particularly the inducible nitric oxide synthase (iNOS) for nitric oxide production and cyclooxygenase (COX-2) for prostaglandin production, have been demonstrated to play central roles in the development of inflammatory diseases. In addition, it is also known that during the initial phase of acute inflammation, neutrophils are one of the first leukocyte populations to migrate towards the damaged tissue sites [9]. Neutrophils play a key role in the pathogenesis of various chronic inflammation diseases such as rheumatoid arthritis [10,11]. Activated neutrophils can secrete the superoxide anion, reactive oxygen species (ROS) and enzymes that are associated with the killing of invading pathogens [12]. Furthermore, elastase secreted by stimulated neutrophils has been recognized to play a key contribution in the demolition of tissues affected by chronic inflammatory disease [13]. Therefore, evaluation of the inhibition of iNOS and COX-2 expression, the production of superoxide anion, and the release of elastase in inflammatory cells/tissues by various natural products have been extensively employed in a spectrum of *in vitro* preliminary screening systems for lead compound or drug discovery. Recently, a number of marine biology and chemistry researchers in Taiwan (including our laboratory) have systematically screened several marine natural products isolated from soft corals for such *in vitro* anti-inflammatory activities, mainly by measuring the inhibition of iNOS, COX-2, superoxide anion or elastase in murine immune cells. Animal models were further used to evaluate the potential therapeutic activities of candidate compounds in specific disease models. This report reviews some recent representative studies and examples of marine natural products with anti-inflammatory and other related bioactivities that have been isolated from soft corals of Taiwan. Soft corals are

abundant in the off-shore environment of the island of Taiwan, and have hence become a focus of local studies of marine nature products. We hope that this review will provide a useful data for the further study of marine natural products.

2. Results and Discussion

In the reports reviewed here, anti-inflammatory activities of natural products from the soft corals of Taiwan were generally determined *in vitro* by their inhibition of LPS-induced expression of iNOS and COX-2 in murine macrophage cells (RAW264.7) or by their inhibition of the production of superoxide anion and the release on the elastase from human neutrophils in response to FMLP/CB.

2.1. Sesquiterpenoids

2.1.1. Triquinane-Type Sesquiterpenoids

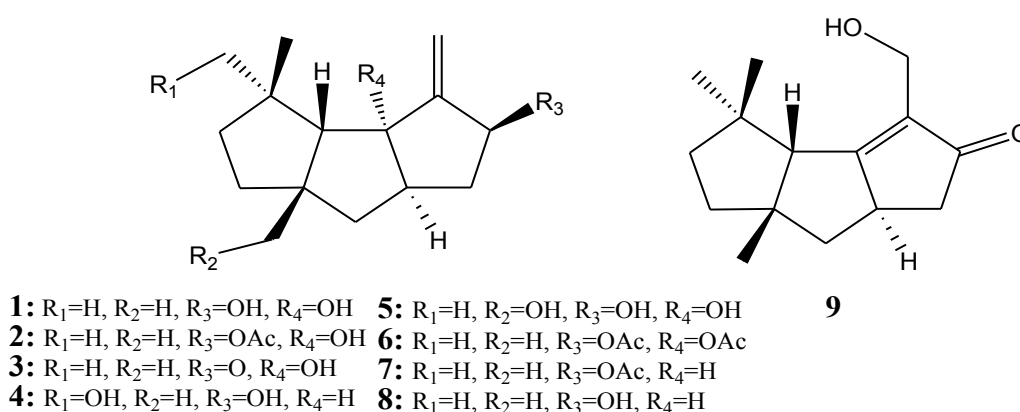
Table 1 summarizes nine triquinane-type sesquiterpenoids (1–9) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 1.

Table 1. Chemical constituents of triquinane-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
1	$\Delta^{9(12)}$ -Capnellene-8 β ,10 α -diol	<i>Capnella imbricata</i>	I,C	[14]
2	8 α -Acetoxy- $\Delta^{9(12)}$ -capnellene-10 α -ol	<i>Capnella imbricata</i>	I,C	[14]
3	$\Delta^{9(12)}$ -Capnellene-10 α -ol-8-one	<i>Capnella imbricata</i>	I	[14]
4	$\Delta^{9(12)}$ -Capnellene-8 β ,15-diol	<i>Capnella imbricata</i>		[14]
5	$\Delta^{9(12)}$ -Capnellene-8 β ,10 α ,13-triol	<i>Capnella imbricata</i>		[14]
6	8 β ,10 α -Diacetoxy- $\Delta^{9(12)}$ -capnellene	<i>Capnella imbricata</i>		[14]
7	8 β -Acetoxy- $\Delta^{9(12)}$ -capnellene	<i>Capnella imbricata</i>		[14]
8	$\Delta^{9(12)}$ -Capnellene-8 β -ol	<i>Capnella imbricata</i>		[14]
9	$\Delta^{9(12)}$ -Capnellene-12-ol-8-one	<i>Capnella imbricata</i>	I,C	[14]

* Inhibition of iNOS (I) and COX-2 (C).

Figure 1. The structures of triquinane-type sesquiterpenoids (1–9).



2.1.2. Nardosinane-Type Sesquiterpenoids

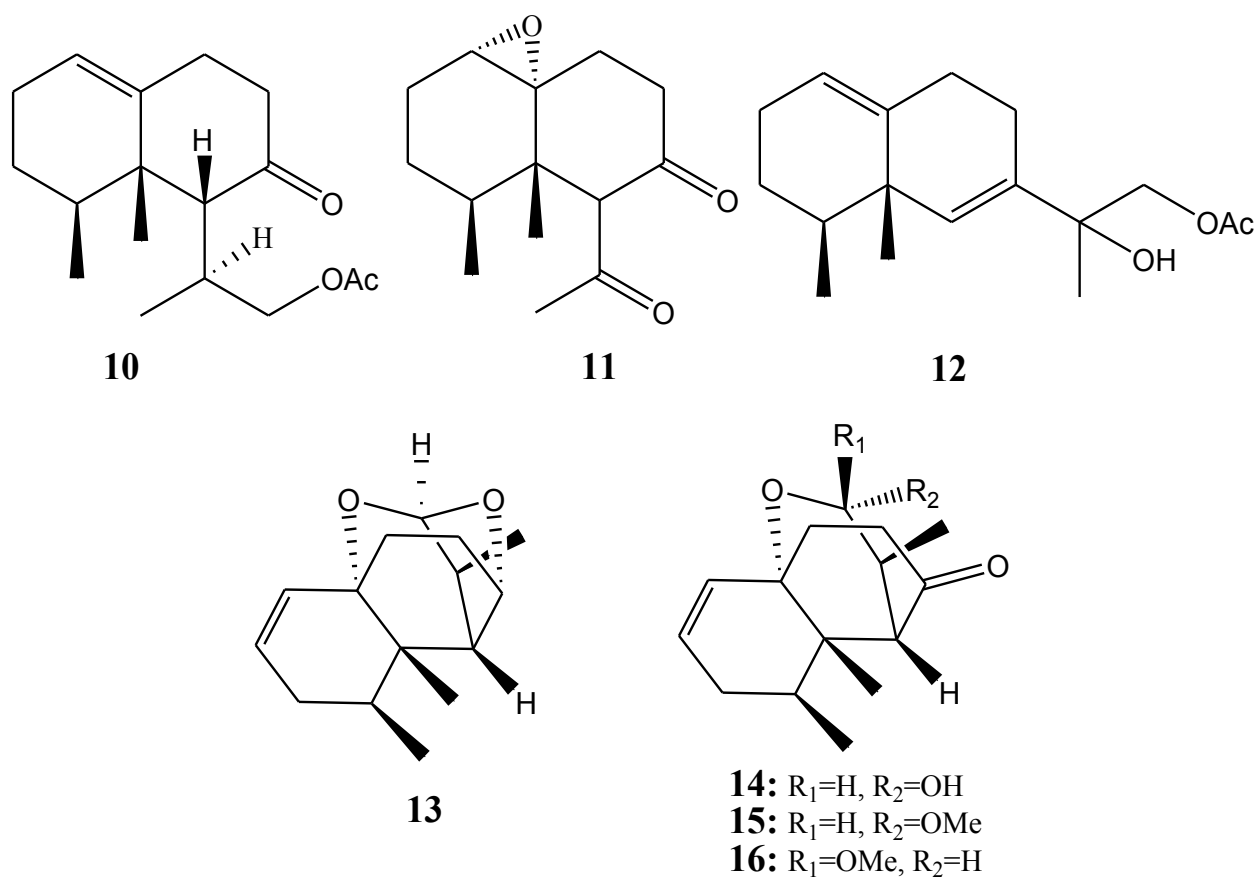
Table 2 summarizes seven nardosinane-type sesquiterpenoids (**10–16**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 2.

Table 2. Chemical constituents of nardosinane-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
10	Paralemnolin J	<i>Paralemnalia thyrsoides</i>		[15]
11	Paralemnolin K	<i>Paralemnalia thyrsoides</i>		[15]
12	Paralemnolin L	<i>Paralemnalia thyrsoides</i>		[15]
13	Flavalin A	<i>Lemnalia flava</i>	I,C	[16]
14	Flavalin B	<i>Lemnalia flava</i>		[16]
15	Flavalin C	<i>Lemnalia flava</i>		[16]
16	Flavalin D	<i>Lemnalia flava</i>		[16]

* Inhibition of iNOS (I) and COX-2 (C).

Figure 2. The structures of nardosinane-type sesquiterpenoids (**10–16**).



2.1.3. Aromadendrane-Type Sesquiterpenoids

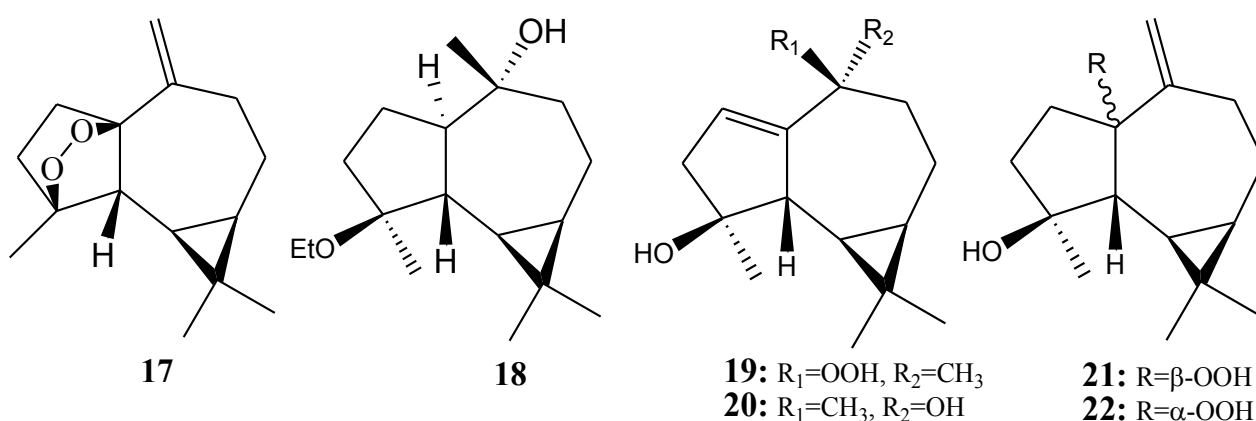
Table 3 summarizes six aromadendrane-type sesquiterpenoids (**17–22**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 3.

Table 3. Chemical constituents of aromadendrane-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
17	Lochmolin A	<i>Sinularia lochmodes</i>	C	[17]
18	Lochmolin B	<i>Sinularia lochmodes</i>	C	[17]
19	Lochmolin C	<i>Sinularia lochmodes</i>		[17]
20	Lochmolin D	<i>Sinularia lochmodes</i>		[17]
21	Lochmolin E	<i>Sinularia lochmodes</i>	C	[17]
22	Lochmolin F	<i>Sinularia lochmodes</i>	C	[17]

* Inhibition of COX-2 (C).

Figure 3. The structures of aromadendrane-type sesquiterpenoids (**17–22**).



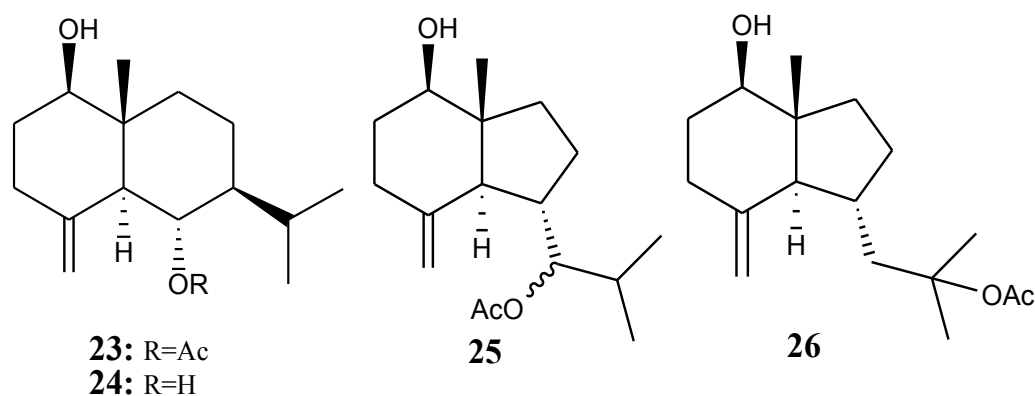
2.1.4. Selinane- and Oppositane-Type Sesquiterpenoids

Table 4 summarizes four selinane- and oppositane-type sesquiterpenoids (**23–26**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 4.

Table 4. Chemical constituents of selinane- and oppositane-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
23	1 β -Hydroxy-6 α -acetoxyeudesm-4(15)-ene	<i>Sinularia leptoclados</i>		[18]
24	1 β ,6 α -Dihydroxyeudesm-4(15)-ene	<i>Sinularia leptoclados</i>	I	[18]
25	Leptocladolin A	<i>Sinularia leptoclados</i>		[18]
26	Leptocladolin B	<i>Sinularia leptoclados</i>		[18]

* Inhibition of iNOS (I).

Figure 4. The structures of selinane- and oppositane-type sesquiterpenoids (**23–26**).

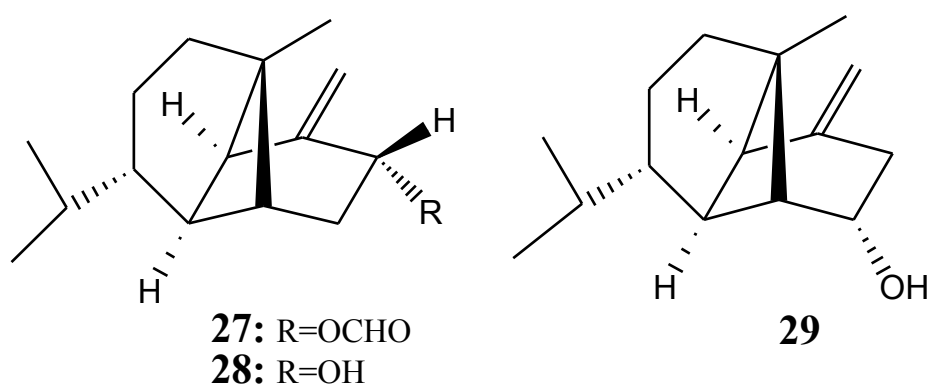
2.1.5. Ylangene-Type Sesquiterpenoids

Table 5 summarizes three ylangene-type sesquiterpenoids (**27–29**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 5.

Table 5. Chemical constituents of ylangene-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
27	(1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,6 <i>S</i> ,7 <i>R</i> ,8 <i>S</i>)-4α-Formyloxy-β-ylangene	<i>Lemnalia flava</i>	I,C	[16]
28	Lemnalol	<i>Lemnalia flava</i>		[16]
29	Isolemnalol	<i>Lemnalia flava</i>		[16]

* Inhibition of NOS (I) and COX-2 (C).

Figure 5. The structures of ylangene-type sesquiterpenoids (**27–29**).

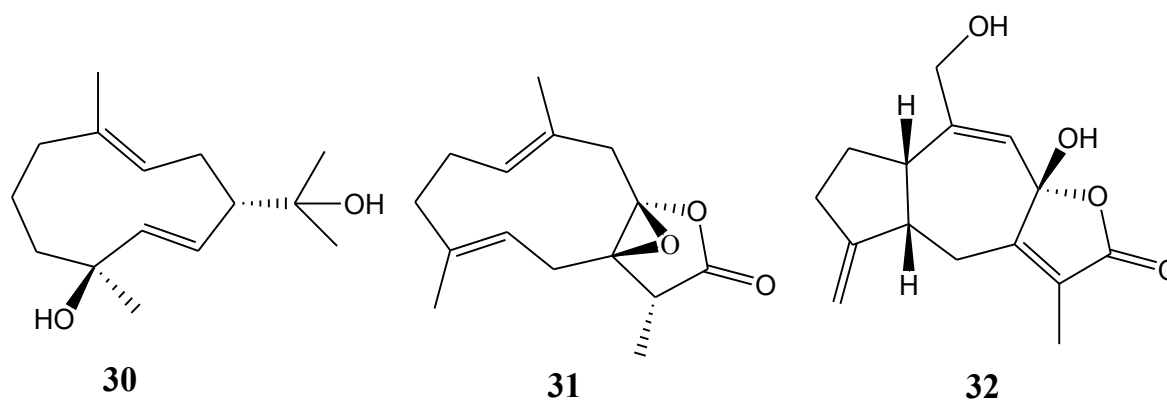
2.1.6. Germacrane-Type Sesquiterpenoids

Table 6 summarizes three germacrane-type sesquiterpenoids (**30–32**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 6.

Table 6. Chemical constituents of germacrane-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
30	Lochmolin G	<i>Sinularia lochmodes</i>		[17]
31	Menelloide D	<i>Menella</i> sp.	E	[19]
32	Menelloide E	<i>Menella</i> sp.		[20]

* Inhibition of elastase (E).

Figure 6. The structures of germacrane-type sesquiterpenoids (30–32).

2.1.7. Other-Type Sesquiterpenoids

Table 7 summarizes six other-type sesquiterpenoids (33–38) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 7.

Table 7. Chemical constituents of other-type sesquiterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
33	Erectathiol	<i>Nephthea erecta</i>	I	[21]
34	Scabralin A	<i>Sinularia scabra</i>	I	[22]
35	Leptocladol A	<i>Sinularia leptoclados</i>		[23]
36	Paralemnolin D	<i>Paralemnalia thyrsoides</i>		[15]
37	1- <i>epi</i> -Chabrolidione A	<i>Sinularia leptoclados</i>		[23]
38	(-)-Hydroxylindestrenolide	<i>Menella</i> sp.	S	[24]

* Inhibition of iNOS (I) and superoxide anion (S).

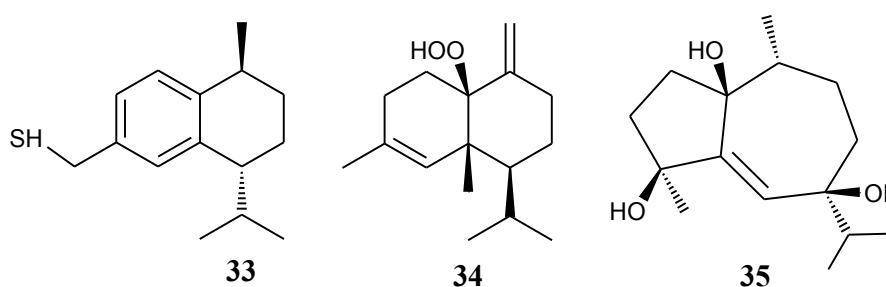
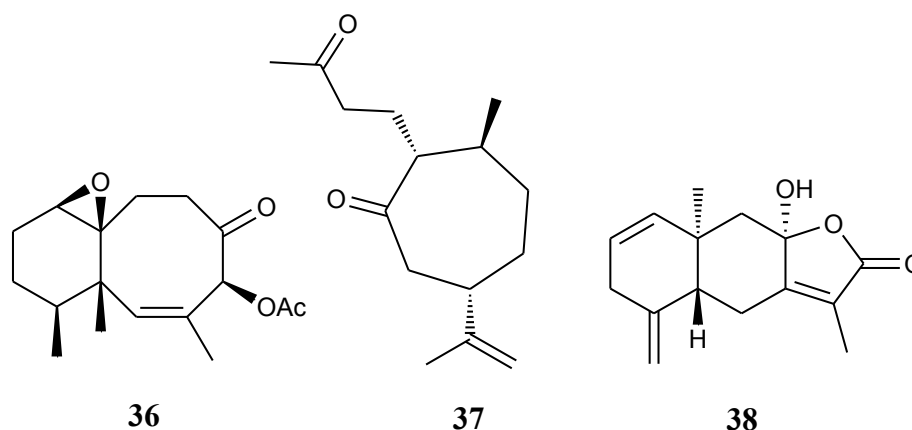
Figure 7. The structures of other-type sesquiterpenoids (33–38).

Figure 7. Cont.



At a concentration of 10 μ M, compounds **1–3**, **13**, **24**, **28**, **33** and **34** reduced LPS-induced expression of iNOS in murine macrophage cells [14–16,18,21,22]. Compounds **1**, **2**, **13**, **17**, **18**, **21** and **28** suppressed LPS-induced expression of COX-2 in these cells [14–17]. At 10 μ g/mL, compound **38** was shown to slightly inhibit the generation of superoxide anion in FMLP/CB-stimulated human neutrophils, and compound **31** weakly inhibited the release of elastase by activated human neutrophils [19,24]. In addition, an inflammation animal model induced by intraplantar injection of carrageenan into rat hind paws was also used to evaluate *in vivo* anti-inflammatory activity of lemnalol (**28**). Intramuscular injection of **28** (15 mg/kg) significantly inhibited the carrageenan-induced rat paw edema and thermal hyperalgesia behavior. Moreover, lemnalol significantly suppressed the carrageenan-induced expression of iNOS and COX-2 in paw tissue of test rats. Post-intrathecal injection of lemnalol provided an antinociceptive effect in carrageenan-injected rats (1 and 5 μ g) [25]. $\Delta^{9(12)}$ -capnellene-8 β ,10 α -diol (GB9, **1**) and its acetylated derivative, 8 α -acetoxy- $\Delta^{9(12)}$ -capnellene-10 α -ol (GB10, **2**) were reported to inhibit the expression of iNOS and COX-2 in BV2 cells post-stimulation by IFN- γ .

Intraperitoneal administration of GB9 reduced CCI-induced thermal hyperalgesia, suppressed microglial cells activation and COX-2 upregulation in the dorsal horn of the lumbar spinal cord, ipsilateral to the injury. Also, intrathecal administration of GB9 and GB10 suppressed activities of CCI-induced nociceptive sensitization and thermal hyperalgesia [26]. The above findings suggest that some of these compounds may warrant systematic investigation for future development as immune-modifiers.

2.2. Diterpenoids

2.2.1. Cembrane-Based Diterpenoids

Table 8 summarizes 92 cembrane-based diterpenoids (**39–130**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 8.

Table 8. Chemical constituents of cembrane-based diterpenoids from soft corals of Taiwan.

	Name	Sources	Activities *	Reference
39	Gibberosene B	<i>Sinularia gibberosa</i>	I,C	[27]
40	(+)-11,12-Epoxy sarcophytol A	<i>Sinularia gibberosa</i>		[27]
41	Grandilobatin B	<i>Sinularia grandilobata</i>		[28]
42	Grandilobatin D	<i>Sinularia grandilobata</i>	I	[28]
43	Durumolide A	<i>Lobophytum durum</i>	I,C	[29]
44	13S-Hydroxylobolide	<i>Lobophytum durum</i>	I,C	[29]
45	13R-Hydroxylobolide	<i>Lobophytum durum</i>	I	[29]
46	Deacetyl-13-hydroxylobolide	<i>Lobophytum durum</i>	I,C	[27]
47	(7E,11E)-13,18-Dihydroxy-3,4-epoxy-7,11,15(17)-cembratrien-16,14-olide	<i>Lobophytum durum</i>	I,C	[27]
48	Durumolide B	<i>Lobophytum durum</i>	I	[28]
49	(3E,7E,11E)-18-Acetoxy-3,7,11,15(17)-cembratetraen-16,14-olide	<i>Lobophytum durum</i>	I,C	[28]
50	Durumolide C	<i>Lobophytum durum</i>	I,C	[29]
51	Durumolide D	<i>Lobophytum durum</i>	I	[29]
52	Durumolide E	<i>Lobophytum durum</i>	I	[29]
53	Granosolide C	<i>Sinularia granosa</i>		[30]
54	Querciformolide E	<i>Sinularia querciformis</i>	I	[30]
55	Granosolide D	<i>Sinularia granosa</i>	I	[30]
56	Flexibilisolid A	<i>Sinularia granosa</i>	I	[30]
57	Flexilarin	<i>Sinularia granosa</i>	I	[30]
58	Sinulariolide	<i>Sinularia granosa</i>	I	[30]
59	Sinulaflexiolide E	<i>Sinularia granosa</i>		[30]
60	Crassumolide A	<i>Lobophytum crassum</i>	I,C	[31]
61	Crassumolide B	<i>Lobophytum crassum</i>	I	[31]
62	Crassumolide C	<i>Lobophytum crassum</i>	I,C	[31]
63	Crassumolide F	<i>Lobophytum crassum</i>	I	[31]
64	Lobohedleolide	<i>Lobophytum crassum</i>	I,C	[31]
65	17-Dimethylaminolobohedleolide	<i>Lobophytum crassum</i>	I	[31]
66	Sinulariol A	<i>Lobophytum crassum</i>	I,C	[31]
67	Dentivulatilide	<i>Lobophytum crassum</i>	I,C	[31]
68	Durumhemiketalolide A	<i>Lobophytum durum</i>	I,C	[32]
69	Durumhemiketalolide B	<i>Lobophytum durum</i>	I	[32]
70	Durumhemiketalolide C	<i>Lobophytum durum</i>	I,C	[32]
71	Durumolide F	<i>Lobophytum durum</i>	I,C	[33]
72	Durumolide G	<i>Lobophytum durum</i>	I	[33]
73	Durumolide H	<i>Lobophytum durum</i>	I	[33]
74	Durumolide I	<i>Lobophytum durum</i>	I	[33]
75	Durumolide J	<i>Lobophytum durum</i>	I	[33]
76	Sinularolide D	<i>Lobophytum durum</i>	I	[33]
77	Durumolide K	<i>Lobophytum durum</i>	I,C	[33]
78	Durumolide L	<i>Lobophytum durum</i>	I	[33]

Table 8. Cont.

79	Sarcocrassocolide A	<i>Sarcophyton crassocaule</i>	I	[34]
80	Sarcocrassocolide C	<i>Sarcophyton crassocaule</i>	I	[34]
81	Sarcocrassocolide B	<i>Sarcophyton crassocaule</i>	I	[34]
82	Sarcocrassocolide D	<i>Sarcophyton crassocaule</i>	I	[34]
83	Sarcocrassocolide E	<i>Sarcophyton crassocaule</i>	I	[34]
84	Sarcocrassolide	<i>Sarcophyton crassocaule</i>	I,C	[34]
85	Sinularolide	<i>Sarcophyton crassocaule</i>	I	[34]
86	13-Acetoxysarcocrassolide	<i>Sarcophyton crassocaule</i>	I	[34]
87	Thioflexibilolide A	<i>Sinularia flexibilis</i>	I,C	[35]
88	Triangulene A	<i>Sinularia triangular</i>		[36]
89	Triangulene B	<i>Sinularia triangular</i>		[36]
90	Sinularin	<i>Sinularia triangular</i>	I	[36]
91	Dihydrosinularin	<i>Sinularia triangular</i>	I,C	[36]
92	(-)-14-Deoxycrassin	<i>Sinularia triangular</i>	I,C	[36]
93	Sarcocrassocolide F	<i>Sarcophyton crassocaule</i>	I	[37]
94	Sarcocrassocolide G	<i>Sarcophyton crassocaule</i>	I	[37]
95	Sarcocrassocolide H	<i>Sarcophyton crassocaule</i>	I	[37]
96	Sarcocrassocolide I	<i>Sarcophyton crassocaule</i>	I,C	[37]
97	Sarcocrassocolide J	<i>Sarcophyton crassocaule</i>	I	[37]
98	Sarcocrassocolide K	<i>Sarcophyton crassocaule</i>	I	[37]
99	Sarcocrassocolide L	<i>Sarcophyton crassocaule</i>	I	[37]
100	Sarcophytolin A	<i>Lobophytum sarcophytoides</i>	I	[38]
101	Sarcophytolin B	<i>Lobophytum sarcophytoides</i>	I	[38]
102	Sarcophytolin C	<i>Lobophytum sarcophytoides</i>		[38]
103	Sarcophytolin D	<i>Lobophytum sarcophytoides</i>	I	[38]
104	11-Dehydrosinulariolide	<i>Sinularia discrepans</i>	I,C	[39]
105	11- <i>epi</i> -Sinulariolide acetate	<i>Sinularia discrepans</i>	I,C	[39]
106	Crassumolide G	<i>Lobophytum crassum</i>	I	[40]
107	Crassumolide H	<i>Lobophytum crassum</i>	I	[40]
108	Crassumolide I	<i>Lobophytum crassum</i>	I	[40]
109	Crassarine A	<i>Sinularia crassa</i>		[41]
110	Crassarine B	<i>Sinularia crassa</i>		[41]
111	Crassarine C	<i>Sinularia crassa</i>		[41]
112	Crassarine D	<i>Sinularia crassa</i>		[41]
113	Crassarine E	<i>Sinularia crassa</i>		[41]
114	Crassarine F	<i>Sinularia crassa</i>	C	[41]
115	Crassarine G	<i>Sinularia crassa</i>		[41]
116	Crassarine H	<i>Sinularia crassa</i>	I	[41]
117	Sarcocrassocolide M	<i>Sarcophyton crassocaule</i>	I	[42]
118	Sarcocrassocolide N	<i>Sarcophyton crassocaule</i>	I	[42]
119	Sarcocrassocolide O	<i>Sarcophyton crassocaule</i>	I	[42]
120	Culobophylin A	<i>Lobophytum crassum</i>		[43]
121	Culobophylin B	<i>Lobophytum crassum</i>		[43]
122	Culobophylin C	<i>Lobophytum crassum</i>		[43]
123	Lobophylin B	<i>Lobophytum crassum</i>		[43]

Table 8. Cont.

124	Lobophylin A	<i>Lobophytum crassum</i>		[43]
125	Lobocrassin A	<i>Lobophytum crassum</i>		[44]
126	Lobocrassin B	<i>Lobophytum crassum</i>	S,E	[44]
127	Lobocrassin C	<i>Lobophytum crassum</i>		[44]
128	Lobocrassin D	<i>Lobophytum crassum</i>		[44]
129	Lobocrassin E	<i>Lobophytum crassum</i>		[44]
130	Lobocrassin F	<i>Lobophytum crassum</i>	E	[20]

* Inhibition of iNOS (I), COX-2 (C), superoxide anion (S) and elastase (E).

Figure 8. The structures of cembrane-based diterpenoids (39–130).

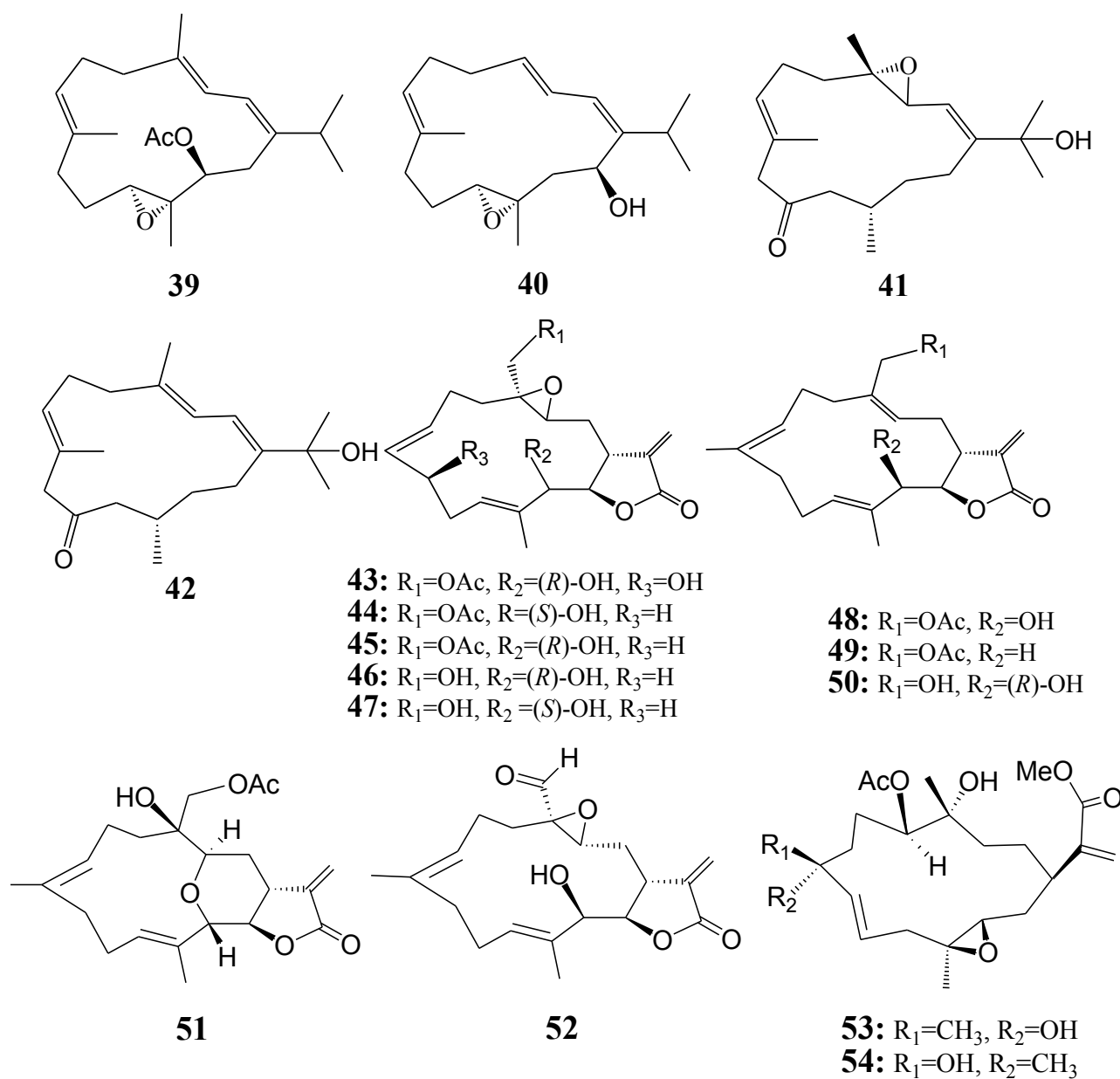


Figure 8. Cont.

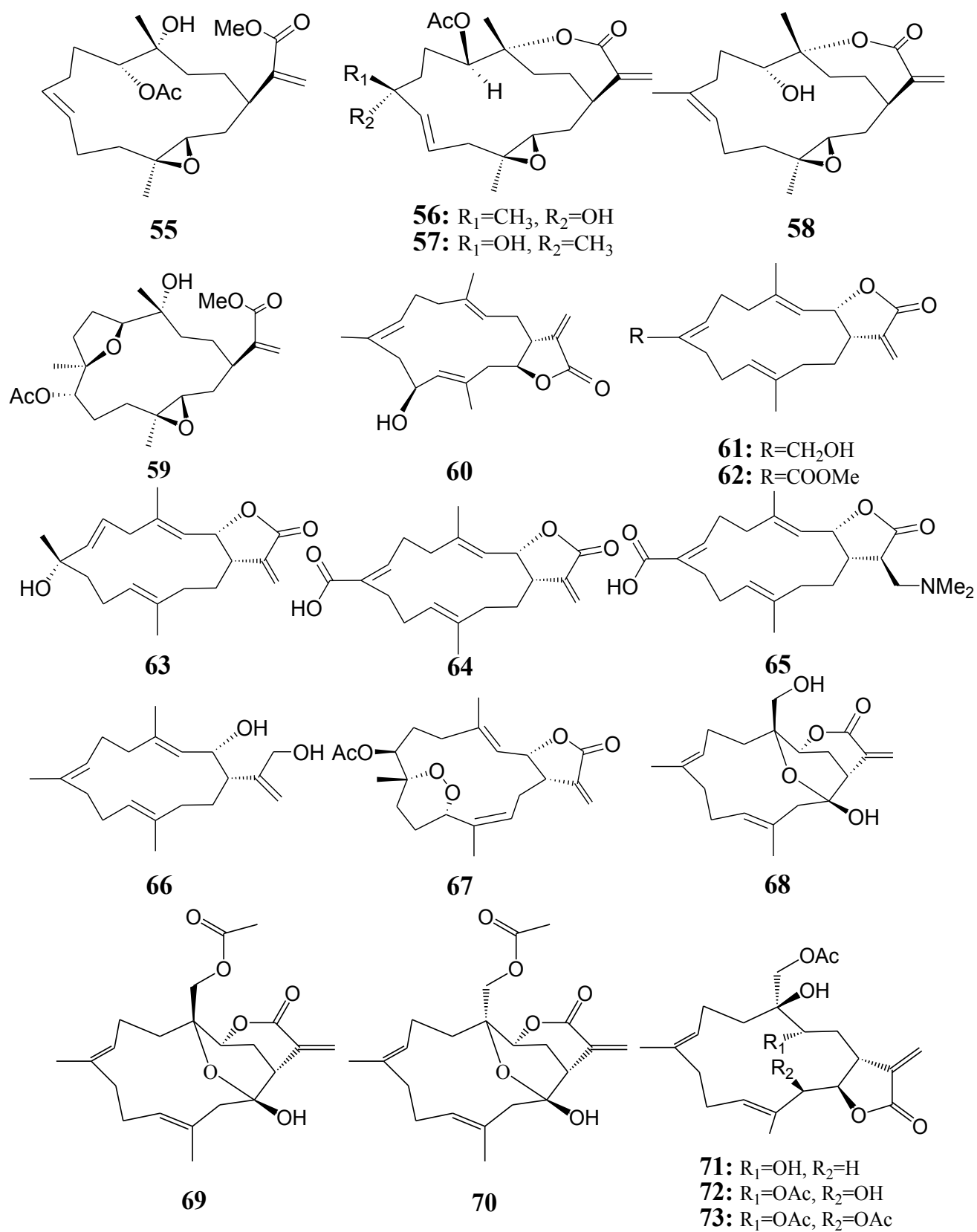


Figure 8. Cont.

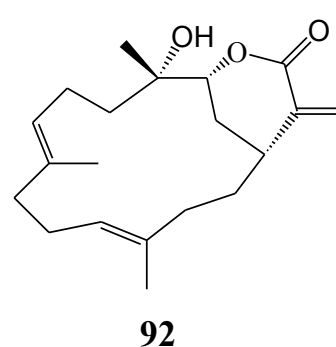
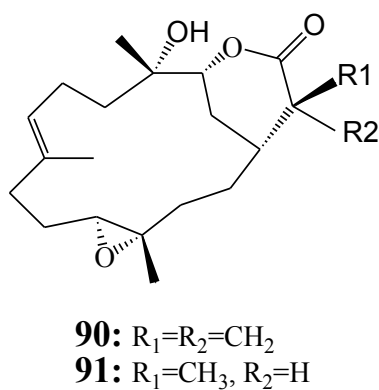
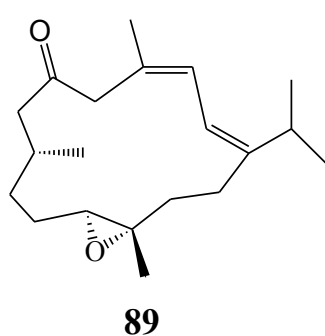
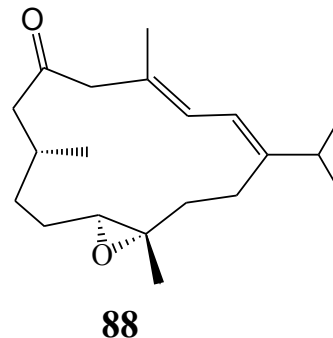
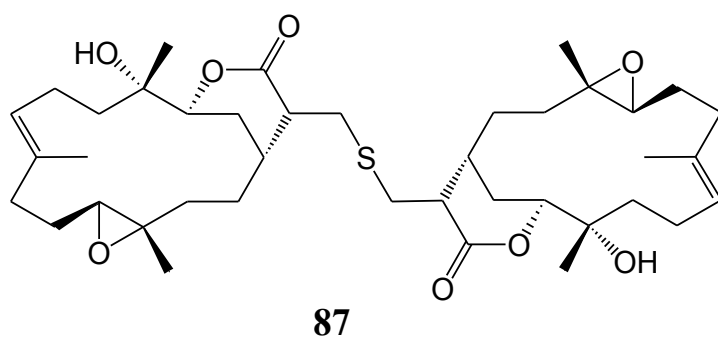
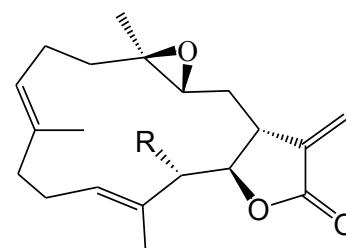
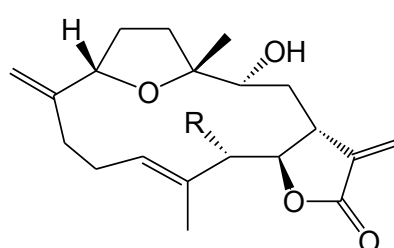
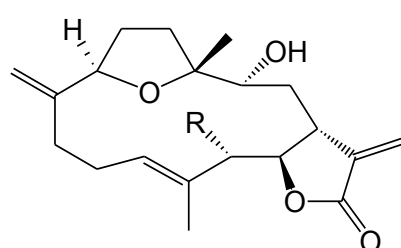
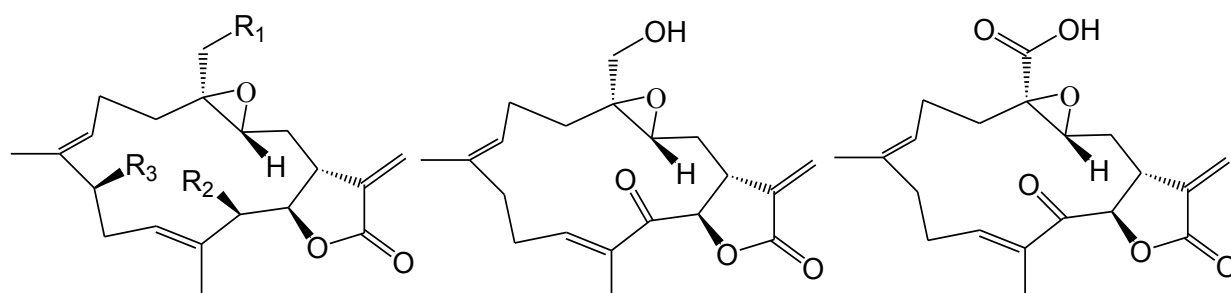


Figure 8. Cont.

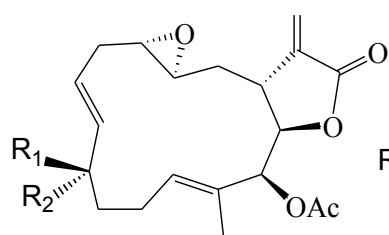
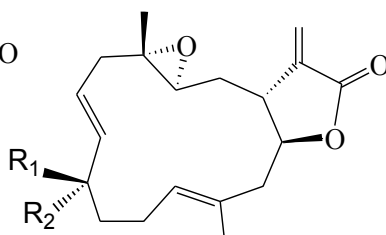
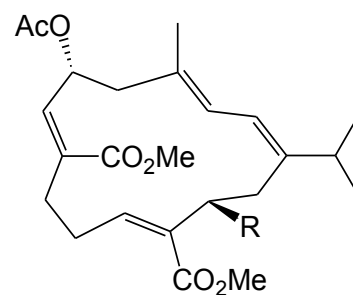
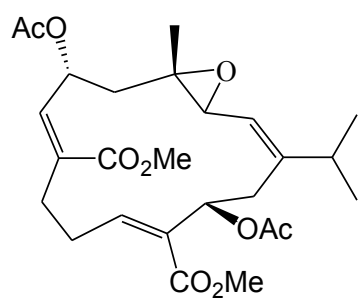
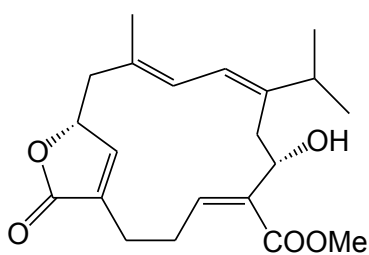
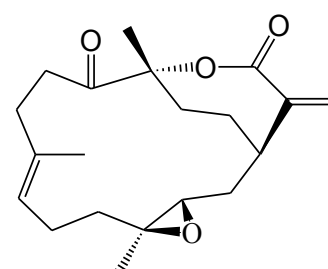
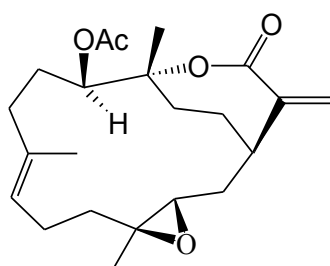
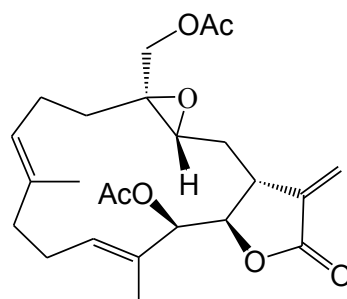
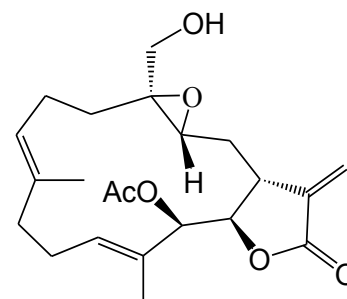
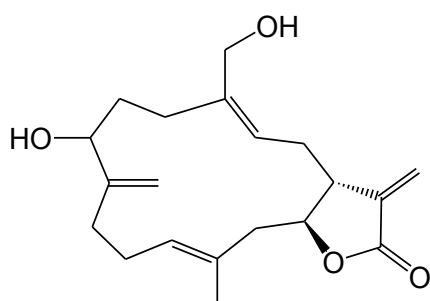
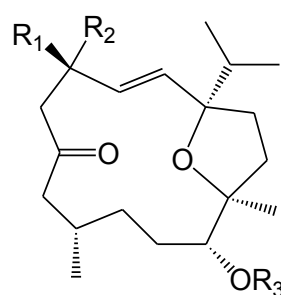
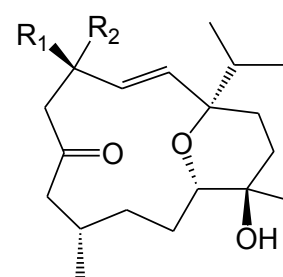
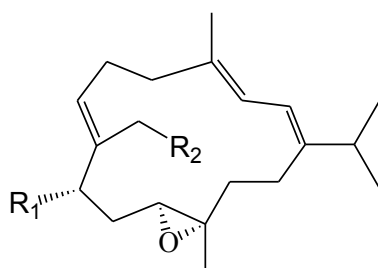
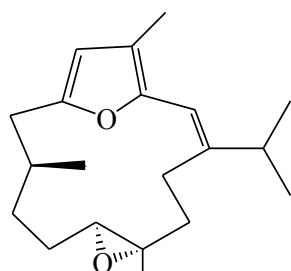
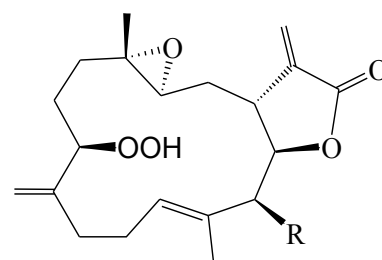
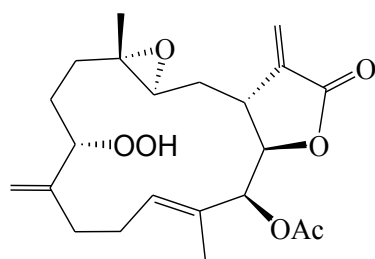
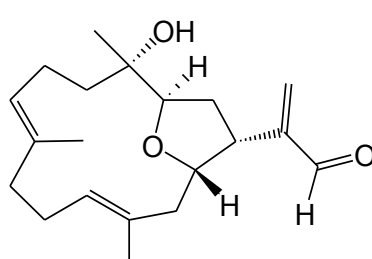
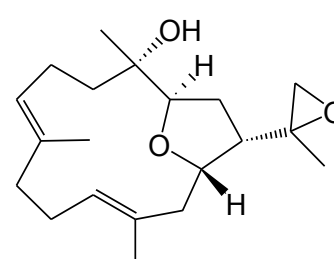
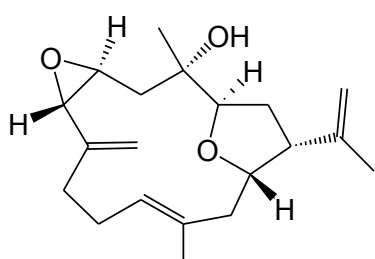
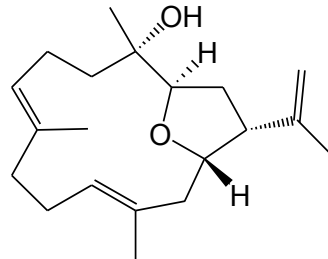
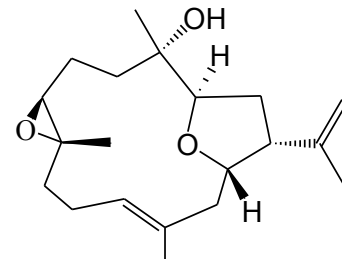
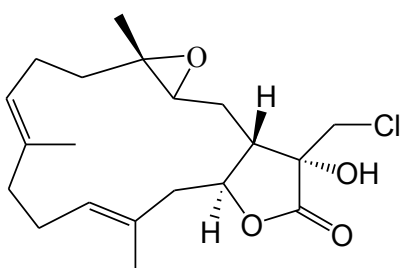
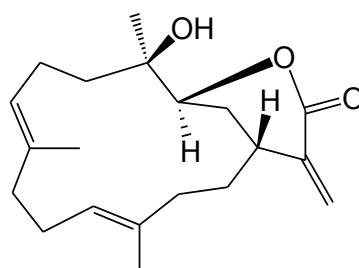
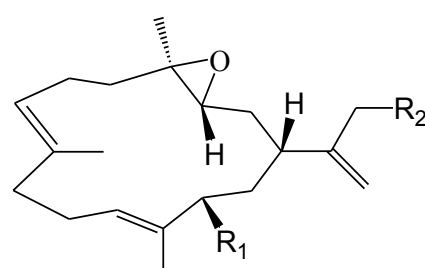
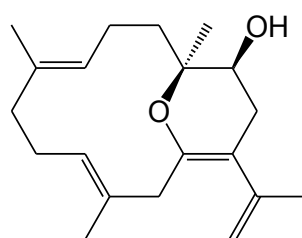
**93:** $R_1=CH_3$, $R_2=OOH$ **94:** $R_1=OOH$, $R_2=CH_3$ **95:** $R_1=CH_3$, $R_2=OH$ **96:** $R_1=OH$, $R_2=CH_3$ **97:** $R_1=CH_3$, $R_2=OOH$ **98:** $R_1=CH_3$, $R_2=OH$ **99:** $R_1=OH$, $R_2=CH_3$ **100:** $R=OH$ **101:** $R=OAc$ **102****103****104****105****106****107****108****109:** $R_1=CH_3$, $R_2=OH$, $R_3=H$ **110:** $R_1=OH$, $R_2=CH_3$, $R_3=Ac$ **111:** $R_1=OH$, $R_2=CH_3$, $R_3=CHO$ **112:** $R_1=OH$, $R_2=CH_3$ **113:** $R_1=CH_3$, $R_2=OH$

Figure 8. Cont.

**114:** $R_1=OH$, $R_2=H$ **115:** $R_1=H$, $R_2=OH$ **116****117:** $R=OAc$ **118:** $R=H$ **119****120****121****122****123****124****125****126****127:** $R_1=H$, $R_2=OH$ **128:** $R_1=H$, $R_2=OAc$ **129:** $R_1=OH$, $R_2=H$ **130**

At the concentration of 10 μ M, compounds **39**, **42–52**, **54–58**, **60–87**, **90–101**, **103–108** and **116–119** reduced LPS-induced expression of iNOS in murine macrophage (RAW264.7) cells [27–42]. Compounds **39**, **43**, **44**, **46**, **47**, **49**, **50**, **62**, **64**, **66–68**, **70**, **71**, **77**, **84**, **87**, **91**, **92**, **96**, **104**, **105** and **114** suppressed LPS-induced expression of COX-2 in these cells [27,29,31–37,39,41]. At 10 μ g/mL, compound **126** inhibited the generation of superoxide anion and the release of elastase in human neutrophils [44]. Compound **130** inhibited the release of elastase by activated human neutrophils [24]. For *in vivo* anti-inflammatory activities, subcutaneous (s.c.) administration of sinularin (**90**) (80 mg/kg) significantly inhibited carrageenan-induced nociceptive behaviors as well as carrageenan-induced activation of microglial and astrocyte, and the iNOS expression in the dorsal horn of the lumbar spinal cord [45]. Due to its promising anti-inflammatory profile, sinularin may warrant future exploration as a lead compound for immune-/inflammation-modulation.

2.2.2. Eunicellin-Based Diterpenoids

Table 9 summarizes 58 eunicellin-based diterpenoids (**131–188**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 9.

Table 9. Chemical constituents of eunicellin-based diterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
131	Simplexin A	<i>Klyxum simplex</i>	I	[46]
132	Simplexin B	<i>Klyxum simplex</i>		[46]
133	Simplexin C	<i>Klyxum simplex</i>		[46]
134	Simplexin D	<i>Klyxum simplex</i>	I	[46]
135	Simplexin E	<i>Klyxum simplex</i>	I,C	[46]
136	Simplexin F	<i>Klyxum simplex</i>		[46]
137	Simplexin I	<i>Klyxum simplex</i>		[46]
138	Klysimplexin I	<i>Klyxum simplex</i>		[47]
139	Klysimplexin J	<i>Klyxum simplex</i>	I	[47]
140	Klysimplexin K	<i>Klyxum simplex</i>	I	[47]
141	Klysimplexin L	<i>Klyxum simplex</i>	I	[47]
142	Klysimplexin M	<i>Klyxum simplex</i>	I	[47]
143	Klysimplexin N	<i>Klyxum simplex</i>	I	[47]
144	Klysimplexin O	<i>Klyxum simplex</i>		[47]
145	Klysimplexin P	<i>Klyxum simplex</i>		[47]
146	Klysimplexin Q	<i>Klyxum simplex</i>		[47]
147	Klysimplexin R	<i>Klyxum simplex</i>	I	[47]
148	Klysimplexin S	<i>Klyxum simplex</i>	I,C	[47]
149	Klysimplexin T	<i>Klyxum simplex</i>		[47]
150	Hirsutalin A	<i>Cladiella hirsuta</i>		[48]
151	Hirsutalin B	<i>Cladiella hirsuta</i>	I,C	[48]
152	Hirsutalin C	<i>Cladiella hirsuta</i>	I	[48]
153	Hirsutalin D	<i>Cladiella hirsuta</i>	I	[48]
154	Hirsutalin E	<i>Cladiella hirsuta</i>		[48]
155	Hirsutalin F	<i>Cladiella hirsuta</i>		[48]

Table 9. Cont.

156	Hirsutalin G	<i>Cladiella hirsuta</i>		[48]
157	Hirsutalin H	<i>Cladiella hirsuta</i>	I	[48]
158	Klysimplexin sulfoxide A	<i>Klyxum simplex</i>	I	[49]
159	Klysimplexin sulfoxide B	<i>Klyxum simplex</i>	I	[49]
160	Klysimplexin sulfoxide C	<i>Klyxum simplex</i>	I,C	[49]
161	Lymollin A	<i>Klyxum molle</i>		[50]
162	Lymollin B	<i>Klyxum molle</i>	I	[50]
163	Lymollin C	<i>Klyxum molle</i>	I,C	[50]
164	Lymollin D	<i>Klyxum molle</i>	I,C	[50]
165	Lymollin E	<i>Klyxum molle</i>	I	[50]
166	Lymollin F	<i>Klyxum molle</i>	I,C	[50]
167	Lymollin G	<i>Klyxum molle</i>	I,C	[50]
168	Lymollin H	<i>Klyxum molle</i>	I,C	[50]
169	Krempfielin A	<i>Cladiella krempfi</i>		[51]
170	Krempfielin D	<i>Cladiella krempfi</i>	I	[51]
171	Krempfielin B	<i>Cladiella krempfi</i>	I	[51]
172	krempfielin C	<i>Cladiella krempfi</i>	I	[51]
173	Litophynol B	<i>Cladiella krempfi</i>	I	[51]
174	(1 <i>R</i> *,2 <i>R</i> *,3 <i>R</i> *,6 <i>S</i> *,7 <i>S</i> *,9 <i>R</i> *,10 <i>R</i> *,14 <i>R</i> *)3-Butanoyloxycladiell-11(17)-en-6,7-diol	<i>Cladiella krempfi</i>	I	[51]
175	Klysimplexin U	<i>Klyxum simplex</i>		[52]
176	Klysimplexin V	<i>Klyxum simplex</i>		[52]
177	Klysimplexin W	<i>Klyxum simplex</i>		[52]
178	Klysimplexin X	<i>Klyxum simplex</i>		[52]
179	Cladieunicellin A	<i>Cladiella</i> sp.	S,E	[53]
180	Cladieunicellin C	<i>Cladiella</i> sp.		[53]
181	Cladieunicellin D	<i>Cladiella</i> sp.		[53]
182	Cladieunicellin E	<i>Cladiella</i> sp.		[53]
183	Cladieunicellin G	<i>Cladiella</i> sp.	S,E	[54]
184	6- <i>epi</i> -Cladieunicellin F	<i>Cladiella</i> sp.		[54]
185	Cladieunicellin F	<i>Cladiella</i> sp.	S,E	[54]
186	(-)-Solenopodin C	<i>Cladiella</i> sp.		[55]
187	Cladielloide A	<i>Cladiella</i> sp.		[56]
188	Cladielloide B	<i>Cladiella</i> sp.	S,E	[56]

* Inhibition of iNOS (I), COX-2 (C), superoxide anion (S) and elastase (E).

Figure 9. The structures of cembrane-based diterpenoids (131–188).

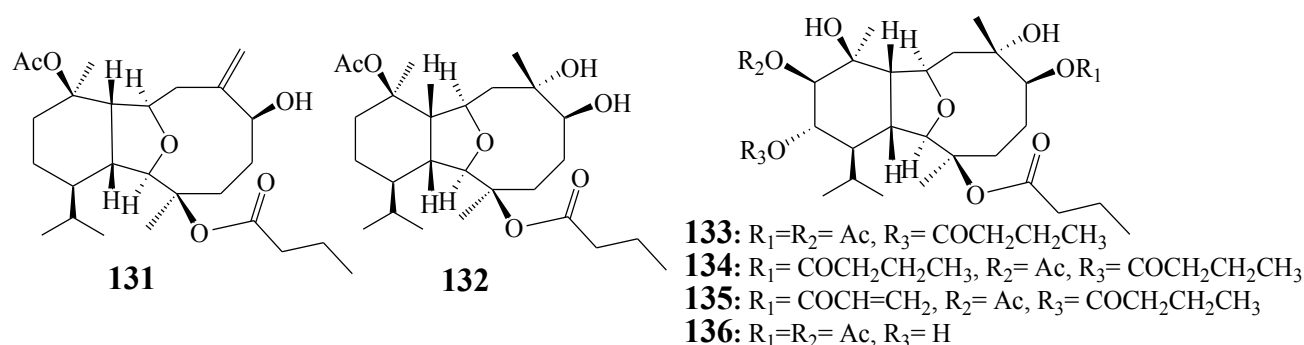


Figure 9. Cont.

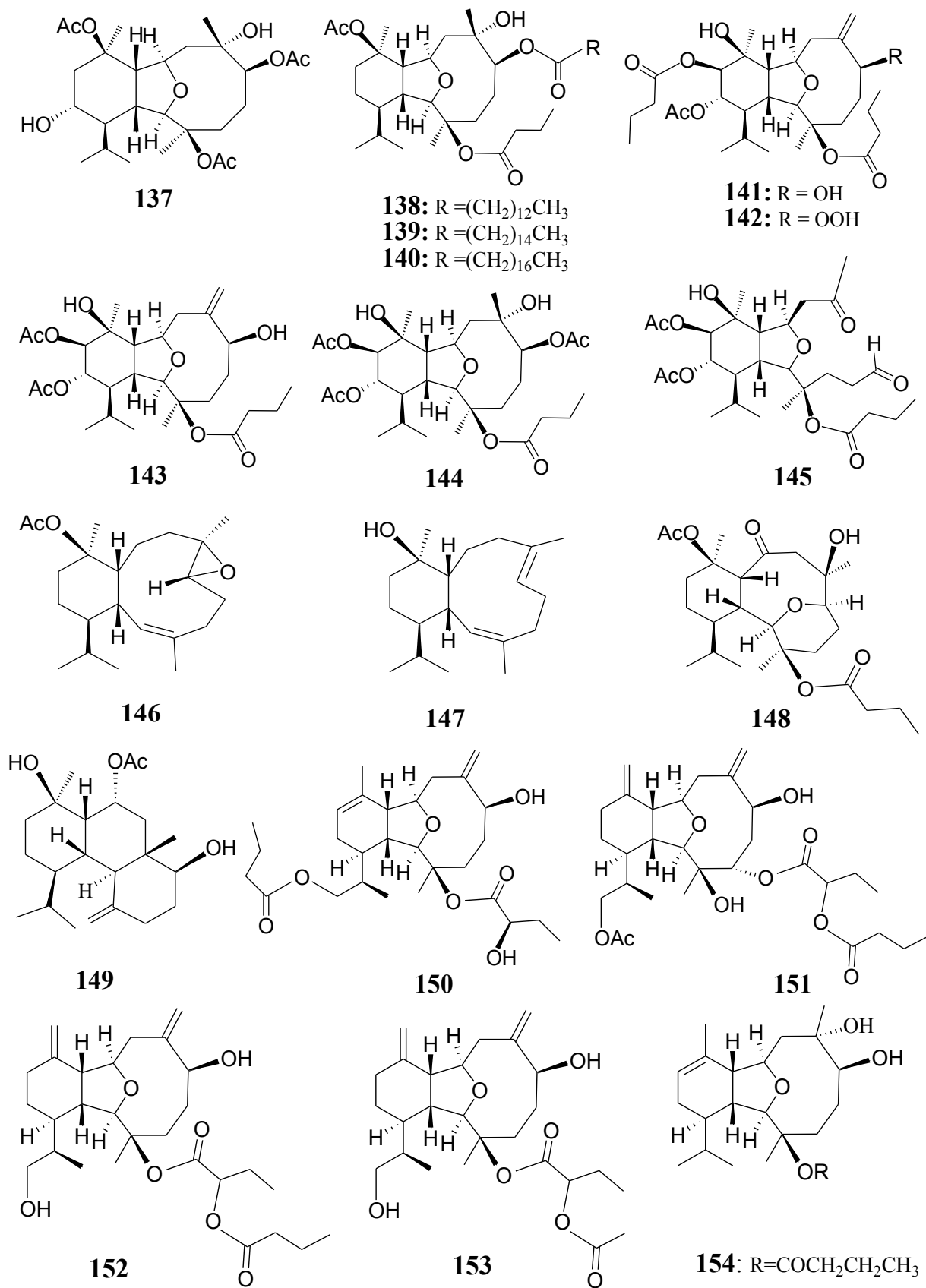


Figure 9. Cont.

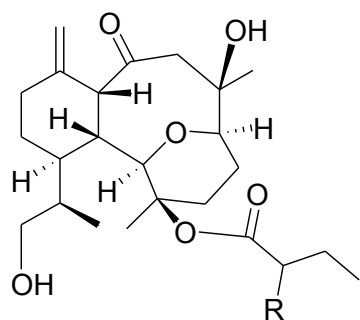
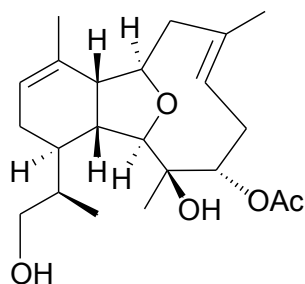
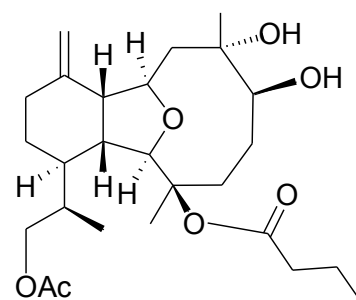
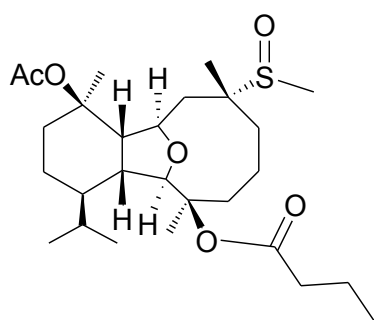
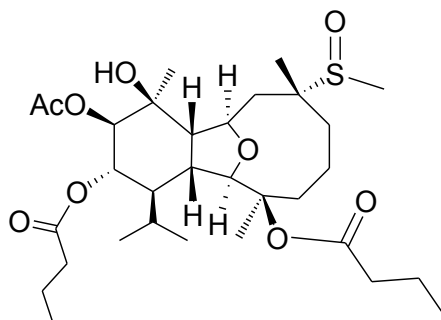
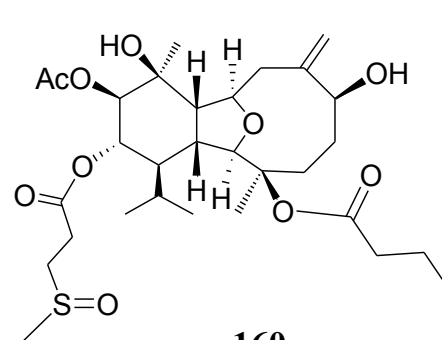
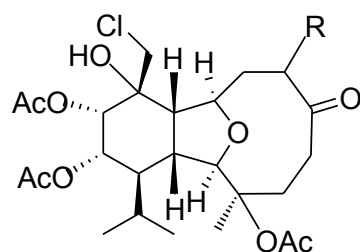
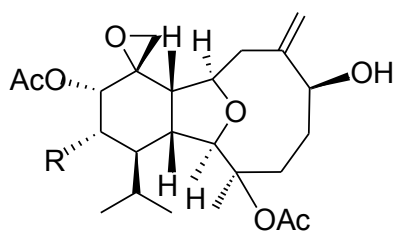
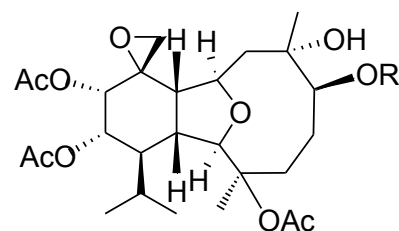
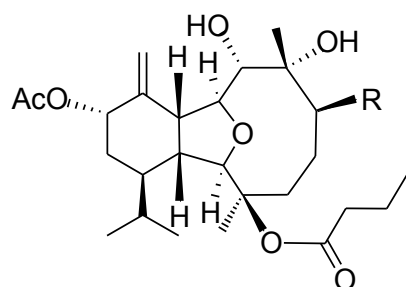
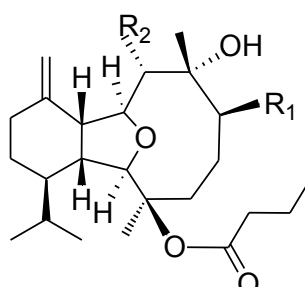
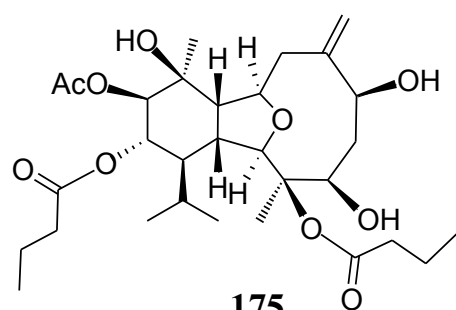
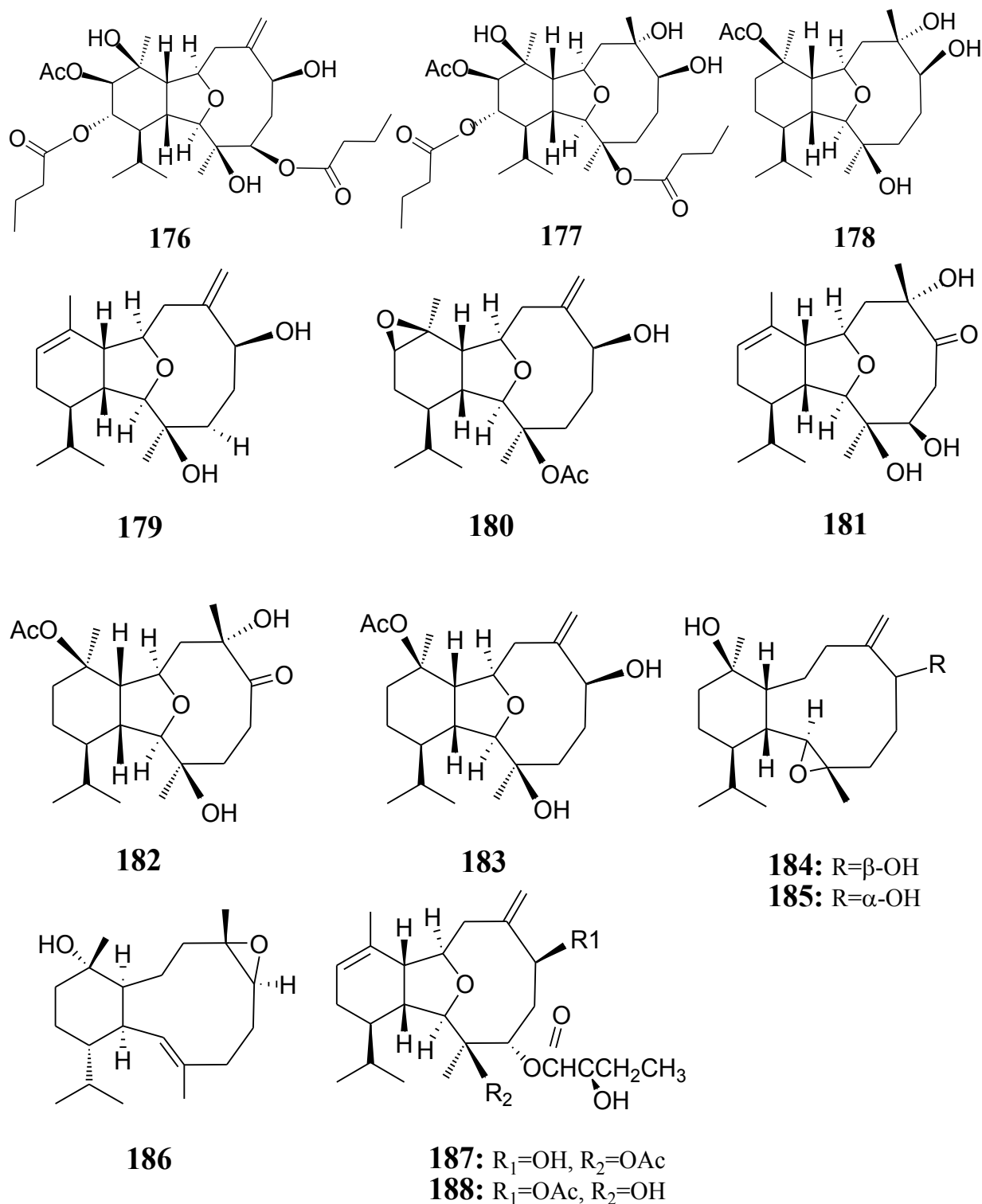
**155:** $R = \text{OCOCH}_2\text{CH}_2\text{CH}_3$ **156****157****158****159****160****161:** $R = \beta\text{-CH}_3$ **162:** $R = \alpha\text{-CH}_3$ **163:** $R = \text{OAc}$ **164:** $R = \text{H}$ **165:** $R = \text{Ac}$ **166:** $R = \text{CH}_3(\text{CH}_2)_{12}\text{CO}$ **167:** $R = \text{CH}_3(\text{CH}_2)_{14}\text{CO}$ **168:** $R = \text{CHO}$ **169:** $R = \text{OH}$ **170:** $R = \text{OMe}$ **171:** $R_1 = \text{OMe}, R_2 = \text{OH}$ **172:** $R_1 = \text{OAc}, R_2 = \text{OH}$ **173:** $R_1 = \text{OH}, R_2 = \text{OH}$ **174:** $R_1 = \text{OH}, R_2 = \text{H}$ **175**

Figure 9. Cont.



2.2.3. Briarane-based Diterpenoids

Table 10 summarizes 35 briarane-based diterpenoids (189–223) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 10.

Table 10. Chemical constituents of briarane-type diterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
189	Excavatolide B	<i>Briareum excavatum</i>		[57]
190	Excavatolide K	<i>Briareum excavatum</i>		[57]
191	Excavatolide F	<i>Briareum excavatum</i>		[57]
192	Briaexcavatolide R	<i>Briareum excavatum</i>		[57]
193	Excavatolide Z	<i>Briareum excavatum</i>		[57]
194	Briaexcavatolide B	<i>Briareum excavatum</i>		[57]
195	Briaexcavatolide K	<i>Briareum excavatum</i>		[57]
196	Briaexcavatolide H	<i>Briareum excavatum</i>		[57]
197	Junceol D	<i>Junceella juncea</i>		[58]
198	Junceol E	<i>Junceella juncea</i>	S	[58]
199	Junceol F	<i>Junceella juncea</i>	S	[58]
200	Junceol G	<i>Junceella juncea</i>	S	[58]
201	Junceol H	<i>Junceella juncea</i>	S	[58]
202	Excavatoid L	<i>Briareum excavatum</i>	S,E	[59]
203	Excavatoid M	<i>Briareum excavatum</i>	S,E	[59]
204	Excavatoid N	<i>Briareum excavatum</i>	S,E	[59]
205	Briarenolide F	<i>Briareum</i> sp.	S	[60]
206	Briarenolide G	<i>Briareum</i> sp.		[60]
207	Fragilide J	<i>Ellisella robusta</i>	E	[61]
208	Robustolide L	<i>Ellisella robusta</i>	S	[61]
209	Briaexcavatin P	<i>Briareum excavatum</i>	S	[62]
210	Frajunolide L	<i>Junceella fragilis</i>	S,E	[63]
211	Frajunolide M	<i>Junceella fragilis</i>		[63]
212	Frajunolide N	<i>Junceella fragilis</i>	E	[63]
213	Frajunolide O	<i>Junceella fragilis</i>	S,E	[63]
214	Juncenolide M	<i>Junceella juncea</i>		[64]
215	Juncenolide N	<i>Junceella juncea</i>	E	[64]
216	Juncenolide O	<i>Junceella juncea</i>	S,E	[64]
217	Frajunolide E	<i>Junceella fragilis</i>	S,E	[65]
218	Frajunolide F	<i>Junceella fragilis</i>		[65]
219	Frajunolide G	<i>Junceella fragilis</i>		[65]
220	Frajunolide H	<i>Junceella fragilis</i>		[65]
221	Frajunolide I	<i>Junceella fragilis</i>		[65]
222	Frajunolide J	<i>Junceella fragilis</i>	S,E	[65]
223	Frajunolide K	<i>Junceella fragilis</i>		[65]

* Inhibition of superoxide anion (S) and elastase (E).

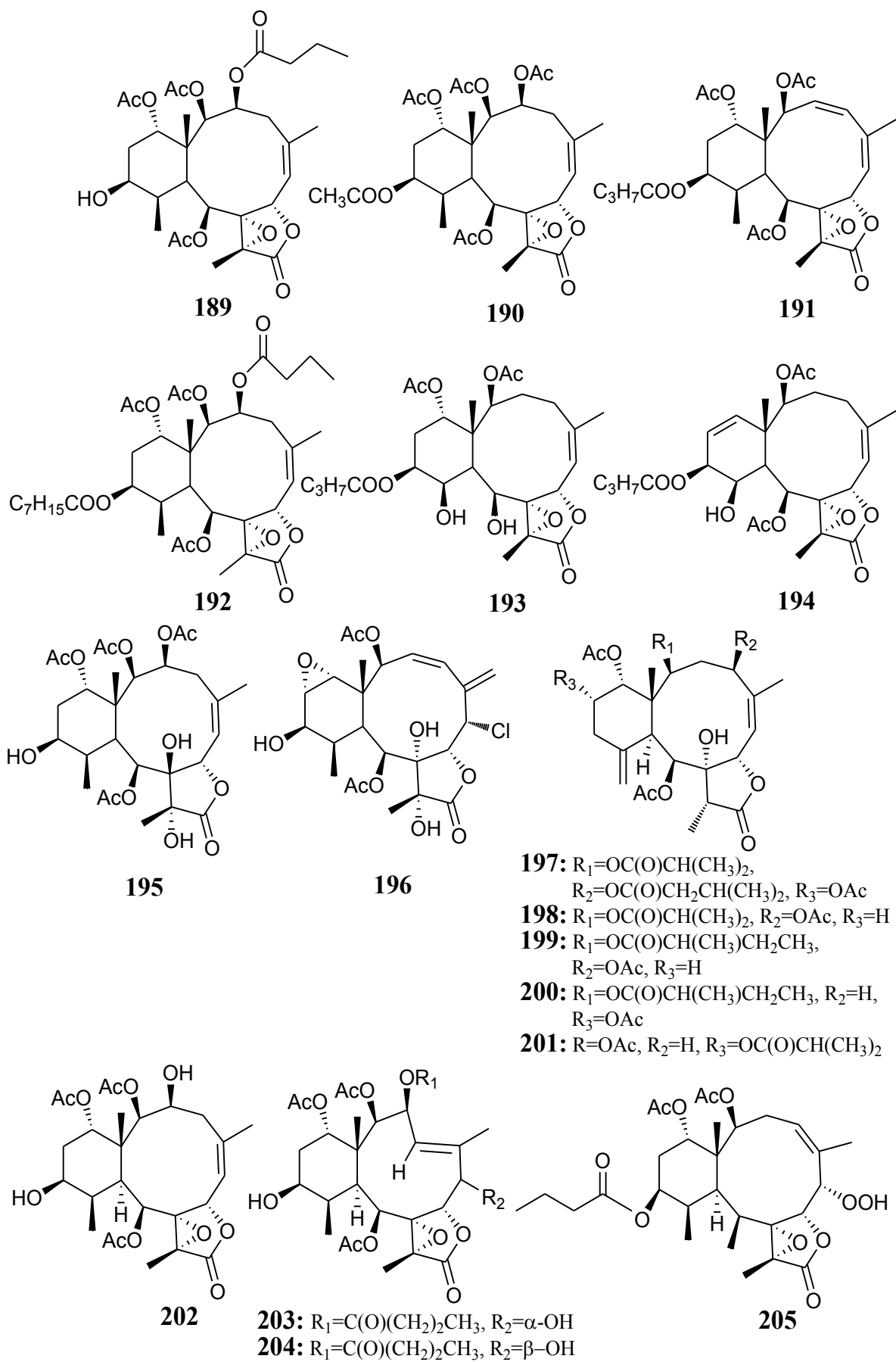
Figure 10. The structures of briarane-type diterpenoids (189–223).

Figure 10. Cont.

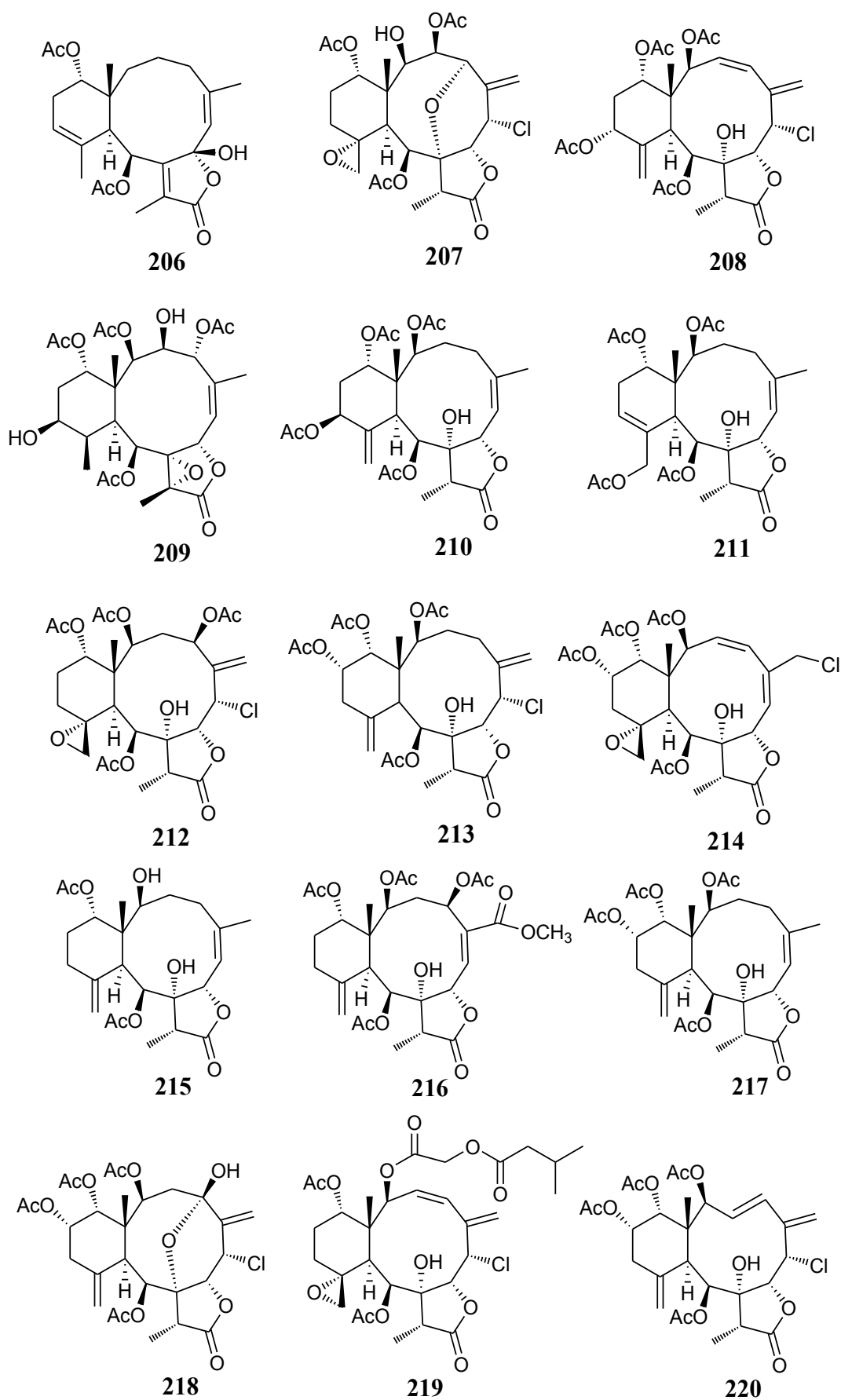
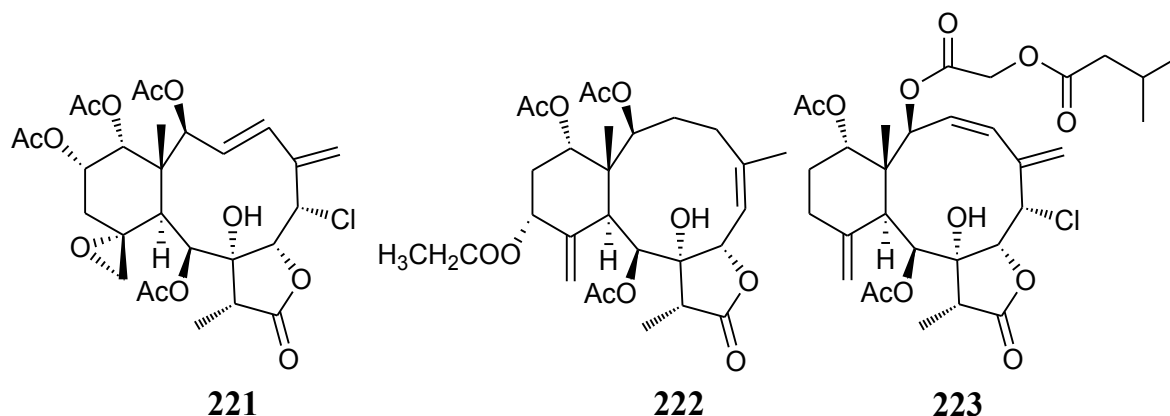


Figure 10. Cont.



2.2.4. Verticillane-Based Diterpenoids

Table 11 summarizes 10 verticillane-based diterpenoids (**224–233**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 11.

Table 11. Chemical constituents of verticillane-type diterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
224	Cespitularin R	<i>Cespitularia hypotentaculata</i>		[66]
225	Cespitularin S	<i>Cespitularia hypotentaculata</i>	I,C	[66]
226	Cespitularin J	<i>Cespitularia hypotentaculata</i>		[66]
227	Cespitularin K	<i>Cespitularia hypotentaculata</i>	I	[66]
228	Cespitularin M	<i>Cespitularia hypotentaculata</i>		[66]
229	Cespitularin I	<i>Cespitularia hypotentaculata</i>	I	[66]
230	Cespitularin F	<i>Cespitularia hypotentaculata</i>	I	[66]
231	Cespitularin Q	<i>Cespitularia hypotentaculata</i>		[66]
232	Cespitulin E	<i>Cespitularia taenuate</i>	S,E	[67]
233	Cespitulin G	<i>Cespitularia taenuate</i>	S,E	[67]

* Inhibition of iNOS (I), COX-2 (C), superoxide anion (S) and elastase (E).

Figure 11. The structures of verticillane-based diterpenoids (**224–233**).

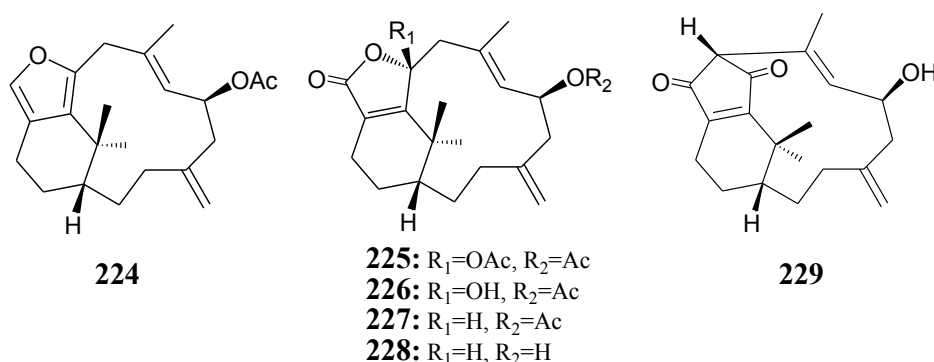
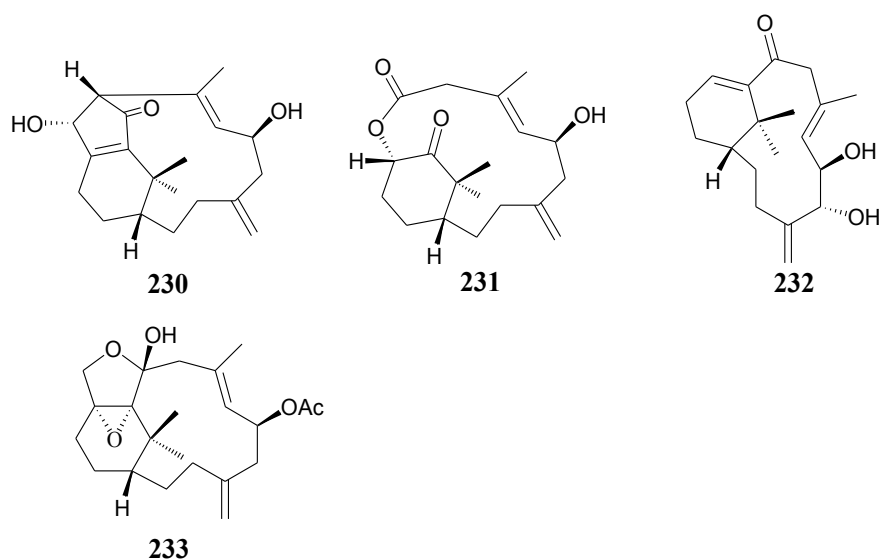


Figure 11. Cont.



2.2.5. Norditerpenoids

Table 12 summarizes 18 norditerpenoids (**234–251**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 12.

Table 12. Chemical constituents of norditerpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
234	Gyrosanolide A	<i>Sinularia gyrosa</i>		[68]
235	Gyrosanolide B	<i>Sinularia gyrosa</i>	I	[68]
236	Gyrosanolide C	<i>Sinularia gyrosa</i>	I	[68]
237	Gyrosanolide D	<i>Sinularia gyrosa</i>		[68]
238	Gyrosanolide E	<i>Sinularia gyrosa</i>		[68]
239	Gyrosanolide F	<i>Sinularia gyrosa</i>	I	[68]
240	Gyrosanin A	<i>Sinularia gyrosa</i>	I	[68]
241	(1 <i>S</i> *,5 <i>R</i> *,8 <i>S</i> *,10 <i>R</i> *,11 <i>S</i> *)-11-Hydroxyl-1-isopropenyl-8-methyl-3,6-dioxo-5,8-epoxycyclotetradec-12-ene-10,12-carbonlactone	<i>Sinularia gyrosa</i>	I	[68]
242	(1 <i>S</i> *,5 <i>S</i> *,8 <i>S</i> *,10 <i>R</i> *,11 <i>S</i> *)-11-Hydroxyl-1-isopropenyl-8-methyl-3,6-dioxo-5,8-epoxycyclotetradec-12-ene-10,12-carbonlactone	<i>Sinularia gyrosa</i>	I	[68]
243	Norcembrene	<i>Sinularia gyrosa</i>		[68]
244	<i>epi</i> -Norcembrene	<i>Sinularia gyrosa</i>		[68]
245	Leptocladolide B	<i>Sinularia gyrosa</i>	I	[68]
246	Scabrolide D	<i>Sinularia gyrosa</i>	I	[68]
247	Norcembrene	<i>Sinularia gyrosa</i>		[68]
248	Ineleganolide	<i>Sinularia gyrosa</i>		[68]
249	Sinulochemodin C	<i>Sinularia gyrosa</i>		[68]
250	Scabrolide A	<i>Sinularia gyrosa</i>		[68]
251	Yanarolide	<i>Sinularia gyrosa</i>		[68]

* Inhibition of iNOS (I).

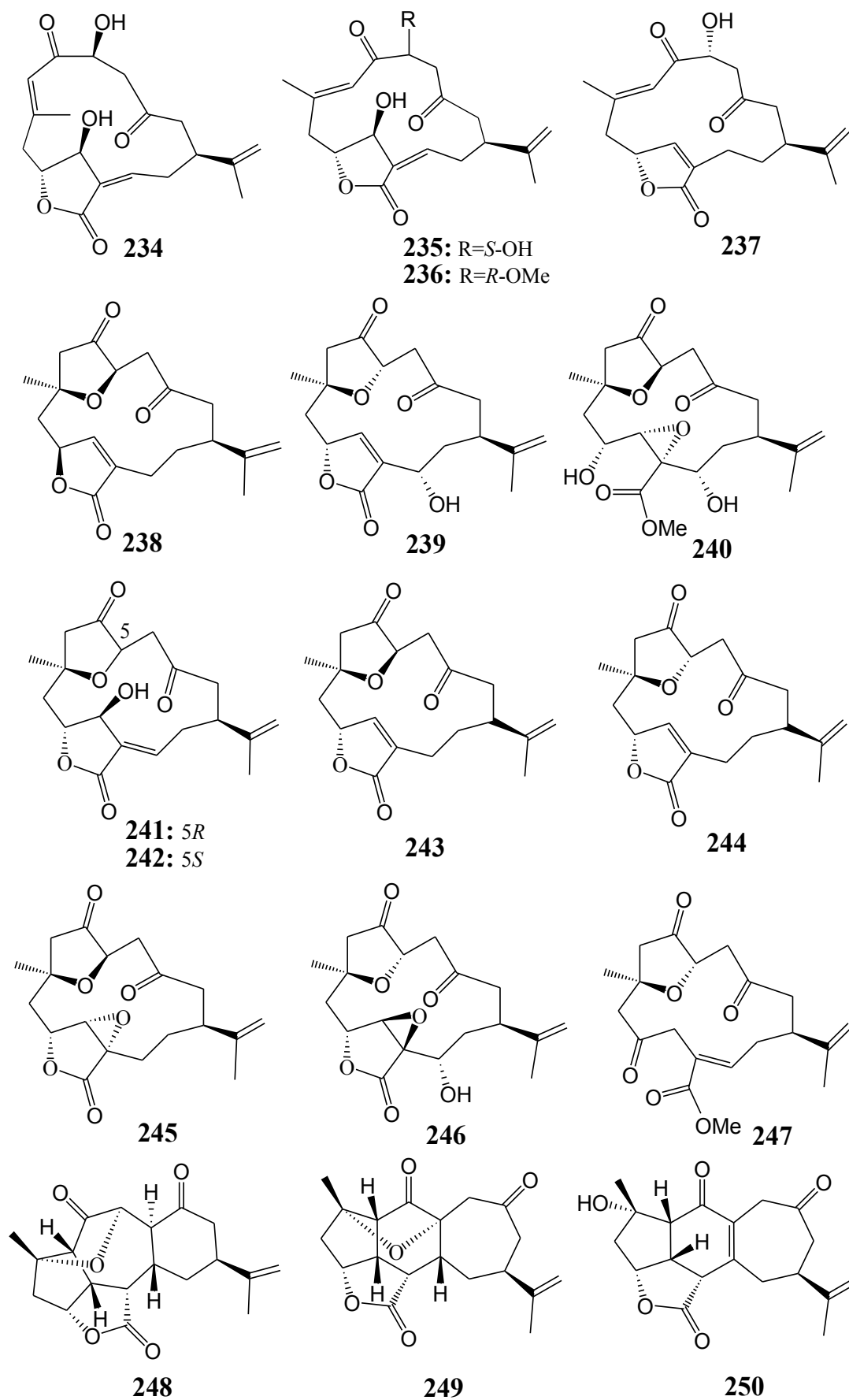
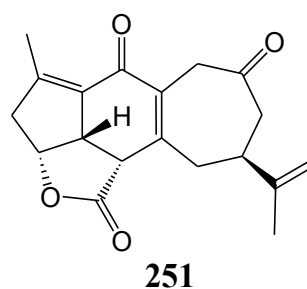
Figure 12. The structures of norditerpenoids (234–251).

Figure 12. Cont.



2.2.6. Xenicane-Type Diterpenoids

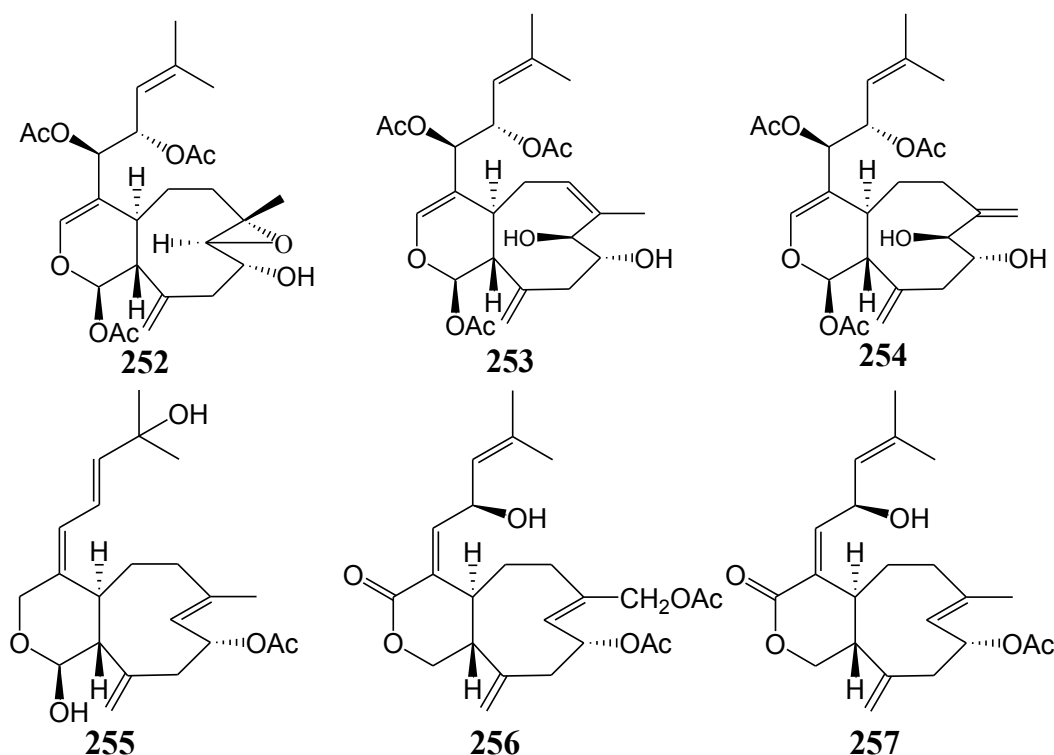
Table 13 summarizes six xenicane-type diterpenoids (**252–257**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 13.

Table 13. Chemical constituents of xenicane-type diterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
252	Asterolaurin A	<i>Asterospicularia laurae</i>		[69]
253	Asterolaurin B	<i>Asterospicularia laurae</i>		[69]
254	Asterolaurin C	<i>Asterospicularia laurae</i>		[69]
255	Asterolaurin D	<i>Asterospicularia laurae</i>	S,E	[69]
256	Asterolaurin E	<i>Asterospicularia laurae</i>		[69]
257	Asterolaurin F	<i>Asterospicularia laurae</i>		[69]

* Inhibition of superoxide anion (S) and elastase (E).

Figure 13. The structures of xenicane-type diterpenoids (**252–257**).



2.2.7. Other-Type Diterpenoids

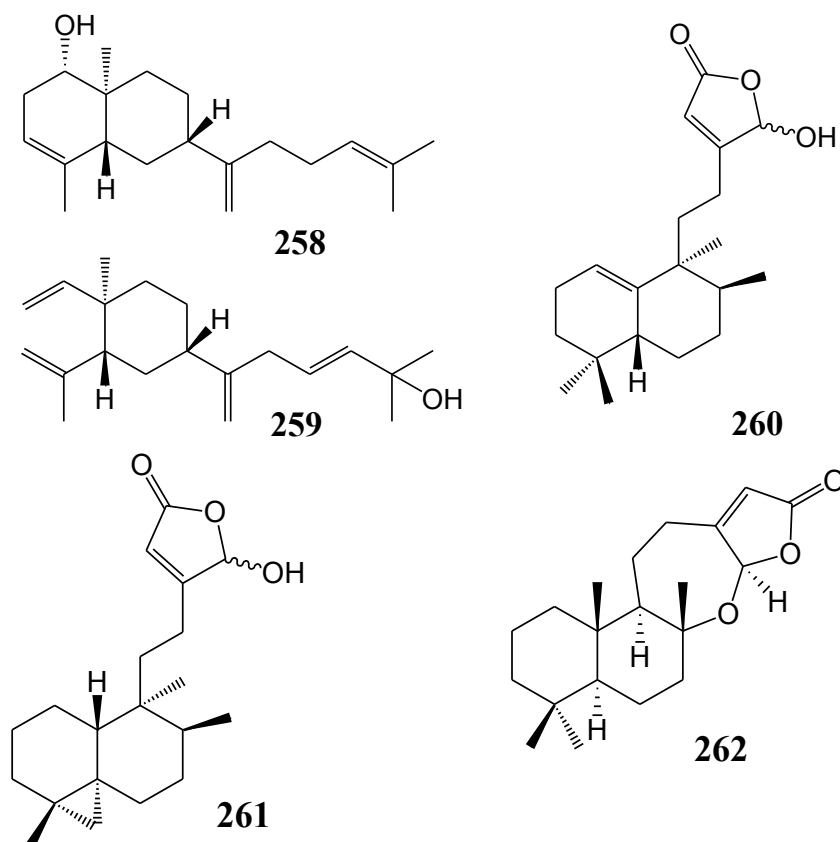
Table 14 summarizes five other-type diterpenoids (**258–262**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 14.

Table 14. Chemical constituents of other type diterpenoids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
258	Gyrosanol A	<i>Sinularia gyrosa</i>	C	[70]
259	Gyrosanol B	<i>Sinularia gyrosa</i>	C	[70]
260	Echinohalimane A	<i>Echinomuricea</i> sp.	E	[71]
261	Echinoclerodane A	<i>Echinomuricea</i> sp.	S,E	[72]
262	Echinolabdane A	<i>Echinomuricea</i> sp.		[73]

* Inhibition of COX-2 (C), superoxide anion (S) and elastase (E).

Figure 14. The structures of other type diterpenoids (**258–262**).



At a concentration of 10 μ M, compounds **131**, **133**, **134**, **139**, **140–143**, **147**, **148**, **151–153**, **157–160**, **162–168**, **170** ceramide and cerebroside **174**, **225**, **229**, **230**, **235**, **236**, **239–242**, **244**, **245**, **258** and **259** reduced LPS-induced expression of iNOS in murine macrophage cells [46–51,66,68,70]. Compounds **134**, **148**, **151**, **160**, **163**, **164**, **166–168**, **225**, **258** and **259** suppressed the LPS-induced expression of COX-2 in these cells [46–50,66,70]. At 10 μ g/mL, compounds **180**, **184**, **186**, **188**, **198–205**, **208–210**, **213**, **216**, **217**, **222**, **232**, **233**, **255** and **261** inhibited the generation of superoxide anion by activated human neutrophils [54–56,58–65,67,69,70,72]. Compounds **180**, **184**, **186**, **188**,

202–204, 207, 210, 212, 213, 215–217, 222, 232, 233, 255, 260 and 261 inhibited the release of elastase from these activated human neutrophils [53–56,59,61,63,65,67,69,71,72]. These results provided useful baseline information on the immune-regulatory and anti-oxidant activities of various marine diterpenoids. Compound **184**, as **185** epimer at C-6, was showed to be more potent in the inhibition of the generation of superoxide anion and in inducing the release of elastase by active human neutrophils, suggesting that the stereochemistry at C-6 may play a key role in the above biological effects [54].

The briarane-type diterpenoid excavatolide B (**189**) has been demonstrated to significantly inhibit TPA-induced cutaneous inflammation activities in mice, including those related to vascular permeability, edema, and TPA-induced expression of iNOS, COX-2 and matrixmetalloproteinase-9. Excavatolide B also suppressed LPS-induced expression of TNF- α and IL-6 in mouse bone marrow derived dendritic cells (BMDCs) [57]. Also, excavatolide F (**191**), K (**190**) and Z (**193**) and briaexcavatolide B (**194**), H (**196**), K (**195**) and R (**192**) exhibited a broad spectrum of activity in inhibition of LPS-induced expression of IL-6 in BMDCs [57]. A study on the structure-activity relationship between the structures of the briarane-type diterpenoids and their inhibition of IL-6 expression in BMDCs revealed that the eight 17-epoxide of briarane-type diterpenoids may play an important role in the inhibition of IL-6 expression in specific immune cells [57]. Replacement of the C-12 hydroxyl group with long esters in briarane-type diterpenoids decreased the inhibition of IL-6 expression [57].

2.3. Steroids

Table 15 summarizes 60 steroids (**263–322**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 15.

Table 15. Chemical constituents of steroids from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
263	Stoloniferone R	<i>Clavularia viridis</i>		[74]
264	Stoloniferone S	<i>Clavularia viridis</i>	I	[74]
265	Stoloniferone T	<i>Clavularia viridis</i>	I,C	[74]
266	(25S)-24-Methylenecholestane-3 β ,5 α ,6 β -triol-26-acetate	<i>Clavularia viridis</i>	I,C	[74]
267	Griffinisterone A	<i>Nephthea griffini</i>	I	[75]
268	Griffinisterone B	<i>Nephthea griffini</i>	I	[75]
269	Griffinisterone C	<i>Nephthea griffini</i>	I	[75]
270	Griffinisterone D	<i>Nephthea griffini</i>	I	[75]
271	Chabrosterol	<i>Nephthea chabroli</i>	I,C	[21]
272	Nebrosteroid A	<i>Nephthea chabroli</i>	I	[76]
273	Nebrosteroid B	<i>Nephthea chabroli</i>	I	[76]
274	Nebrosteroid C	<i>Nephthea chabroli</i>	I	[76]
275	Nebrosteroid D	<i>Nephthea chabroli</i>	I,C	[76]
276	Nebrosteroid F	<i>Nephthea chabroli</i>	I,C	[76]
277	Nebrosteroid E	<i>Nephthea chabroli</i>		[76]

Table 15. Cont.

278	Nebrosteroid G	<i>Nephtea chabroli</i>	I,C	[76]
279	Nebrosteroid H	<i>Nephtea chabroli</i>	I	[76]
280	Griffinisterone F	<i>Dendronephthya griffini</i>	I,C	[77]
281	Griffinisterone G	<i>Dendronephthya griffini</i>	I,C	[77]
282	Griffinisterone H	<i>Dendronephthya griffini</i>	I	[77]
283	Griffinipregnane	<i>Dendronephthya griffini</i>	I,C	[77]
284	1 α ,3 β -Dihydroxy-24S-methylcholesta-5-ene	<i>Sinularia sp.</i>	I,C	[78]
285	1 α ,3 β -Dihydroxy-24-methylenecholesta-5-ene	<i>Sinularia sp.</i>	I,C	[78]
286	5,24(28)-Ergostadien-3 β ,23S-diol	<i>Nephtea erecta</i>	I,C	[79]
287	5,24(28)-Ergostadien-3 β ,23R-diol	<i>Nephtea erecta</i>	I	[79]
288	(22S)-5,24(28)-Ergostadien-3 β ,17 α ,22-triol	<i>Nephtea erecta</i>	I,C	[79]
289	Ergostanoid	<i>Nephtea erecta</i>	I	[79]
290	Nebrosteroid I	<i>Nephtea chabroli</i>	I,C	[80]
291	Nebrosteroid J	<i>Nephtea chabroli</i>	I,C	[80]
292	Nebrosteroid K	<i>Nephtea chabroli</i>		[80]
293	Nebrosteroid L	<i>Nephtea chabroli</i>	I,C	[80]
294	Nebrosteroid M	<i>Nephtea chabroli</i>	IC	[80]
295	Sarcophytosterol	<i>Lobophytum sarcophytoides</i>		[38]
296	5 α ,8 α -Epidioxy-24-methylcholesta-6-en-3 β -ol	<i>Lobophytum sarcophytoides</i>		[38]
297	5 α ,8 α -Epidioxy-22,23-methylene-24-methylcholest-6-en-3 β -ol	<i>Lobophytum sarcophytoides</i>	I	[38]
298	Paraminabeolide A	<i>Paraminabea acronocephala</i>	I	[81]
299	Paraminabeolide B	<i>Paraminabea acronocephala</i>	I	[81]
300	Paraminabeolide C	<i>Paraminabea acronocephala</i>	I	[81]
301	Paraminabeolide D	<i>Paraminabea acronocephala</i>	I	[81]
302	Paraminabeolide E	<i>Paraminabea acronocephala</i>		[81]
303	Minabeolide-1	<i>Paraminabea acronocephala</i>	I,C	[81]
304	Minabeolide-2	<i>Paraminabea acronocephala</i>	I,C	[81]
305	Minabeolide-4	<i>Paraminabea acronocephala</i>	I,C	[81]
306	Minabeolide-5	<i>Paraminabea acronocephala</i>	I,C	[81]
307	Minabeolide-8	<i>Paraminabea acronocephala</i>		[81]
308	Hirsutosterol A	<i>Cladiella hirsuta</i>		[82]
309	Hirsutosterol B	<i>Cladiella hirsuta</i>		[82]
310	Hirsutosterol C	<i>Cladiella hirsuta</i>		[82]
311	Hirsutosterol D	<i>Cladiella hirsuta</i>		[82]
312	Hirsutosterol E	<i>Cladiella hirsuta</i>		[82]
313	Hirsutosterol F	<i>Cladiella hirsuta</i>		[82]
314	Hirsutosterol G	<i>Cladiella hirsuta</i>		[82]
315	Crassarosterol A	<i>Sinularia crassa</i>		[83]
316	Crassarosteroside A	<i>Sinularia crassa</i>	I	[83]
317	Crassarosteroside B	<i>Sinularia crassa</i>	I	[83]
318	Crassarosteroside C	<i>Sinularia crassa</i>	I	[83]

Table 15. Cont.

319	8 α H-3 β ,11-Dihydroxy-5 α ,6 α - expoxy-24-methylene-9,11- secocholestan-9-one	<i>Sinularia granosa</i>	I,C	[84]
320	3 β ,11-Dihydroxy-5 β ,6 β -expoxy-24- methylene-9,11-secocholestan-9-one	<i>Sinularia granosa</i>	I	[84]
321	6- <i>epi</i> -Yonarasterol B	<i>Echinomuricea</i> sp.	S,E	[73]
322	Carijoxide A	<i>Carijoa</i> sp.	S,E	[85]

* Inhibition of iNOS (I), COX-2 (C), superoxide anion (S) and elastase (E).

Figure 15. The structures of steroids (263–322).

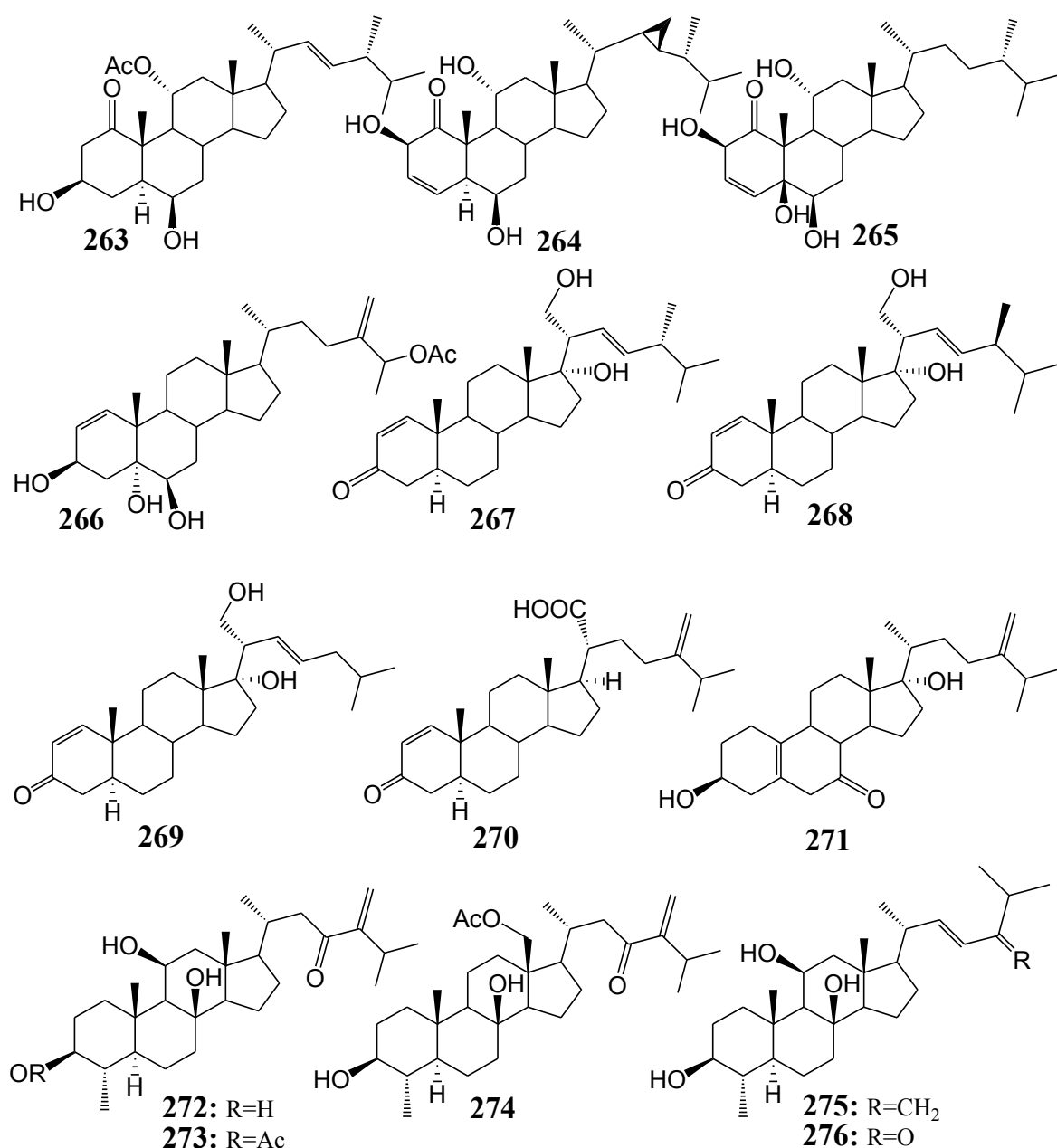


Figure 15. Cont.

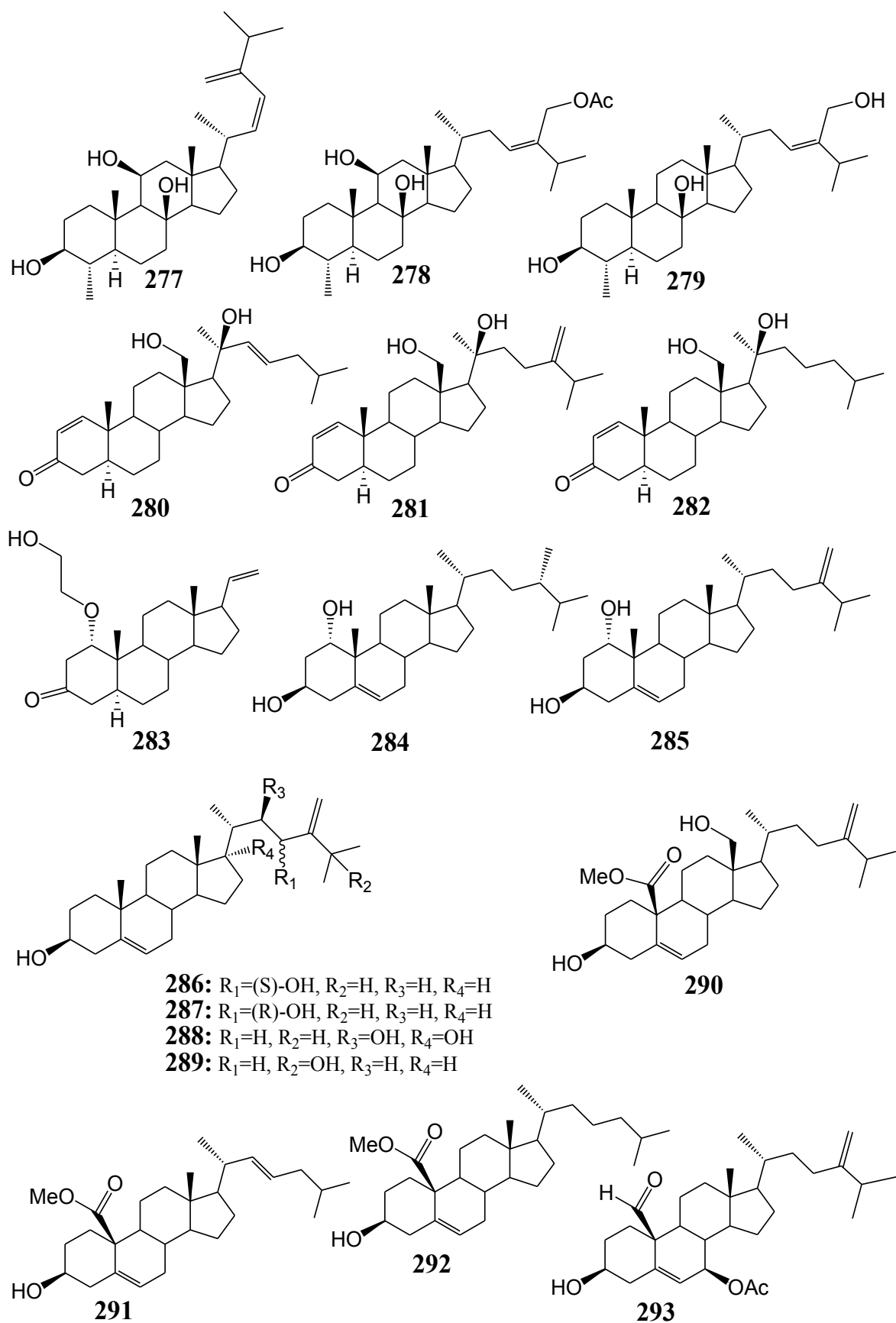


Figure 15. Cont.

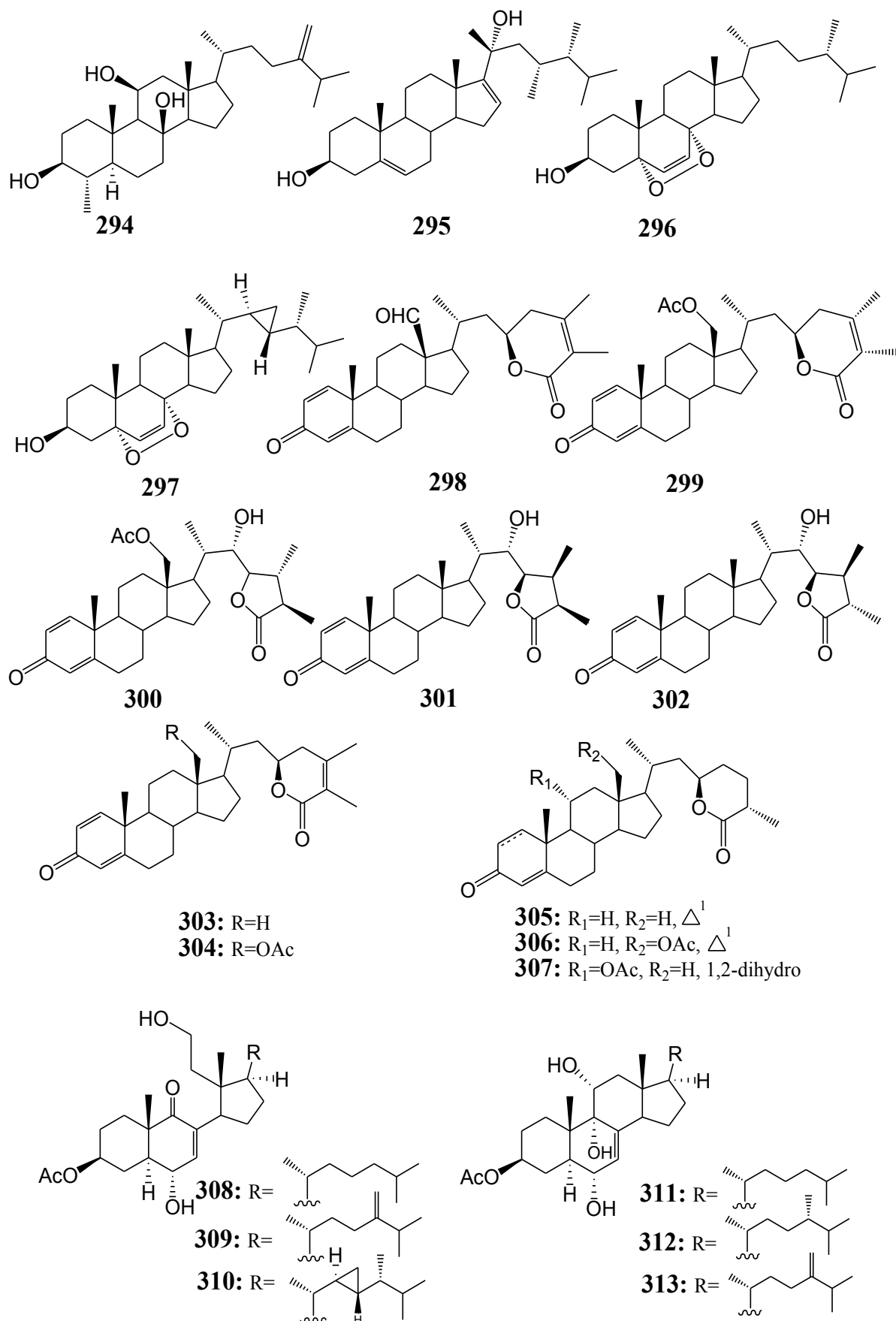
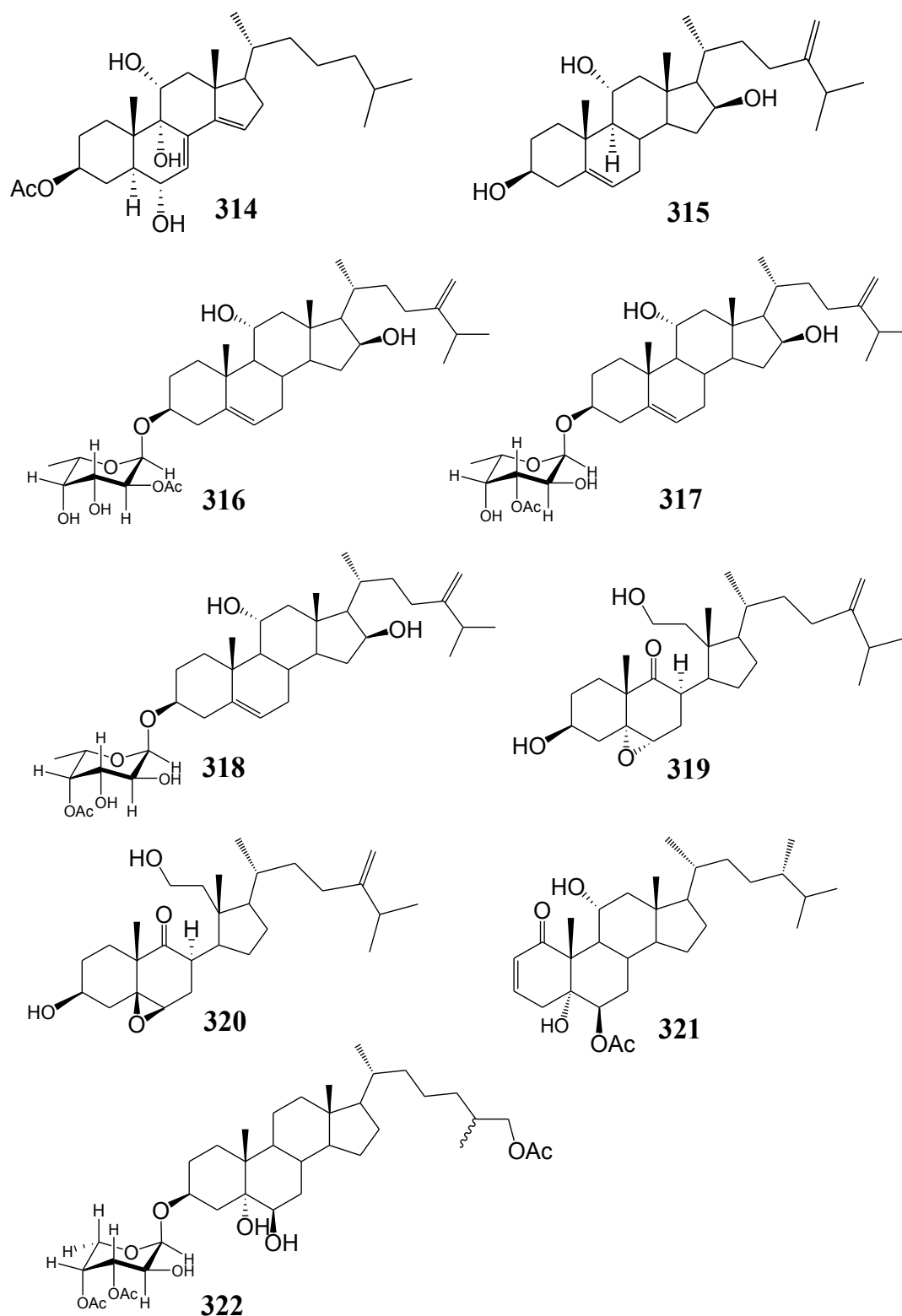


Figure 15. Cont.



At a concentration of 10 μ M, compounds **264–275**, **277–291**, **293**, **294**, **297**, **303–307** and **316–320** reduced LPS-induced expression level of iNOS in murine macrophage cells (RAW264.7) [21,74–81,83,84]. Compounds **265**, **266**, **271**, **275**, **277**, **278**, **280**, **281**, **283–286**, **288**, **290**, **291**, **293** and **319** suppressed LPS-induced expression level of COX-2 in murine macrophage

cells (RAW264.7) [21,74–80,84]. At 10 $\mu\text{g/mL}$, compounds **321** and **322** inhibited the generation of superoxide anion and the release of elastase by activated human neutrophils [73,85].

2.4. Ceramide and Cerebrosides

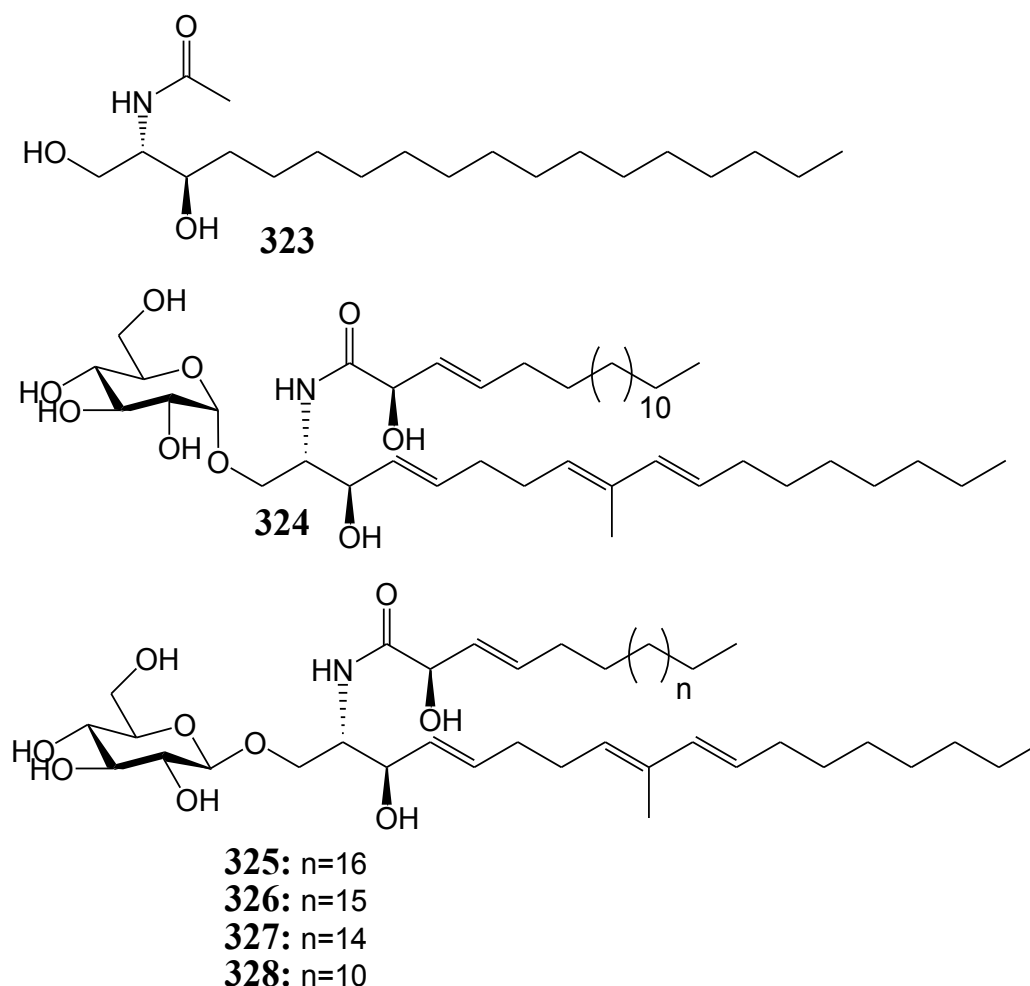
Table 16 summarizes ceramide (**323**) and five cerebroside (**324–328**) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 16.

Table 16. Chemical constituents of ceramide and cerebroside from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
323	Ceramide	<i>Sarcophyton ehrenbergi</i>	I,C	[86]
324	Sarcoehrenoside A	<i>Sarcophyton ehrenbergi</i>	I	[86]
325	Sarcoehrenoside B	<i>Sarcophyton ehrenbergi</i>		[86]
326	Cerebroside-3	<i>Sarcophyton ehrenbergi</i>	I	[86]
327	Cerebroside-5	<i>Sarcophyton ehrenbergi</i>	I	[86]
328	Cerebroside-6	<i>Sarcophyton ehrenbergi</i>	I	[86]

* Inhibition of iNOS (I) and COX-2 (C).

Figure 16. The structures of ceramide and cerebroside (**323–328**).



2.5. Other Metabolites

Table 17 summarizes 11 secondary metabolites of other types (329–339) evaluated for *in vitro* anti-inflammatory activity in literature published from 2008 to 2012. The corresponding chemical structures are reported in Figure 17.

Table 17. Chemical constituents of other metabolites from soft corals of Taiwan.

No.	Name	Sources	Activities *	Reference
329	Capilloquinone	<i>Sinularia capillosa</i>	I	[87]
330	Capillobenzopyranol	<i>Sinularia capillosa</i>	I	[87]
331	Capillobenzofuranol	<i>Sinularia capillosa</i>		[87]
332	Capillofuranocarboxylate	<i>Sinularia capillosa</i>		[87]
333	(<i>E</i>)-5-(2,6-Dimethylocta-5,7-dienyl)furan-3-carboxylic acid	<i>Sinularia capillosa</i>		[87]
334	2-[(2 <i>E</i> ,6 <i>E</i>)-3,7-Dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylcyclohexa-2,5-diene-1,4-dione	<i>Sinularia capillosa</i>	I,C	[87]
335	2-[(2 <i>E</i> ,6 <i>E</i>)-3,7-Dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylbenzene-1,4-diol	<i>Sinularia capillosa</i>	I	[87]
336	(–)-Loliolide	<i>Sinularia capillosa</i>		[87]
337	3,4,11-Trimethyl-7-methylenebicyclo[6.3.0]undec-2-en-11R-ol	<i>Sinularia capillosa</i>		[87]
338	Austrasulfone	<i>Cladiella australis</i>		[88]
339	Dihydroaustrasulfone alcohol	<i>Cladiella australis</i>	I,C	[88]

* Inhibition of iNOS (I) and COX-2 (C).

Figure 17. Structures of other metabolites (329–339).

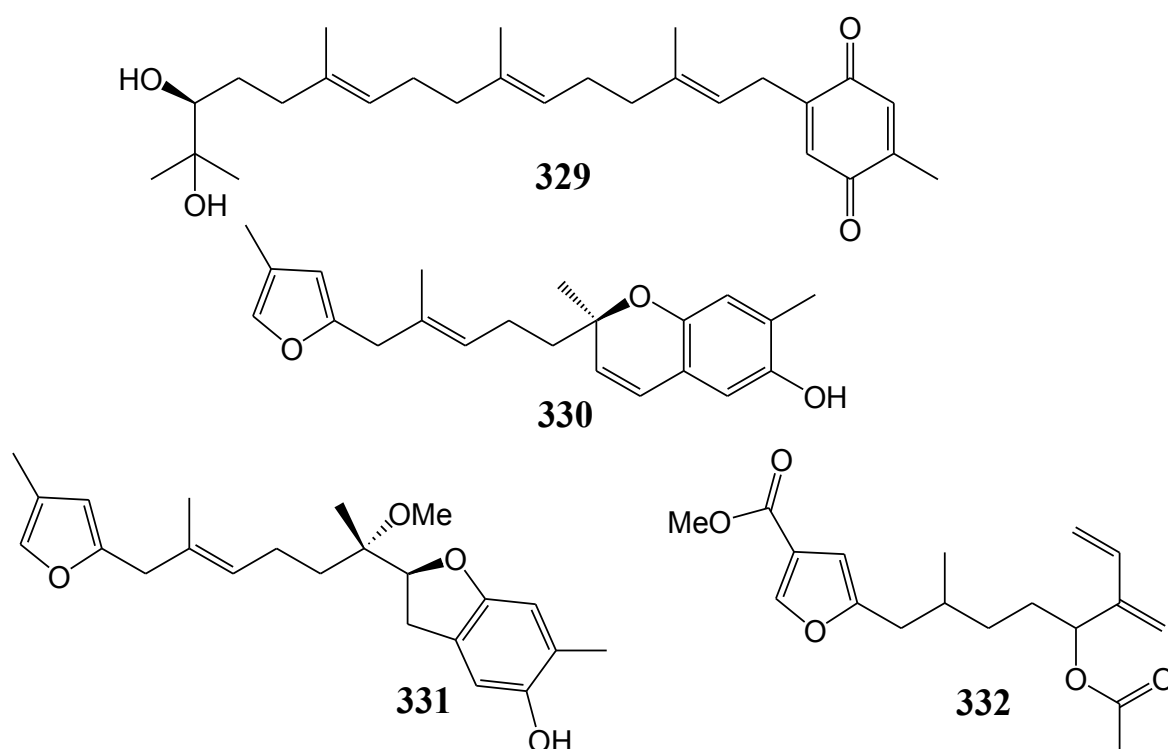
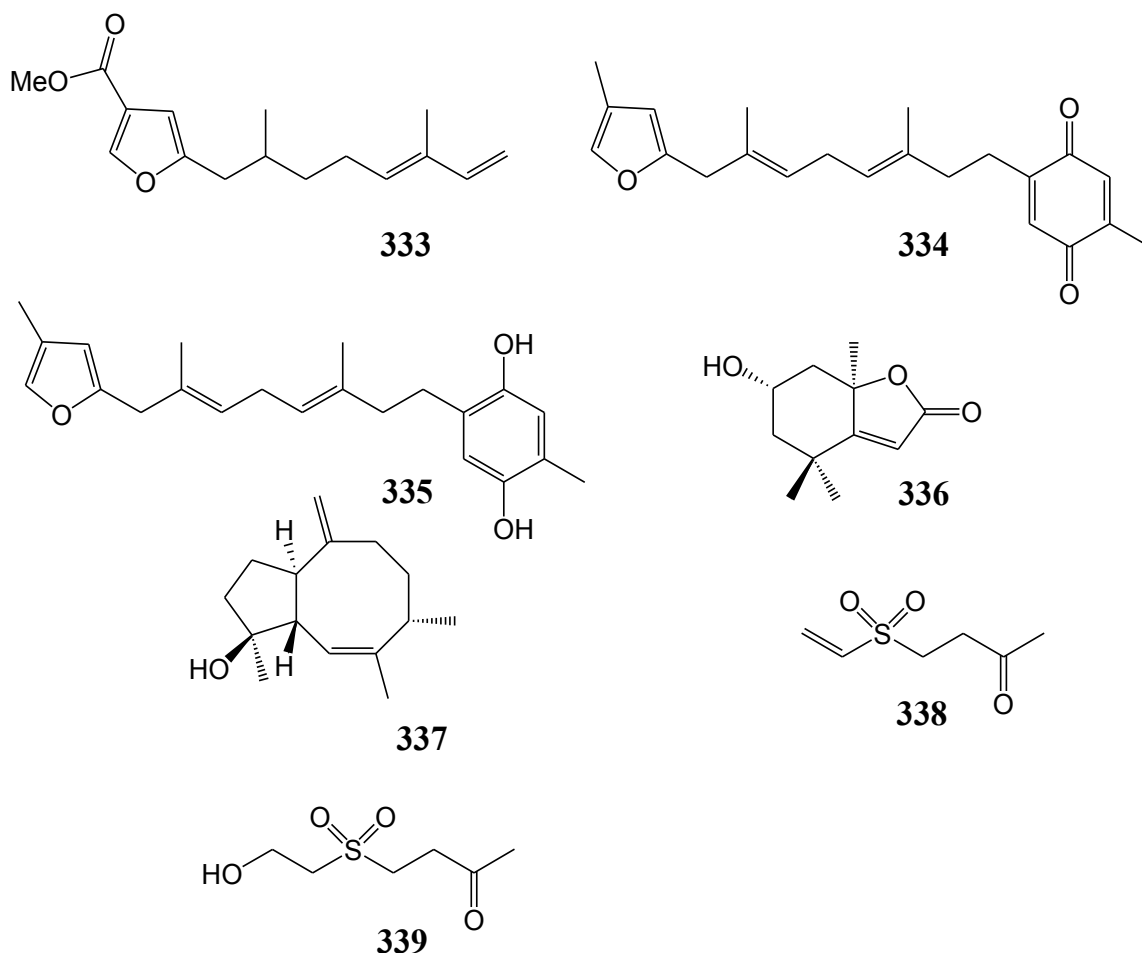


Figure 17. Cont.



At a concentration of 10 μ M, compounds **323**, **324**, **326–330**, **334**, **335** and **339** reduced LPS-induced expression level of iNOS in murine macrophage cells (RAW264.7) [86–88]. Compounds **323**, **334** and **339** suppressed LPS-induced expression levels of COX-2 in murine macrophage cells (RAW264.7) [86,88]. Austrasulfone (**338**) was found to exhibit a potent neuroprotective effect in human dopaminergic neuron cells (SH-SY5Y) [89,90]. In animal disease models, the synthetic precursor of austrasulfone dihydroaustrasulfone alcohol (**339**) was not only demonstrated to attenuate neuropathic pain, but also to suppress the progression of multiple sclerosis and atherosclerosis [88].

3. Conclusions

Marine invertebrates, particularly octocorals, are rich potential sources of drug leads. Most of our own and other studies on anti-inflammatory activities of natural products from soft corals have been focused on “screening-like” assays using COX-2 and iNOS as target markers. These assay studies have been useful in generating small libraries of anti-oxidant and anti-inflammatory activities from a broad spectrum of soft corals. These results, however, apparently have limitations. For example, the findings are usually generic in nature, and there is often difficulty in immediate or specific application of such results to drug/pharmaceutical discovery, as compared to the existing synthetic chemicals or phytochemicals or those being developed for clinical use. We [45,57,88] and others [25,26] have recently initiated a number of cross-disciplinary studies, employing bio-organic chemistry, cellular

immunology and animal disease models for systematic and in-depth studies. As a result, we believe that useful information on the possible application of specific natural products from soft corals for future clinical studies have been obtained. We consider such approaches [57] may need to be encouraged and organized at the international level, and hopefully be integrated into systematic studies, aiming to create translational research of marine natural products for pharmaceuticals/nutraceuticals. Special emphasis may need to be placed on new or specific cell biological/disease model systems.

In terms of evaluating marine natural products for future pharmaceutical application, despite the abundance of unique marine natural products identified, the extremely low quantity of a given compound of interest that can be isolated from marine organisms may be a big hurdle for evaluation of *in vivo* bioactivities and development for pharmaceutical applications.

Fortunately, due to the recent advancement in aquaculture technologies, aquacultural cultivation of various types of specific soft corals is becoming possible. Our team has successfully cultured a number of species of soft corals, including *Klyxum simplex* and *Briareum excavatum* [47,91]. As a result, more abundant and routine preparations of experimental materials will become available for global distribution and collaborative research purposes. Nonetheless, the vast volume of marine organisms and the small base of knowledge so far assembled on soft coral-derived marine chemicals calls for increased international cooperation in this field.

Acknowledgments

We thank Ms. Miranda Loney of the Agricultural Biotechnology Research Center, Academia Sinica, Taiwan; and Subramanian Senthilkumar of Shanmugha Arts, Science, Technology & Research Academy, India for editing the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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