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## Review



## Marine life as a source for breast cancer treatment: A comprehensive review

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## ABSTRACT

Breast cancer, one of the most significant tumors among all cancer cells, still has deficiencies for effective treatment. Moreover, substitute treatments employing natural products as bioactive metabolites has been seriously considered. The source of bioactive metabolites are not only the most numerous but also represent the richest source. A unique source is from the oceans or marine species which demonstrated intriguing chemical and biological diversity which represents an astonishing reserve for discovering novel anticancer drugs. Notably, marine sponges produce the largest amount of diverse bioactive peptides, alkaloids, terpenoids, polyketides along with many secondary metabolites whose potential is mostly therapeutic. In this review, our main focus is on the marine derived secondary metabolites which demonstrated cytotoxic effects towards numerous breast cancer cells and have been isolated from the marine sources such as marine sponges, cyanobacteria, fungi, algae, tunicates, actinomycetes, ascidians, and other sources of marine organisms.

## 1. Introduction

The development of modern pharmaceuticals represents one of the major challenges of this century. Drugs like penicillin, streptomycin, and vincristine, among others, have largely contributed to the control of

human disease since their discovery early in the 20th century. Novel treatments have enhanced the life expectancy of people and improved their standard of living. Society has become increasingly dependent on the availability of effective and safe pharmaceutical drugs for this improved societal development. Almost 50% of the drugs are either

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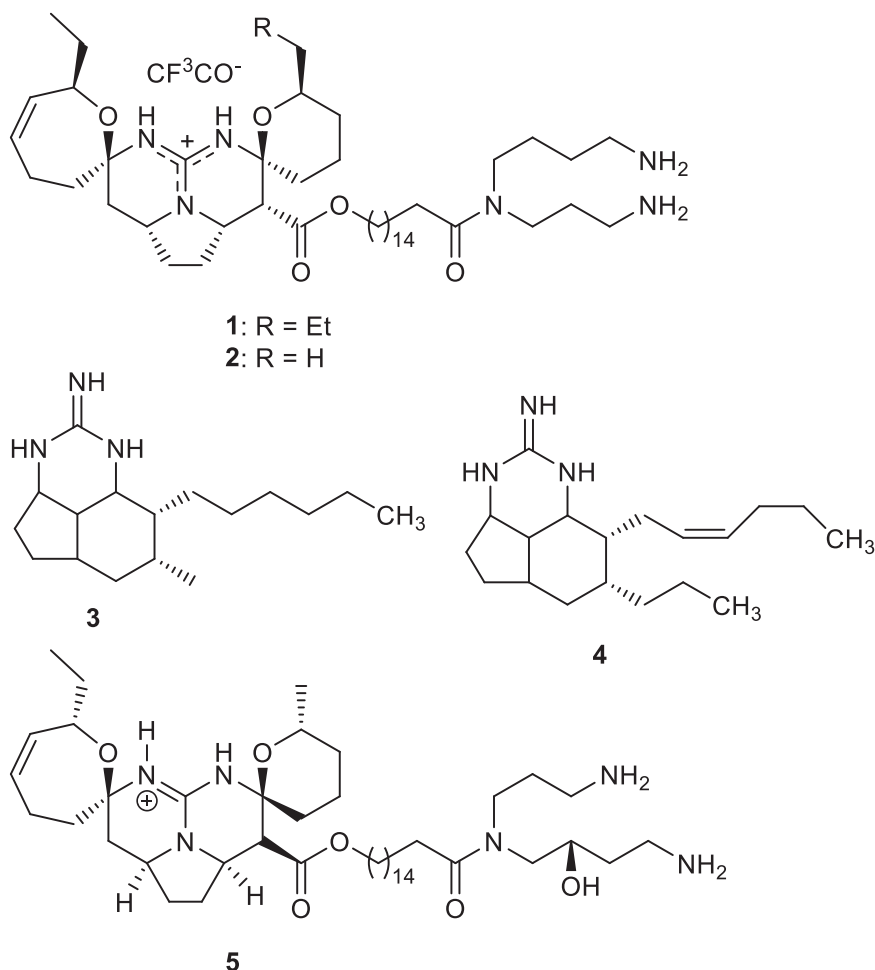


Fig. 1. Structures of guanidine alkaloids 1–5.

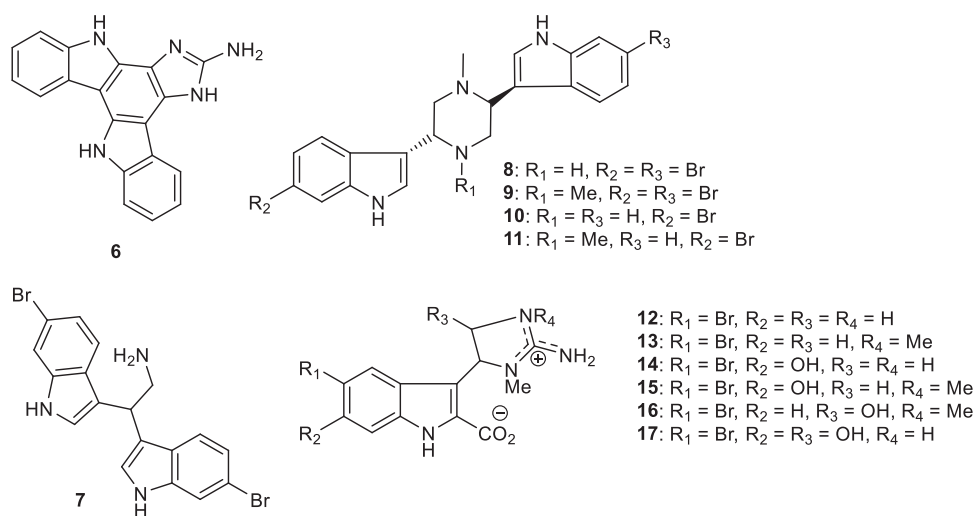


Fig. 2. Structures of guanidine alkaloids 6–17.

extracted from natural sources or manufactured by employing natural products as scaffolds or initiative materials. These natural products have a remarkable chemical variety that has progressed over thousands of years, resulting in a marvellous diversity in their pharmacological processes and drug-like qualities [1–3].

The marine environment has become a rich target for discovering

natural drugs due to the comparatively undiscovered biodiversity compared to terrestrial environments. The Ocean's world, with its 70% coverage of the global surface makes 95% of the total biosphere to potentially provide a great source of bioactive natural compounds [3,4]. Marine organisms are a tremendous resource of marine natural products (MNPs) which can be employed to treat life-threatening diseases

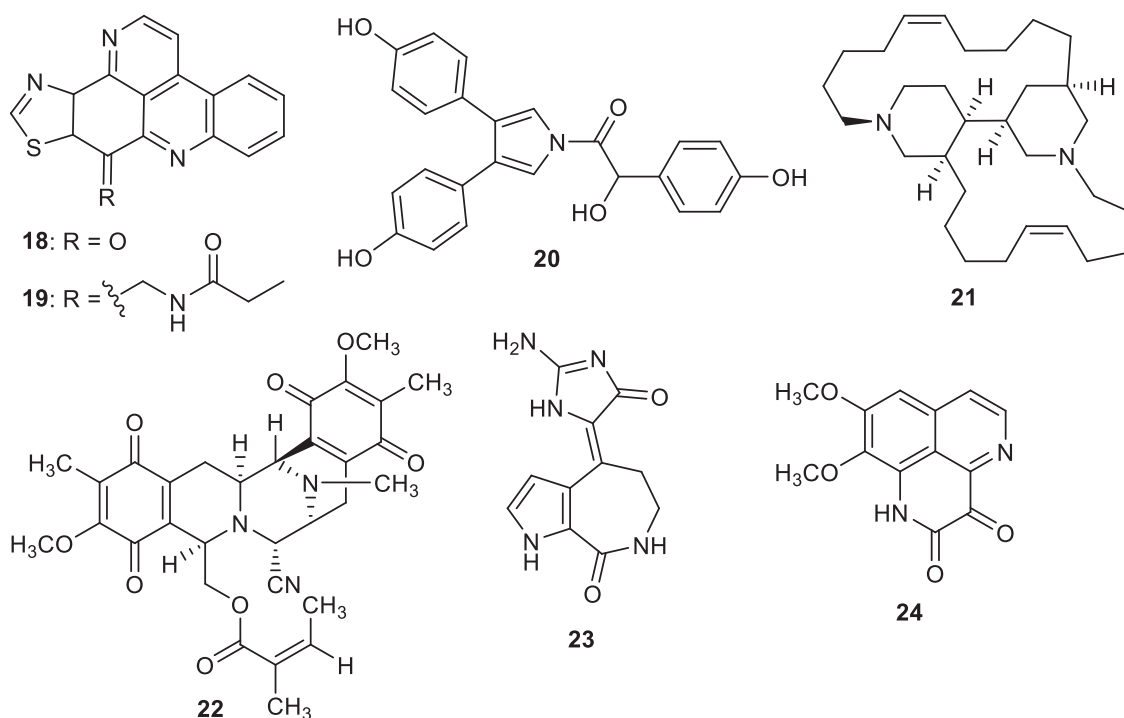


Fig. 3. Structures of alkaloids 18–24.

such as cancer [3,4]. So far, over 30,000 marine natural products have been isolated from the marine world [5]. Due to this exceptional diversity in varied chemical skeletons/scaffolds produced by marine organisms and microorganisms, the marine biosphere field is considered as the largest potential reservoir of bioactive natural products, able to offer a huge variety of active drugs [3,4].

There are some examples of approved anticancer therapeutic agents which can be considered analogs of MNPs. The anticancer drugs cytarabine (ara-C), and ecteinascidin 743 which were isolated from tunicate *Ecteinascidia turbinata*. Another example is eribulin mesylate which is a synthetic analog of the MNP halichondrin B. Another approved anticancer drug is brentuximab vedotin an antibody–drug conjugate (ADC), comprising of a tumor-specific antibody and the dolastatin 10 derivatives named monomethyl auristatin E [4]. Breast cancer is one of the most serious causes of death in women worldwide, especially in developed countries, and its occurrence is increasing. Breast cancer is a very common type of cancer and ~2–2.5 million cases are detected globally in women each year. An interesting statistic is that ~627,000 women died in 2018 due to breast cancer [6].

Regarding actual clinical trials, more than 50% of drugs are obtained directly from nature or are derivatives of natural products. To date, nature has provided almost 60% of approved drugs for cancer treatment or management. The marine world, more recently explored, is a most challenging source for investigations, offering new pathways of promising molecule development with anti-mammary activities. Quite recently Ahmed et al. [7] published a review about marine peptides used for the treatment of breast cancer and in 2014 Kalimuthu et al. [8] in their review covered only around thirty marine derived natural products which illustrated anticancer effects towards breast and prostate cancer cells. This current review deals with an overview of potential secondary metabolites which demonstrate cytotoxicity towards numerous breast cancer cells and which are isolated from marine sources such as marine sponges, marine seaweeds, tunicates, marine bacteria, and fungi covering a reasonable period up to December 2021.

## 2. Marine sponges

### 2.1. Alkaloids

#### 2.1.1. Guanidine alkaloids

Monanchomycalin C (1) and the previously identified ptilomycalin (2) (Fig. 1) are both pentacyclic guanidine alkaloids obtained from the far-eastern sponge *Monanchora pulchra*. Compounds 1 and 2 possessed cytotoxic effects towards the MDA-MB-231 with  $IC_{50}$ : of 8.2  $\mu$ M and 4.3  $\mu$ M, respectively [9]. Netamines C (3) and D (4) are also guanidine alkaloids which were produced by marine sponge *Biemna laboutei* and these compounds revealed cytotoxicity against the human breast MDA-MB-231 cell line with  $GI_{50}$  values of 2.6  $\mu$ M and 6.3  $\mu$ M, respectively [10].

Cramescidin 800 (5) belongs to the chemical class of guanidine alkaloids produced by the marine-derived sponge *Monanchora Viridis*. This compound 5 illustrated potent cytotoxic effects towards various triple negative breast cancer cells. Notably, 5 showed potent effects towards T11 and SUM159PT cells with  $IC_{50}$  values: 0.07 and 0.59  $\mu$ M (72 h), respectively. Interestingly, the cytotoxic effects of this alkaloid was higher (against T11 cells) than the standard cisplatin ( $IC_{50}$ : 0.70  $\mu$ M) and 5-Fluorouracil ( $IC_{50}$ : 0.87  $\mu$ M) [11].

#### 2.1.2. Indole alkaloids

Damirine A (6) (Fig. 2) was produced by sponge *Damiria* sp. and demonstrated significant cytotoxicity towards MDA-MB-468 with  $GI_{50}$  = 2.0  $\mu$ M [12]. 3,3'-BIEA (7) was isolated from sponge *Gellius* sp. and possessed cytotoxic effects towards MCF-7, MDA-MB-231 and VERO cells with  $IC_{50}$ : 3.4, 3.4, and 3.8  $\mu$ M respectively [13]. Dragmacidins A (8), B (9), I (10) and J (11) were produced by sponge *Dragmacidon* sp. Compounds 8, 10, 11 showed significant cytotoxic effects towards MDA-MB-231 with  $IC_{50}$ : 3.8, 4.7, and 7.5  $\mu$ M respectively while the  $IC_{50}$  of 16 was 28.0  $\mu$ M [14]. Capon et al. [15] reported trachycladindoles A–F (12–17) from marine sponge *Trachycladus laevispirulifer*. Interesting all compounds (except alkaloid 14) possessed significant cytotoxic effects towards MDA-MB-231 with  $GI_{50}$  < 3  $\mu$ M.

**Table 1**  
Compounds 1–94 having anti-breast cancer properties.

Name	Organism	Cell line	Cytotoxicity	Ref.
Monanchomycalin C (1)	<i>Monanchora pulchra</i>	MDA-MB-231	IC <sub>50</sub> : 8.2 μM	[9]
Ptilomycalin (2)	<i>Monanchora pulchra</i>	MDA-MB-231	IC <sub>50</sub> : 4.3 μM	[9]
Netamine C (3)	<i>Biemna laboutei</i>	MDA-MB-231	GI <sub>50</sub> : 2.6 μM	[10]
Netamine D (4)	<i>Biemna laboutei</i>	MDA-MB-231	GI <sub>50</sub> : 6.3 μM	[10]
Crambescidin 800 (5)	<i>Monanchora Viridis</i>	T11	IC <sub>50</sub> : 0.07 μM	[11]
		SUM159PT	IC <sub>50</sub> : 0.59 μM	
Damirine A (6)	<i>Damiria</i> sp.	MDA-MB-231	GI <sub>50</sub> : 2.0 μM	[12]
3,3'-BIEA (7)	<i>Gellius</i> sp.	MCF-7	IC <sub>50</sub> : 3.4 μM	[13]
		MDA-MB-231	IC <sub>50</sub> : 3.4 μM	
		VERO cells	IC <sub>50</sub> : 3.8 μM	
Dragmacidin A (8)	<i>Dragmacidon</i> sp.	MDA-MB-231	IC <sub>50</sub> : 3.8 μM	[14]
Dragmacidin B (9)	<i>Dragmacidon</i> sp.	MDA-MB-231	IC <sub>50</sub> : 28.0 μM	[14]
Dragmacidin I (10)	<i>Dragmacidon</i> sp.	MDA-MB-231	IC <sub>50</sub> : 4.7 μM	[14]
Dragmacidin J (11)	<i>Dragmacidon</i> sp.	MDA-MB-231	IC <sub>50</sub> : 7.5 μM	[14]
Trachycladindoles A (12)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 1.2 μM	[15]
Trachycladindoles B (13)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 2.7 μM	[15]
Trachycladindoles C (14)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 12.2 μM	[15]
Trachycladindoles D (15)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 2.4 μM	[15]
Trachycladindoles E (16)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 1.1 μM	[15]
Trachycladindoles F (17)	<i>Trachycladus laevispirulifer</i>	MDA-MB-231	GI <sub>50</sub> : 2.3 μM	[15]
Kuanoniamines A (18)	<i>Oceanapia Sagittaria</i>	MCF-7	GI <sub>50</sub> : 0.81 μM;	[16]
		MDA-MB-231	GI <sub>50</sub> : 10.23 μM	
Kuanoniamine C (19)	<i>Oceanapia Sagittaria</i>	MCF-7	GI <sub>50</sub> : 0.12 μM;	[16]
		MDA-MB-231	GI <sub>50</sub> : 0.73 μM	
7-Hydroxyneolamellarin A (20)	<i>Dendrilla nigra</i>	Human T-47D	IC <sub>50</sub> : 1.9 μM	[17]
Neopetrosiamine A (21)	<i>Neopetrosia proxima</i>	MCF-7	IC <sub>50</sub> : 3.5 μM	[18]
Renieramycin M (22)	<i>Xestospongia</i> sp.	MDA-MB-231	IC <sub>50</sub> : 3.8 nM	[19,20]
Debromohymenialdisine (DBH) (23)	<i>Stylissa flabeliformis</i>	MCF-7	IC <sub>50</sub> : 25 nM	[21]
2,3-Dihydro-2,3-dioxo aaptamine (24)	<i>Aaptos aaptos</i>	MCF-7	IC <sub>50</sub> : 40.7 μM	[22]
Microcionamides A (25)	<i>Clathria (Thalysias) abietina</i>	MCF-7	IC <sub>50</sub> : 125 nM	[23]
		SKBR-3	IC <sub>50</sub> : 98 nM	
Microcionamides B (26)	<i>Clathria (Thalysias) abietina</i>	MCF-7	IC <sub>50</sub> : 177 nM	[23]
		SKBR-3	IC <sub>50</sub> : 172 nM	
Pembamide (27)	<i>Cribrochalina</i> sp.	MDA-MB-231	GI <sub>50</sub> : 3.35 μM	[24]
Pipecolidepsin A (28)	<i>Homophymia lamellose</i>	MDA-MB-231	GI <sub>50</sub> : 0.7 μM	[25]
Pipecolidepsin B (29)	<i>Homophymia lamellose</i>	MDA-MB-231	GI <sub>50</sub> : 0.2 μM	[25]
Stylopeptide 2 (30)	<i>Stylorella</i> sp.	BT-549	Inhibition: 23%	[26]
Stylopeptide 2 (30)	<i>Stylorella</i> sp.	HS 578 T	Inhibition: 44%	[26]
Hemiasterlin A (31)	<i>Cymbastela</i> sp.	MCF-7	ED <sub>50</sub> : 0.089 μg/mL	[27]
Hemiasterlin B (32)	<i>Cymbastela</i> sp.	MCF-7	ED <sub>50</sub> : 0.066 μg/mL	[27]
Criamide B (33)	<i>Cymbastela</i> sp.	MCF-7	ED <sub>50</sub> : 6.8 μg/mL	[27]
Motuporin (34)	<i>Theonella swinhoei</i>	MCF-7	IC <sub>50</sub> : 12.4 μg/mL	[28]
Geodiamolides A (35), B (36), and H (37)	<i>Geodia</i> sp.	MCF-7, T47D	ED <sub>50</sub> : 9.82–620 nM	[29]
Cyclo(L-leucyl-L-prolyl) (CLP) (38)	<i>Rhaphisia pallida</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 73.4 μM IC <sub>50</sub> : 67.4 μM	[32]
Stylissatin B (39)	<i>Stylissa massa</i>	MCF-7	IC <sub>50</sub> : 4.8 μM	[33]
Scleritodermin A (40)	<i>Scleritoderma nodosum</i>	SKBR3	IC <sub>50</sub> : 0.670 μM	[34]
Compounds 41–44	<i>Lendenfeldia</i> sp.	MCF-7, MDA-MB-231, and T47D	IC <sub>50</sub> : 0.2–29 μM	[35]
Thorectandrol A (45)	<i>Thorectandra</i> sp.	MCF-7	IC <sub>50</sub> : 40.0 μg/mL	[36,37]
Thorectandrol B (46)	<i>Thorectandra</i> sp.	MCF-7	IC <sub>50</sub> : 30.0 μg/mL	[36,37]
palauolol (47)	<i>Thorectandra</i> sp.	MCF-7	IC <sub>50</sub> : 14.0 μg/mL	[36,37]
Sesterterpenoids 48–59	<i>Dysidea</i> sp.	MDA-MB-231	IC <sub>50</sub> : 4.2–72.4 μM	[38]
Sipholane A (60)	<i>Callyspongia siphonella</i>	MDA-MB-231	IC <sub>50</sub> : 37.5 μM	[39]
Sipholenone A (61)	<i>Callyspongia siphonella</i>	MDA-MB-231	IC <sub>50</sub> : 28.1 μM	[39]
3- <i>epi</i> -sodwanone K 3-acetate (63)	<i>Axinella</i> sp.	T47D	IC <sub>50</sub> : 22 μM	[41]
Sodwanones V (64)	<i>Axinella</i> sp.	MDA-MB-231	IC <sub>50</sub> : 23 μM	[41]
Dolabellane diterpene, 6,10,18-triacetoxy-2E,7E-dolabelladien (65)	<i>Luffariella variabilis</i>	MDA-MB-231	IC <sub>50</sub> : 11.5 μM	[42]
Metachromin U (66)	<i>Thorecta reticulate</i>	MCF-7	GI <sub>50</sub> : 29 μM	[43]
Metachromin V (67)	<i>Thorecta reticulate</i>	MCF-7	GI <sub>50</sub> : 3.2 μM	[43]
Metachromin W (68)	<i>Thorecta reticulate</i>	MCF-7	GI <sub>50</sub> : 107 μM	[43]
3'-Aminoavarone (69)	<i>Dysidea</i> sp.	MCF-7-MB-231	IC <sub>50</sub> : 2.0 μg/mL	[44]
Liphagal (70)	<i>Aka coralliphaga</i>	MDA-468	IC <sub>50</sub> : 1.58 μM	[45,46]
Aplysamine-2 (71)	<i>Pseudoceratina purpurea</i>	MCF-7	IC <sub>50</sub> : 25.7 μM	[47]
<i>E,Z</i> -Psammaphin A (72)	<i>Dendrilla lacunose</i>	MDA-MB-231	IC <sub>50</sub> : 0.019 μM	[48]
Psammaphin E (73)	<i>Dendrilla lacunose</i>	MDA-MB-231	IC <sub>50</sub> : 0.257 μM	[48]
<i>E,E</i> -Psammaphin K (74)	<i>Dendrilla lacunose</i>	MDA-MB-231	IC <sub>50</sub> : 0.038 μM	[48]
<i>(E,E)</i> -Psammaphin A (75)	<i>Dendrilla lacunose</i>	MDA-MB-231	IC <sub>50</sub> : 0.037 μM	[48]
Bisaprasin (76)	<i>Dendrilla lacunose</i>	MDA-MB-231	IC <sub>50</sub> : 0.948 μM	[48]
Aragusterol A (YTA0040) (77)	<i>Xestospongia</i>	MCF-7	IC <sub>50</sub> : 0.28 nM	[49]
Dictyostatin-1 (78)	<i>Spongia</i> sp.	MCF-7	IC <sub>50</sub> : 1.5 nM	[50]
Peloruside A (79)	<i>Mycale hentscheli</i>	MDA-MB-231	IC <sub>50</sub> : 3.8 nM	[51]
Hemimycalins C (80)	<i>Hemimycale</i> sp.	MDA-MB-231	IC <sub>50</sub> : 28.5, μM	[52]
Hemimycalins D (81)	<i>Hemimycale</i> sp.	MDA-MB-231	IC <sub>50</sub> : 31.7, μM	[52]
Hemimycalins E (82)	<i>Hemimycale</i> sp.	MDA-MB-231	IC <sub>50</sub> : 21.5 μM	[52]
Hippotulosas A (83)	<i>Hippospongia fistulosa</i>	MCF-7	IC <sub>50</sub> : 75.6 μM	[53]

(continued on next page)

Table 1 (continued)

Name	Organism	Cell line	Cytotoxicity	Ref.
Furospinulosin-1 (84)	<i>Hippospongia fistulosa</i>	MCF-7	IC <sub>50</sub> : 86.9 μM	[53]
13-Apoastaxanthinone (85)	<i>Clathria reinwardti</i>	MCF-7	IC <sub>50</sub> : 79.2 μM	[54]
9-apoastaxanthinone (86)	<i>Clathria reinwardti</i>	MCF-7	IC <sub>50</sub> : 84.4 μM	[54]
2,3-Dehydro-4-oxo-β-Ionone (87),	<i>Clathria reinwardti</i>	MCF-7	IC <sub>50</sub> : 75.7 μM	[54]
9 4-(2',3',4'-Trimethylphenyl)-but-3(E)-en-2-one (88)	<i>Clathria reinwardti</i>	MCF-7	IC <sub>50</sub> : 33.1 μM	[54]
22,23-dihydro-24-nordankasterone A (89)	<i>Luffariella variabilis</i>	MDA-MB-231	IC <sub>50</sub> : 7.4 μM	[45]
Steroid 90	<i>Phyllospongia sp.</i>	MCF-7	IC <sub>50</sub> : 8.8 μM	[55]
Steroid 91	<i>Phyllospongia sp.</i>	MCF-7	IC <sub>50</sub> : 10.3 μM	[55]
Steroid 92	<i>Phyllospongia sp.</i>	MCF-7	IC <sub>50</sub> : 36.5 μM	[55]
Steroid 93	<i>Phyllospongia sp.</i>	MCF-7	IC <sub>50</sub> : 47.1 μM	[55]
Steroid 94	<i>Phyllospongia sp.</i>	MCF-7	IC <sub>50</sub> : 3.9 μM	[55]

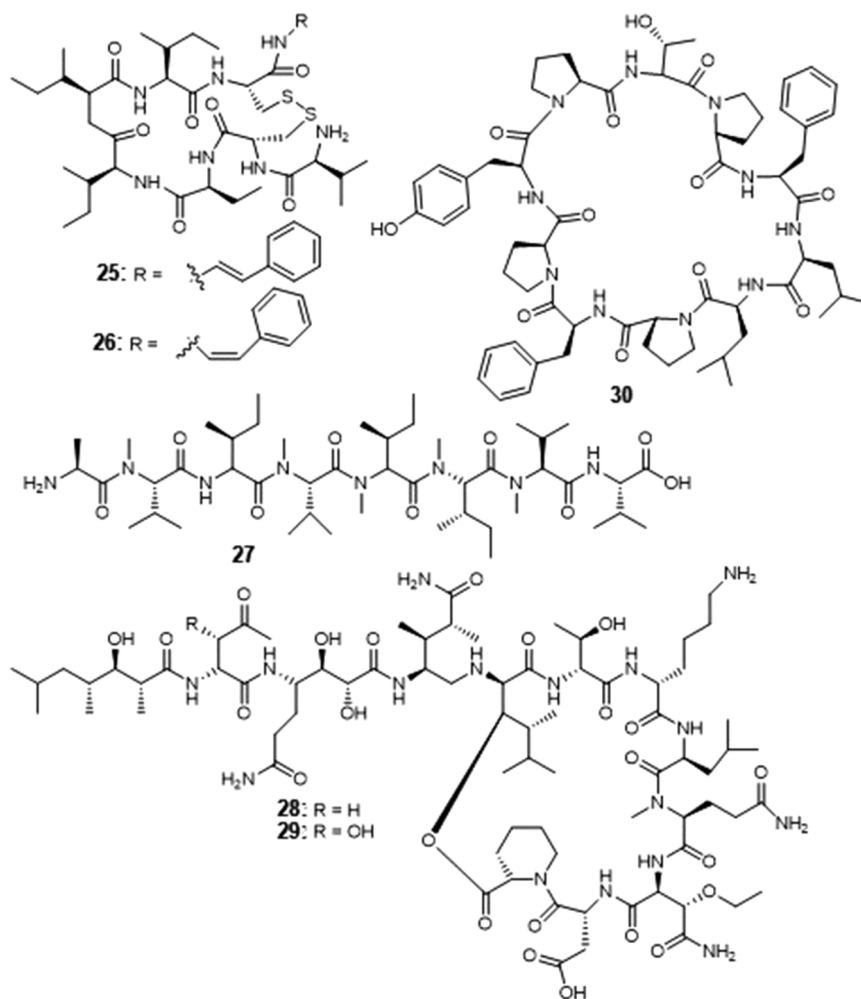


Fig. 4. Structures of peptides 25–30.

### 2.1.3. Miscellaneous alkaloids

Kuanoniamines A (18) and C (19) (Fig. 3) represent pyridoacridine alkaloids that were isolated from marine sponge *Oceanapia Sagittaria* (Sollas). Kuanoniamine A (18) revealed inhibitory activity against the growth of MCF-7 and MDA-MB-231 cell lines with GI<sub>50</sub>: 0.81 ± 0.11 and 10.23 ± 3.35 μM, respectively. Kuanoniamine C (19), although less effective, showed a higher selectivity against the MCF-7 and MDA-MB-231 cells with GI<sub>50</sub>: 0.12 ± 0.07 and 0.73 ± 0.27 μM, respectively [16]. 7-Hydroxyneolamellarin A (20) is a lamellarin-like phenolic pyrrole purified from the marine sponge *Dendrilla nigra* and was shown to prevent hypoxia-induced HIF-1 stimulation and hypoxia-induced vascular endothelial growth factor (VEGF) initiation in the human T47D cell line with an IC<sub>50</sub>: 1.9 μM [17]. Neopetrosiamine A (21) is another tetracyclic

bis-piperidine alkaloid produced by sponge *Neopetrosia proxima*, collected from the western side of the beach Puerto Rico. Compound 8 possesses resilient inhibitory activity against MCF-7 with an IC<sub>50</sub>: 3.5 μM [18].

Renieramycin M (22) (Fig. 3) is a tetrahydroisoquinoline reported from the blue sponge *Xestospongia sp.* [19]. Compound 22 displayed cytotoxic activity against human MDA-MB-231 cell lines with an IC<sub>50</sub> value of 3.8 nM [20]. Debromohymenialdisine (DBH) (23) was produced by the marine sponge *Stylissa flabeliformis*, collected from Motupore Island in Papua New Guinea. DBH also showed moderate cytotoxicity towards MCF-7 cancer cell lines with an IC<sub>50</sub> value of 25 nM. In association with radiotherapy, DBH at a non-cytotoxic concentration of 3 μM was shown to reduce pCHK1/2 expression and

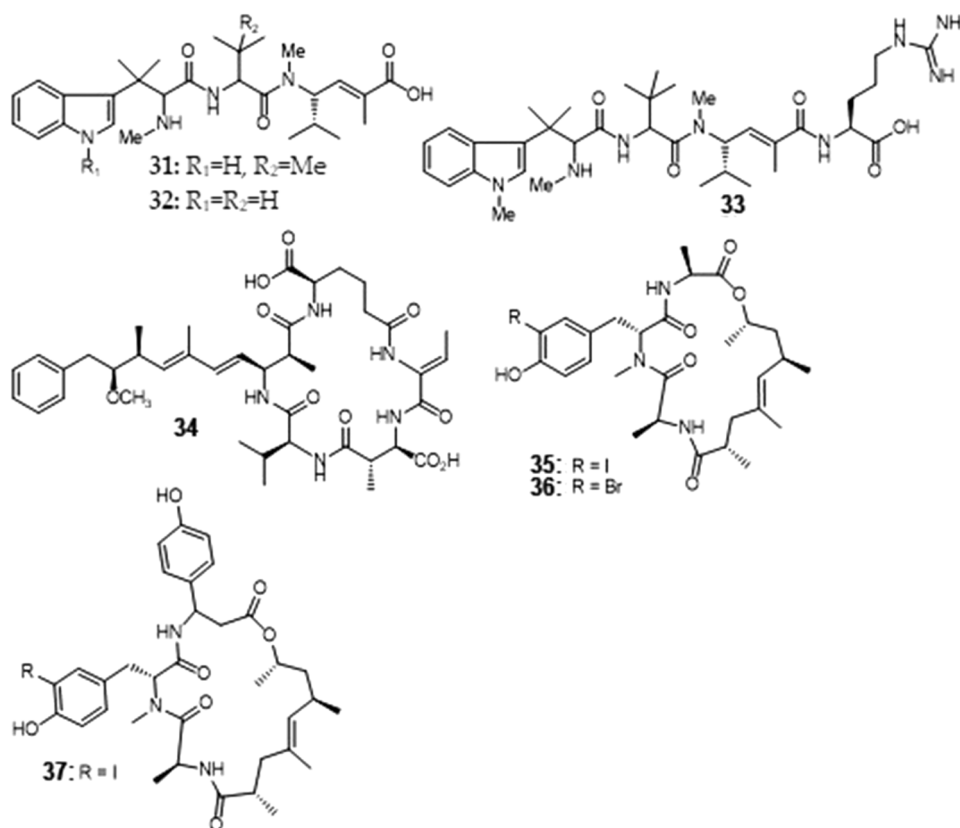


Fig. 5. Structures of peptides 31–37.

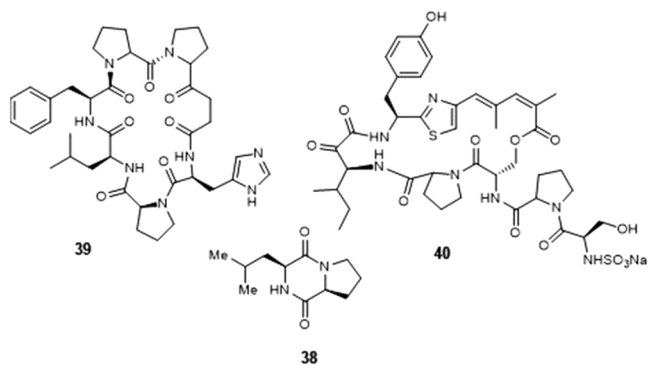


Fig. 6. Structures of peptides 38–40.

proliferation in MCF-7 breast cancer cells. It also decreased the growth rates of stem cell cancer in a time-dependent manner [21]. On the other hand, 2,3-dihydro-2,3-dioxo aptamine (24) showed activity against MCF-7 with  $IC_{50}$ : 40.7  $\mu M$  (Table 1) and this compound was produced by Sponge *Aaptos aaptos* [22].

## 2.2. Peptides

The two linear peptides microcionamides A (25) and B (26) (Fig. 4), were produced by sponge *Clathria (Thalysias) abietina* reported from the coastline of the Philippines. These geometric isomeric peptides 25 and 26 displayed potential cytotoxicity towards MCF-7 with  $IC_{50}$ : 125 and 177 nM, respectively. In addition peptides 25 and 26 demonstrated significant effects against SKBR-3 with  $IC_{50}$ : 98 and 172 nM, respectively. Notably, the effects of these peptides towards MCF-7 were higher than standard doxorubicin ( $IC_{50}$ : 257 nM) [23]. Pembamide (27) is

produced by the marine sponge *Cribrorchalina* sp. and possesses potent cytotoxicity against MDA-MB-231 with a  $GI_{50}$ : 3.35  $\mu M$  [24]. In another report, pipecolidepsin A (28) and B (29) were described as being isolated from the marine sponge *Homophymia lamellose* and displayed potent cytotoxic effects against MDA-MB-231 with a  $GI_{50}$ : 0.7 and 0.2  $\mu M$ , respectively [25]. The cycloheptapeptide, stylopeptide 2 (30) was isolated from the marine sponge *Stylotella* sp. and illustrated cytotoxicity against BT-549 and HS 578 T with growth inhibition of 77% and 56%, respectively [26].

Hemiasterlin A (31), B (32), and criamide B (33) (Fig. 5) were produced by the marine sponge *Cymbastela* sp. Notably, peptides 31–33 displayed potent cytotoxicity against MCF-7 with the  $ED_{50}$ : values of 0.089, 0.066, and 6.8  $\mu g/mL$  respectively [27]. Motuporin (34), a cytotoxin was produced by sponge *Theonella swinhoei* and exhibited cytotoxicity towards MCF-7 with  $IC_{50}$ : 12.4  $\mu g/mL$  [28]. Another series of cyclic depsipeptides known as geodiamolides A (35), B (36), and H (37) were isolated from the Caribbean sponges *Geodia* sp. All these peptides were significantly active towards T47D and MCF-7 with  $EC_{50}$  ranging from 9.82 to 620 nM. Compounds 35 and 37 were active against T47D cells with  $EC_{50}$  values of 18.82 and 38.36 nM, respectively. In addition, peptides 35 and 37 revealed a strong activity against MCF-7 cancer cell lines with  $EC_{50}$  values of 17.83 and 9.82 nM, respectively [29]. In another study, geodiamolide H (37) was also shown to be active against MDA-MB-231/ATCC with  $TGI: 4.33 \times 10^{-7} M$  [30].

Cyclo(L-leucyl-L-prolyl) (CLP, 38) (Fig. 6) is a homo-detic cyclic peptide, isolated from the marine sponge *Rhaphisia pallida* [31] and exhibited an anti-propagative cytotoxic effect towards human the triple-negative breast cancers MDA-MB-231 and MDA-MB-468 with  $IC_{50}$  values of 73.4 and 67.4  $\mu M$ , respectively [32]. It has confirmed that 38 induced cell cycle arrest with the result of reducing the expression of cyclins D<sub>1</sub>, CDK4, PAK, Rac<sub>1</sub>, and p27kip<sub>1</sub>, suggesting a mechanism of action through EGFR and CD151 signaling pathways [32]. Stylistatin B (39) is a heptapeptide produced by marine sponge *Stylissa massa*, which

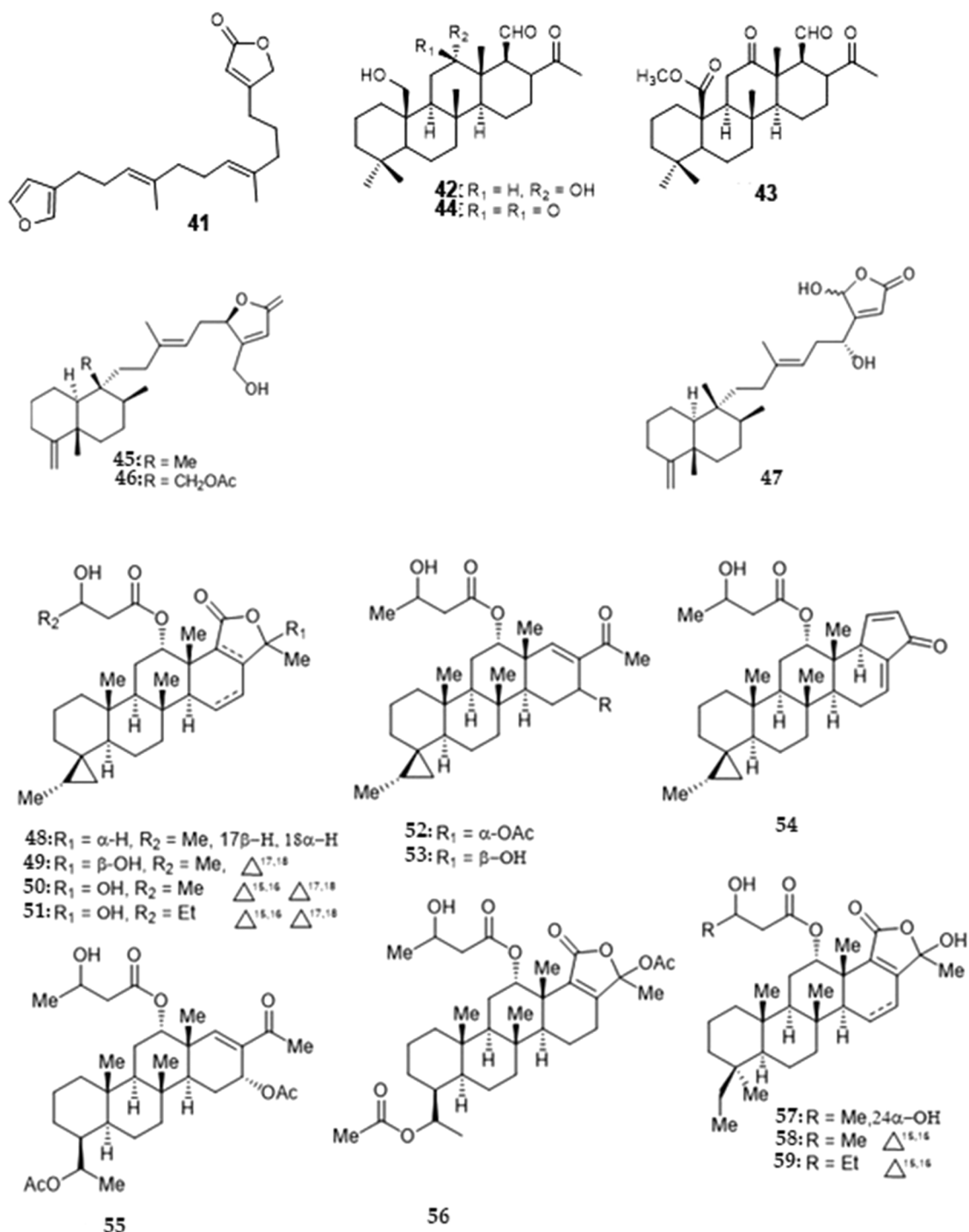


Fig. 7. Structures of Sesterterpenes 41–59.

demonstrated inhibitory effects towards MCF-7 with an IC<sub>50</sub> value of 4.8 μM [33]. Scleritodermin A (40) is a cyclic peptide isolated from the lithistid sponge *Scleritoderma nodosum*, was highly cytotoxic against the human breast SKBR3 cancer cell line with an IC<sub>50</sub> value of 0.670 μM [34].

### 2.3. Terpenes

#### 2.3.1. Sesterterpenes

Furospongolide (41) (Fig. 7), a furanolipid-type terpene, together with the sesterterpenes 22-hydroxy-24-methyl-12α-hydroxy-24-

oxoscalar-16-en-25-al (42), 24-methyl-12,24,25-trioxoscalar-16-en-22-oate (43) and 22-hydroxy-24-methyl-12,24-dioxoscalar-16-en-25-al (44) were isolated from the marine sponge *Lendenfeldia* sp., collected off the islands of the State of the Northern Mariana [35]. These compounds were evaluated for their hypoxia-inducible factor-1 (HIF-1) inhibitory activity and tumor cell lines cytotoxicity. The HIF-1 transcription factor is a heterodimer constituted of two sub-units HIF-1α and ARNT1/HIF-1β. Terpenes 41–44 were tested towards the MCF-7, MDA-MB-231, and T47D cells proliferation in normoxic hypoxic (Hyp, 1% O<sub>2</sub>) and normal (95% air) conditions and revealed IC<sub>50</sub> values ranging from 0.2 to 29 μM [35].



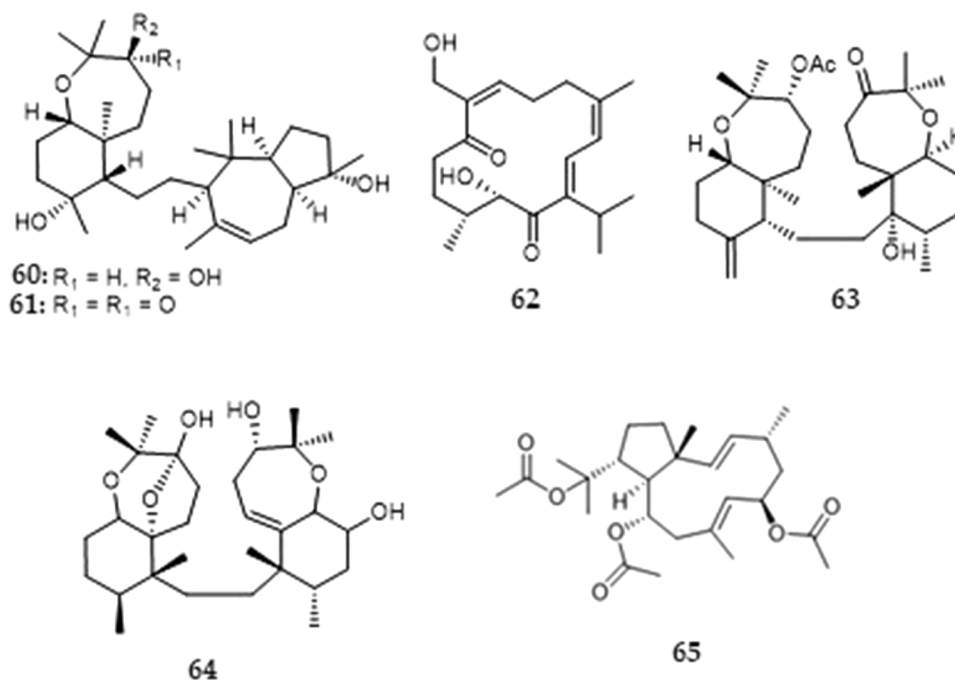


Fig. 8. Structures of Diterpenes and triterpenes 60–65.

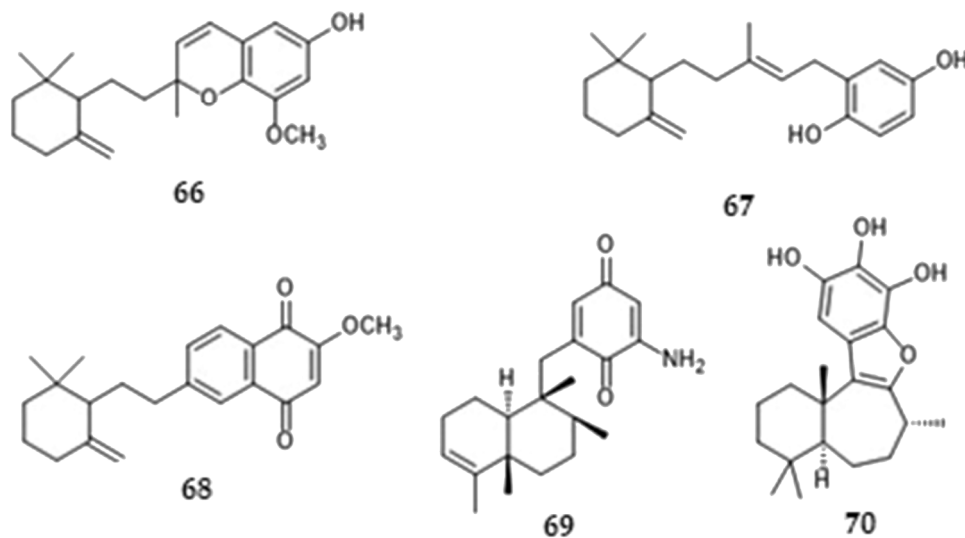


Fig. 9. Structures of Meroterpenoids 66–70.

Thorectandrols A (45), B (46), and palauolol (47), sesterterpenoids containing a bicarbocyclic frame, were identified from a marine Palauan sponge *Thorectandra* sp. Thorectandrols A (45) and B (46) displayed good cytotoxicity towards the MCF-7 cell line with  $IC_{50}$ : 40.0 and 30.0  $\mu\text{g}/\text{mL}$ , respectively. It is interesting to note that compound 47 displayed better effects than metabolites 45 and 46 with an  $IC_{50}$  value of 14.0  $\mu\text{g}/\text{mL}$  [36,37]. Sesterterpenoids 48–59, were produced by sponge *Dysidea* sp. and possessed cytotoxicity towards MDA-MB-231 with  $IC_{50}$  ranging from 4.2 and 72.4  $\mu\text{M}$  respectively. Notably compound 65 was the most potent against MDA-MB-231 with  $IC_{50}$ : 4.2  $\mu\text{M}$  [38].

### 2.3.2. Diterpenes and triterpenes

Sipholane A (60) and sipholenone A (61) are unusual cyclized triterpenes isolated from the Red Sea sponge *Callyspongia siphonella* (Fig. 8). Compounds 60 and 61 showed mild cytotoxicity against the metastatic human breast MDA-MB-231 cancer cell line, demonstrating

$IC_{50}$  values of 37.5 and 28.1  $\mu\text{M}$ , respectively [39]. Flabellatene A (62), a diterpene isolated from the marine sponge *Lissodendoryx flabellate*, illustrated anti-proliferative effects against MCF-7 in a dose-dependent manner [40]. The marine sponge *Axinella* sp. produced sodwanone triterpenes named 3-*epi*-sodwanone K 3-acetate (63) and sodwanones V (64). Triterpene 63 displayed cytotoxic effects towards T47D cell with  $IC_{50}$ : 22  $\mu\text{M}$  while 64 showed inhibited MDA-MB-231 with an  $IC_{50}$ : 23  $\mu\text{M}$  [41]. Dolabellane diterpene, 6,10,18-triacetoxy-2E,7E-dolabelladien (65) was produced by sponge *Luffariella variabilis* and demonstrated cytotoxicity towards MDA-MB-231 with  $IC_{50}$ : 11.5  $\mu\text{M}$  [42].

### 2.3.3. Meroterpenoids

Metachromins U-W (66–68) (Fig. 9) are merosesquiterpenoids isolated from the marine sponge *Thorecta reticulata*. Metachromin V (67) illustrated cytotoxicity towards the MCF-7 cell line with a  $GI_{50}$ : 3.2  $\mu\text{M}$ , while compounds 66 and 68 showed lower potent activity with  $GI_{50}$ :

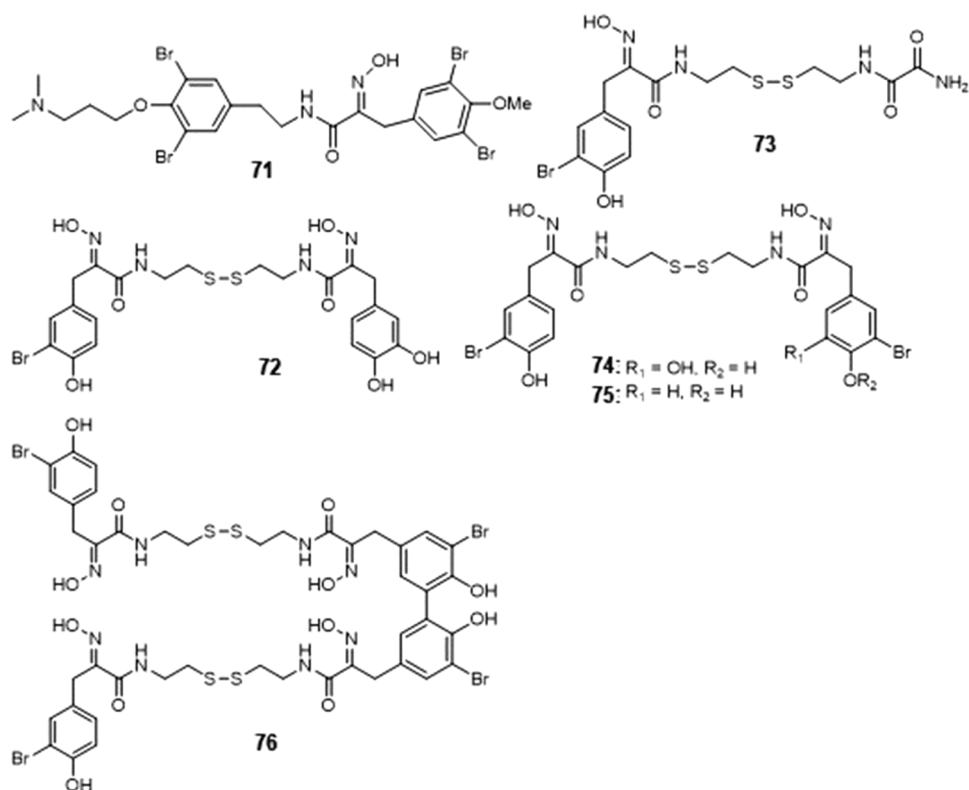


Fig. 10. Structures of bromotyrosine and psammoplin derivatives 71–76.

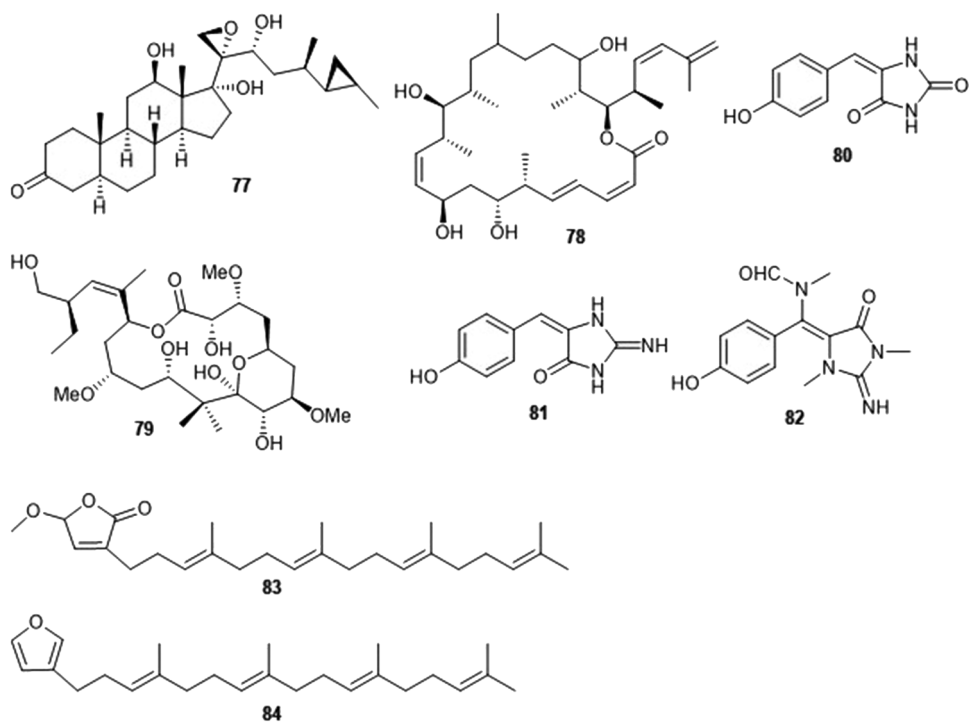


Fig. 11. Structures of miscellaneous compounds 77–84.

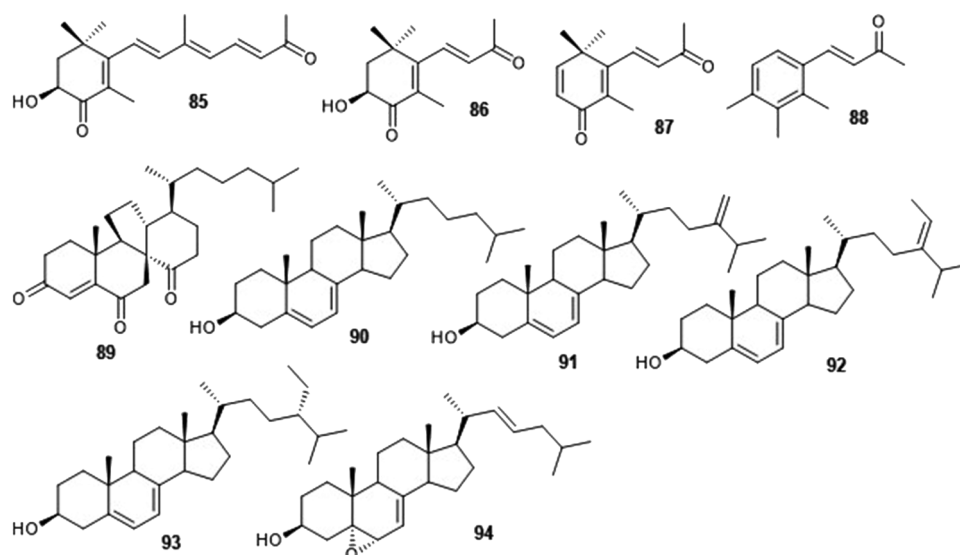


Fig. 12. Structures of miscellaneous compounds 85–94.

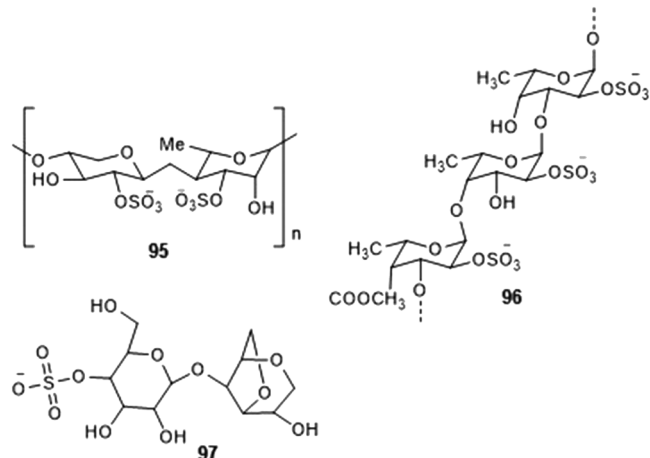


Fig. 13. Structures of polysaccharides 95–97.

values of 29 and 107  $\mu\text{M}$ , respectively [43]. Meroterpene, 3'-amino-avarone (69), is produced by the marine sponge *Dysidea* sp. and inhibited the MDA-MB-231 cancer cell with an  $\text{IC}_{50}$  of 2  $\mu\text{g}/\text{mL}$  [44]. The meroterpene liphagal (70) was produced by marine sponge *Aka coralliphaga* collected off the Dominican coast [45]. Liphagal (70) showed cytotoxic effects towards the MDA-468 cell line with an  $\text{IC}_{50}$ : 1.58  $\mu\text{M}$  [46].

#### 2.4. Bromotyrosine and psammaphin derivatives

The bromotyrosine derivative aplysamine-2 (71) (Fig. 10), was produced by marine sponge *Pseudoceratina purpurea*. This compound displayed cytotoxicity against MCF-7 with an  $\text{IC}_{50}$  value of 25.7  $\mu\text{M}$  [47]. Five known compounds viz. (*E,Z*)-psammaphin A (72), psammaphin E (73), (*E,E*)-psammaphin K (74), (*E,E*)-psammaphin A (75), and bisaprasin (76) were obtained from the marine sponge *Dendrilla lacunose*. Compounds 72–76 illustrated potent activity against the MDA-MB-231-derived organotropic subclones with  $\text{IC}_{50}$ : 0.019, 0.257, 0.038, 0.037, and 0.948  $\mu\text{M}$ , respectively [48].

#### 2.5. Miscellaneous

Aragusterol A (YTA0040) (77) (Fig. 11), a steroid obtained from marine sponge *Xestospongia* collected from Okinawan, showed potent potential towards MCF-7 with an  $\text{IC}_{50}$ : 0.28 nM [49]. Dictyostatin-1 (78) is a macrocyclic lactone from the Republic of the Maldives and was identified from a marine sponge *Spongia* sp. Compound 78 showed effective activity against MCF-7 cell lines with  $\text{IC}_{50}$ : 1.5 nM [50]. The polyketide peloruside A (79) isolated from the marine sponge *Mycale hentscheli* possesses a non-toxic and specific binding site. This molecule possessed effects towards MCF-7 cancer cell line, possessing an  $\text{IC}_{50}$  value of 3.8 nM and blocking the  $\text{G}_2/\text{M}$  at 25 nM. Compound 79 was shown to reduce the average growth rate and length of the tumor by 24% and 41%, respectively [51]. Hemimycalins C–E (80–82) were produced by sponge *Hemimycale* sp. and demonstrated cytotoxicity

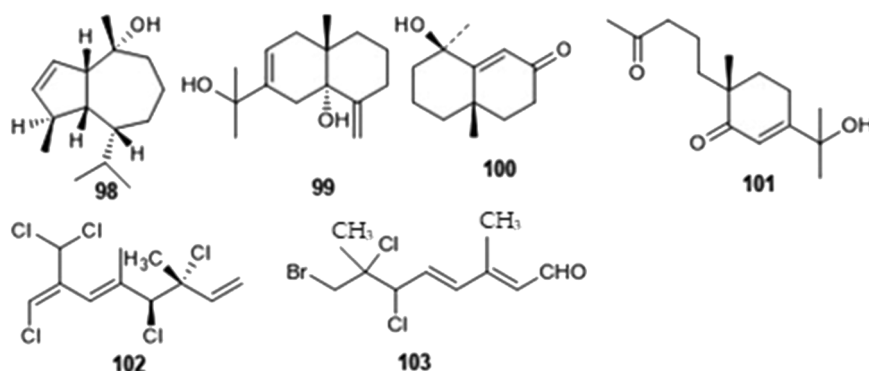


Fig. 14. Structures of sesquiterpenes and monoterpenes 98–103.

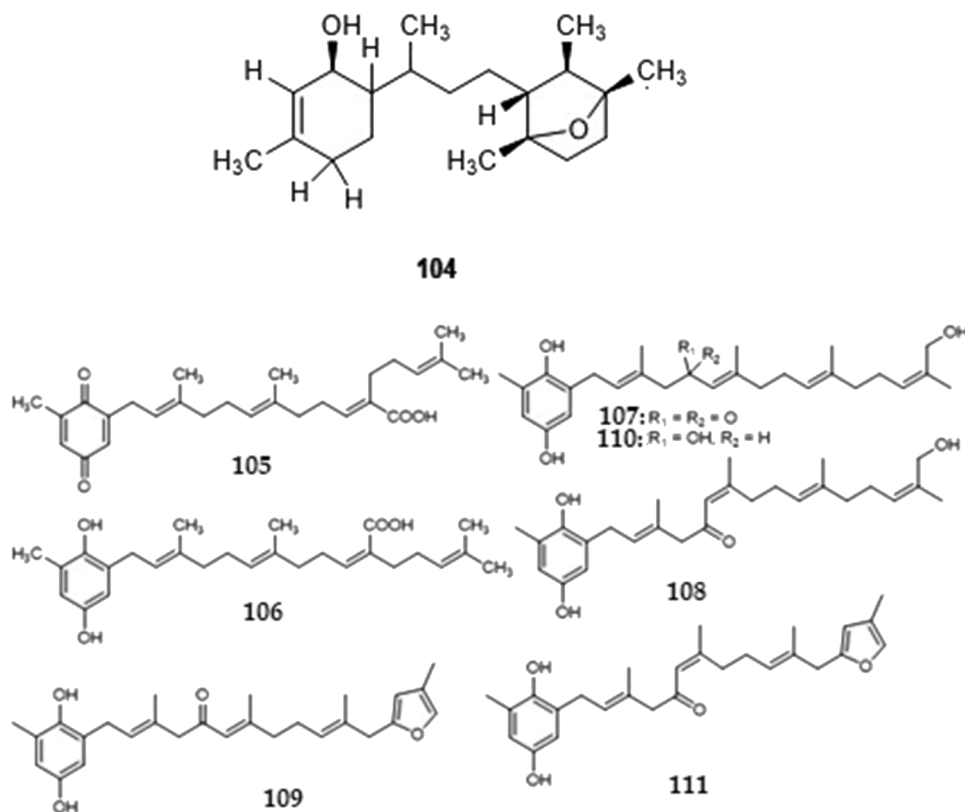


Fig. 15. Structures of Meroterpenoids and Diterpenes 104–111.

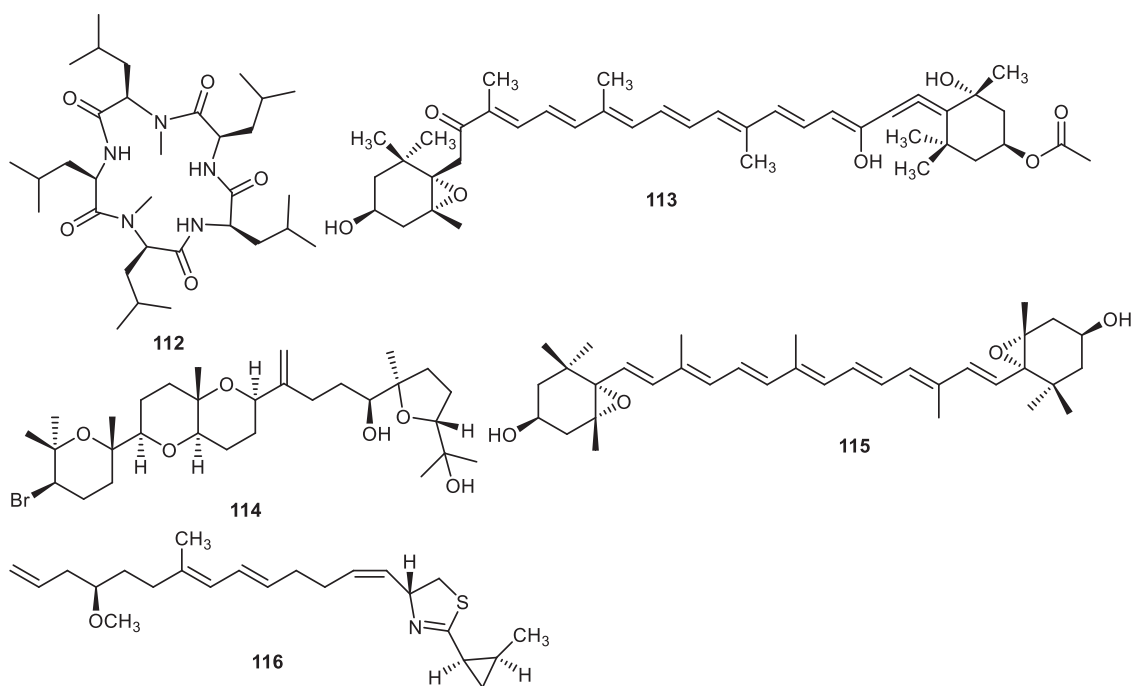


Fig. 16. Structures of Miscellaneous compounds 112–116.

towards MDA-MB-231 with IC<sub>50</sub>: 28.5, 31.7, and 21.5  $\mu$ M, respectively [52]. In another study, hippotulosas A (83) and furospinulosin-1 (84) were produced by sponge *Hippospongia fistulosa* and both compounds possessed cytotoxic effects towards MCF-7 as 75.6 and 86.9  $\mu$ M, respectively [53].

13-Apoastaxanthinone (85), 9-apoastaxanthinone (86), 2,3-dehydro-4-oxo- $\beta$ -ionone (87), and 4-(2',3',4'-trimethylphenyl)-but-3(E)-en-2-one (88) were reported from Sponge *Clathria reinwardti* and demonstrated cytotoxicity towards MCF-7 with IC<sub>50</sub>: 79.2, 84.4, 75.7 and 33.1  $\mu$ M respectively [54]. Steroid, 22,23-dihydro-24-nordankasterone

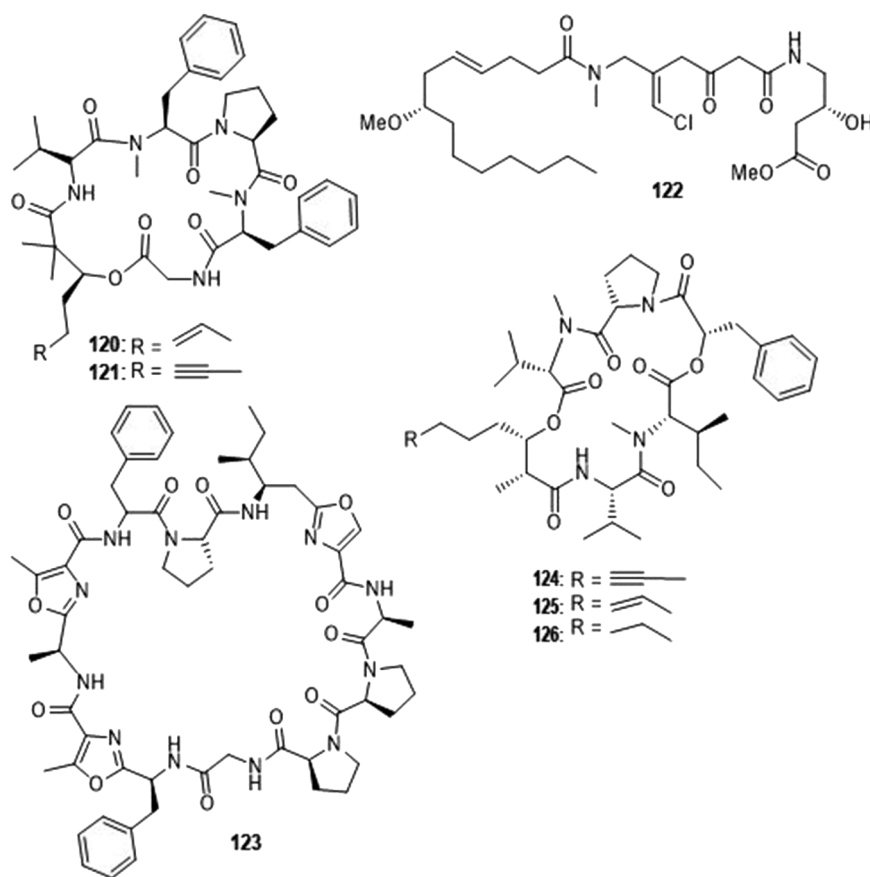


Fig. 18. Structures of peptides 120–126.

A (**89**) was produced by sponge *Luffariella variabilis* and demonstrated cytotoxicity towards MDA-MB-231 with  $IC_{50}$ :  $7.4 \mu M$  [45]. Steroids **90–94** were reported from sponge *Phyllospongia* sp. and showed activities towards MCF-7 with  $IC_{50}$ : 8.8, 10.3, 36.5, 47.1, and  $3.9 \mu M$  respectively [55] (Fig. 12).

### 3. Marine seaweeds or algae

#### 3.1. Polysaccharides

The polysaccharide **95** (Fig. 13) isolated from the green algae *Ulva lactuca*, has been proven to possess *in vivo* and *in vitro* anti-breast cancer activity. In human MCF-7 cancer cells, compound **95** showed an inhibitory effect with an  $IC_{50}$  value of  $224.716 \mu g/mL$ . In DMBA cancer cells-induced rats, compound **95** hindered the breast-histological and carcinogenic lesions when treated for ten weeks. It is also reported that polysaccharides extracted from this seaweed have possible chemopreventive properties against mammary carcinogenesis by increasing apoptosis, reducing oxidative stress, and enhancing the antioxidant defense system [56]. Fucooidan **96** represents a sulfated polysaccharide isolated from different marine brown seaweeds such as *Saccharina japonica*. At  $200 mg/mL$ , this material showed antitumor activity against T-47D with 46% proliferation inhibition after 48 h [57]. Native carrageenan ( $\kappa$ ) (**97**) was isolated from the red seaweed *Kappaphycus alvarezii*. Compound **97** showed activity against cell viability in a dose-dependent manner in breast adenocarcinoma MCF-7 cell lines, displaying an  $IC_{50}$  value of  $123.8 \mu g/mL$  [58].

#### 3.2. Sesquiterpenes and monoterpenes

The guai-2-en-10 $\alpha$ -ol (**98**) (Fig. 14) is a guaiane sesquiterpenoid,

reported from the marine green seaweed *Ulva fasciata*. Compound **98** revealed growth inhibition in the triple-negative breast cancer (TNBC) MDA-MB-231 cancer cell line with  $IC_{50}$  values of  $17.35 \pm 1.23$  (after 12 h) and  $12.98 \pm 1.11 \mu M$  (after 24 h), respectively. Compound **98** hindered the cell cycle in the G1 phase of the MDA MB-231 cancer cell line, leading to apoptosis. The downregulation of both PI3K and EGFR proteins was observed and this suggesting its anticancer potential via the EGFR/PI3K/Akt pathway [59].

Two eudesmane sesquiterpenes named eudesma-4(15),7-diene-5,11-diol (**99**) and chabrolidione B (**101**), along with trinor-sesquiterene, teuhetenone (**100**) were produced by the red alga *Laurencia obtuse*. Compounds **99–101** displayed cytotoxic effects towards MCF-7 with  $IC_{50}$ : of 39.5, 22.8, and  $63.6 \mu M$ , respectively. Notably, teuhetenone (**100**) displayed a higher activity than cisplatin ( $IC_{50}$ :  $59 \mu M$ ) [60]. RU015 (**102**) and RU008 (**103**) represent polyhalogenated monoterpenes isolated from the marine red algae *Plocamium* sp. Compound **102** showed potential cytotoxicity against three breast cancer cells including MDA-MB-231, MCF-7 and MCF12A with  $IC_{50}$ : 6.2, 3.6 and  $3.5 \mu M$ , respectively. Similarly, compound **103** illustrated cytotoxicity towards the MDA-MB-231 with an  $IC_{50}$ :  $82.7 \mu M$  [61].

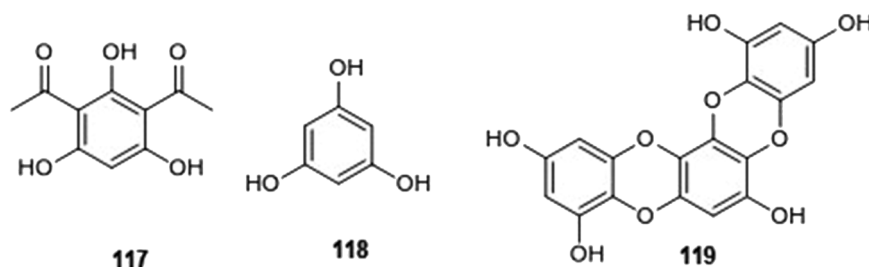
#### 3.3. Meroterpenoids and diterpenes

Laurenditerpenol (**104**) (Fig. 15), a diterpene isolated from the lipid extract of the marine red alga *Laurencia intricate*, was shown to inhibit Hypoxia-Inducible Factor-1 (HIF-1). This latter is a heterodimer constituted of two subunits: HIF-1 $\alpha$ , which is regulated by cellular oxygen levels, and HIF-1 $\beta$  that is constitutively expressed and identified as a valuable molecular target for anticancer drug discovery. More precisely, compound **104** inhibited HIF-1 activation in T-47D cell line with an  $IC_{50}$ :  $0.4 \mu M$  [62]. Sargaquinoic acid (SQA, **105**) and

**Table 2**  
Compounds 95–119 with cytotoxic effects.

Name	Organism	Cell line	Cytotoxicity	Ref.
Polysaccharide (95)	<i>Ulva lactuca</i>	MCF-7	IC <sub>50</sub> : 224.716 µg/ mL	[56]
Fucoidan (96)	<i>Saccharina japonica</i>	T-47D	Inhibition: 46%	[57]
Carrageenan (κ) (97)	<i>Kappaphycus alvarezii</i>	MCF-7	IC <sub>50</sub> : 123.8 µg/mL	[58]
Guai-2-en-10α-ol (98)	<i>Ulva fasciata</i>	MDA-MB-231	IC <sub>50</sub> : 12.98 µM	[59]
Eudesma-4(15),7-diene-5,11-diol (99)	<i>Laurencia obtuse</i>	MCF-7	IC <sub>50</sub> : 39.5 µM	[60]
Teuhenone (100)	<i>Laurencia obtuse</i>	MCF-7	IC <sub>50</sub> : 22.8 µM	[60]
chabrolidione B (101)	<i>Laurencia obtuse</i>	MCF-7	IC <sub>50</sub> : 63.6 µM	[60]
RU015 (102)	<i>Plocamium</i> sp.	MDA-MB-231 MCF-7 MCF12A	IC <sub>50</sub> : 6.2 µM IC <sub>50</sub> : 3.6 µM IC <sub>50</sub> : 3.5 µM	[61]
RU008 (103)	<i>Plocamium</i> sp.	MDA-MB-231	IC <sub>50</sub> : 82.7 µM	[61]
Laurenditerpenol (104)	<i>Laurencia intricata</i>	T-47D	IC <sub>50</sub> : 0.4 µM	[62]
Sargaquinoic acid (SQA) (105)	<i>Sargassum heterophyllum</i>	MBA-MB-231	IC <sub>50</sub> : 67.4 µM	[61]
Sargahydroquinoic acid (SHQA) (106)	<i>Sargassum heterophyllum</i>	MBA-MB-231	IC <sub>50</sub> : 159.5 µM	[61]
tetraprenyltoluquinol derivatives (107–111)	<i>Cystoseira crinite</i>	MCF-7	GI <sub>50</sub> : 0.9–2.5 µg/ mL	[63]
Galaxamide (112)	<i>Galaxaura filamentosa</i>	MCF-7	IC <sub>50</sub> : 14.0 µg/mL	[64]
Fucoxanthin (FXN) (113)	<i>Sargassum heterophyllum</i>	MBA-MB-231	IC <sub>50</sub> : 109.4 µM	[61]
Dehydrothyriferol (114)	<i>Sargassum heterophyllum</i>	T-47D MBA-MB-231	IC <sub>50</sub> : 7.09 µM IC <sub>50</sub> : 14.8 µM	[65]
Violaxanthin (115)	<i>Dunaliella tertiolecta</i>	MCF-7	GI <sub>50</sub> : 56.1 µg/mL	[66]
Curacin A (116)	<i>Lyngbya majuscula</i>	MCF-7	GI <sub>50</sub> : 0.038 µM	[69]
2,4-Diacetylphloroglucinol (DAPG) (117)	<i>Ceratodiction spongiosum</i>	MDA-MB-231	IC <sub>50</sub> : 0.08 µM	[70]
Phloroglucinol (118)	marine brown algae	MDA-MB231	IC <sub>50</sub> : 50 µM	[71]
Dioxinodehydroeckol (119)	<i>Ecklonia cava</i>	MCF-7	Inhibition: 64%	[72]

sargahydroquinoic acid (SHQA, 106) (Fig. 16) are produced by the marine algae *Sargassum heterophyllum* and illustrated cytotoxicity towards MBA-MB-231 with IC<sub>50</sub>: 67.4, and 159.5 µM, respectively [61]. Meroterpenoids, tetraprenyltoluquinol derivatives 107–111 produced by the brown algae *Cystoseira crinite* illustrated significant cytotoxicity towards MCF-7 with GI<sub>50</sub> values ranging from 0.9 and 2.5 µg/mL, respectively. Notably, compounds 109 and 110 bearing the furan ring possessed better effects with GI<sub>50</sub>: 1.3 and 0.9 µg/mL, respectively [63].



**Fig. 17.** Structures of micellaneous compounds 117–119.

### 3.4. Miscellaneous

Galaxamide (112), a cyclic pentapeptide produced by *Galaxaura filamentosa*, was shown to possess three leucines and two *N*-methyl leucine moieties. It exhibited cytotoxic effects towards MCF-7 cell lines with an IC<sub>50</sub>: 14.0 µg/mL [64]. Fucoxanthin (FXN, 113) (Fig. 16) is produced by the marine algae *Sargassum heterophyllum* and illustrated cytotoxicity towards MBA-MB-231 with IC<sub>50</sub>: 109.4 µM [61]. Dehydrothyriferol (114) is an anti-toxin terpenoid isolated from the marine algae *Laurencia viridis*. Compound 114 exhibited cytotoxicity against T-47D and MBA-MB-231 with IC<sub>50</sub>: 7.09 and 14.8 µM, respectively [65]. *Dunaliella tertiolecta* (DT), a green microalgae, produced violaxanthin (115) as the major antiproliferative pigment and induced MCF-7 growth inhibition [66].

Curacin A (116), containing a thiazoline moiety, cyclopropane group, and cis-alkenyl group, terminal double bond alkaloid that was discovered by Gerwick and his coworkers from the marine cyanobacterium *Lyngbya majuscula* [67] found in Curaçao. Its absolute configuration was established some years later by comparing degradative fragments with materials produced by enantioselective synthesis [68]. Compound 116 revealed anti-proliferative effects against the MCF-7 human cancer cell line with a GI<sub>50</sub> value of 0.038 µM. It showed to block cell cycle progression by inhibiting the tubulin polymerization due to its high affinity to the colchicine-binding site on tubulin [69].

2,4-Diacetylphloroglucinol (DAPG) (117) (Fig. 18) is a polyketide reported from *Pseudomonas* sp. isolated from the surface of marine red alga *Ceratodiction spongiosum*. Compound 117 inhibited the proliferation of MDA-MB-231 with IC<sub>50</sub>: 0.08 µM [70] (Table 2). Phloroglucinol (118) is a phlorotannin isolated from marine brown algae and it significantly suppressed the invasive and migratory ability of the cell line MDA-MB231 in a dose-dependent manner [71]. Dioxinodehydroeckol (119), a phloroglucinol derivative, was reported from the edible marine brown alga *Ecklonia cava*. At a concentration at 100 µM, this compound induced apoptosis in MCF-7 cells at the rate of 64%. Further investigations suggested that apoptosis in MCF-7 cells may be modulated through the NF-kappaB family and NF-kappaB dependent pathway [72] (Fig. 17).

## 4. Marine bacteria

### 4.1. Peptides

Cocosamides A (120) and B (121) along with malyngamide 3 (122) were isolated from *Moorea producens* (formerly *Lyngbya majuscula*) (Fig. 18). Compounds 120–122 demonstrated cytotoxicity towards MCF-7 with IC<sub>50</sub>: 30, 39, and 29 µM, respectively [73]. Wewakazole B (123) is a cytotoxic peptide isolated from the red sea cyanobacteria *Moorea producens*. Compound 123 has shown potent cytotoxicity towards the MCF-7 human mammary cancer cell line with an IC<sub>50</sub> value of 0.58 µM [74]. Hantupeptins A–C (124–126) are cyclodepsipeptides produced by cyanobacterium *Lyngbya majuscula* [75]. Compounds 124–126 displayed cytotoxicity against MCF-7 with IC<sub>50</sub>: 4.0, 0.5, and 1.0 µM, respectively [76].

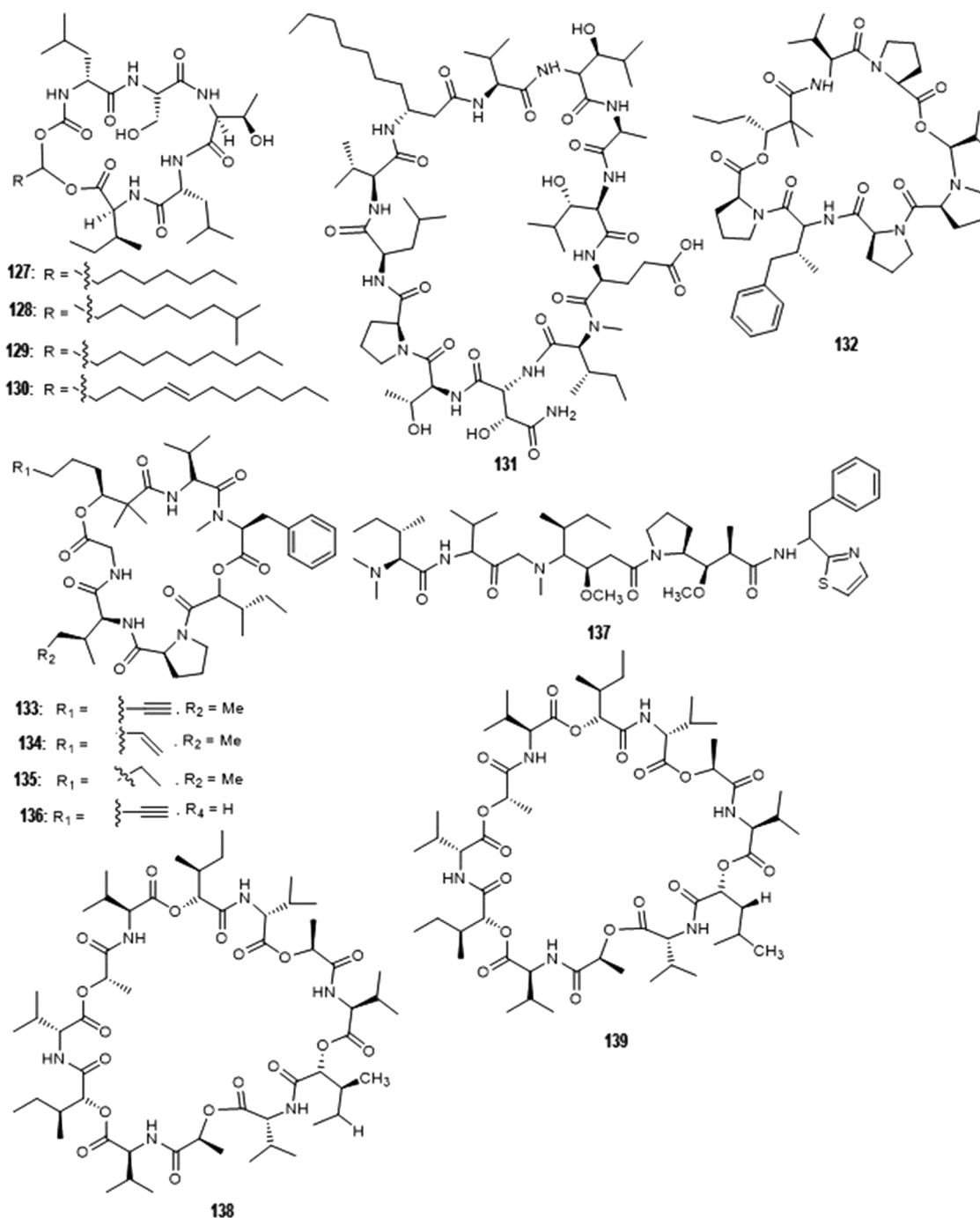


Fig. 19. Structures of peptides 127–139.

Kailuins A–D (127–130) (Fig. 19) are cyclic acyldepsipeptides isolated from a liquid culture of the gram-negative bacterium *BH-107*, collected from the beach of Kailua. Compounds 127–130 demonstrated cytotoxicity against MCF-7 with GI<sub>50</sub>: 3, 2, 4, and 3 μg/mL, respectively [77]. Laxaphycins B (131) is a cytotoxic cyclopeptide obtained from the marine cyanobacteria *Lyngbya majuscula* and it showed inhibition of the MCF-7 proliferation with IC<sub>50</sub>: 0.5 μM [78]. Pitiprolamide (132) is a cyclic depsipeptide and obtained from the cyanobacterium *Lyngbya majuscula*. Compound 132 showed mild inhibitory effects towards the MCF-7 breast cancer cell line with an IC<sub>50</sub> value of 33.0 μM [79]. Pitipeptolides A–C (133–135), and F (136) are cyclic depsipeptides obtained from the marine cyanobacterium *Lyngbya majuscula* from the Piti Bomb holes of Guam [80,81]. Compounds 133–136 showed cytotoxicity

towards the MCF-7 cell line with IC<sub>50</sub>: 13, 11, 73, and 83 μM, respectively [81].

Symplostatin 1 (137) is a linear peptide that corresponds to the dolastatin 132. It was taken off from the marine cyanobacteria *Symploca hydroides*. Compound 137 was shown to inhibit cell propagation of MDA-MB-435 very efficiently, displaying an IC<sub>50</sub> value of 0.15 nM [82]. Bacillistatins 1 (138) and 2 (139) are 12-unit cyclic cyclodepsipeptides, taken from cultures of *Bacillus silvestris*, obtained from the Pacific Ocean. Bacillistatin 1 (138) possesses a 2*R*-hydroxy-3*S*-methylvaleric acid. On the other hand, bacillistatin 2 (139) possesses the isomeric 2*R*-hydroxy-4-methylvaleric acid moiety residue. The relative stereochemistry of bacillistatin 1 is confirmed by X-ray crystallographic techniques. Compounds 138 and 139 showed potent cytotoxic activity towards MCF-7

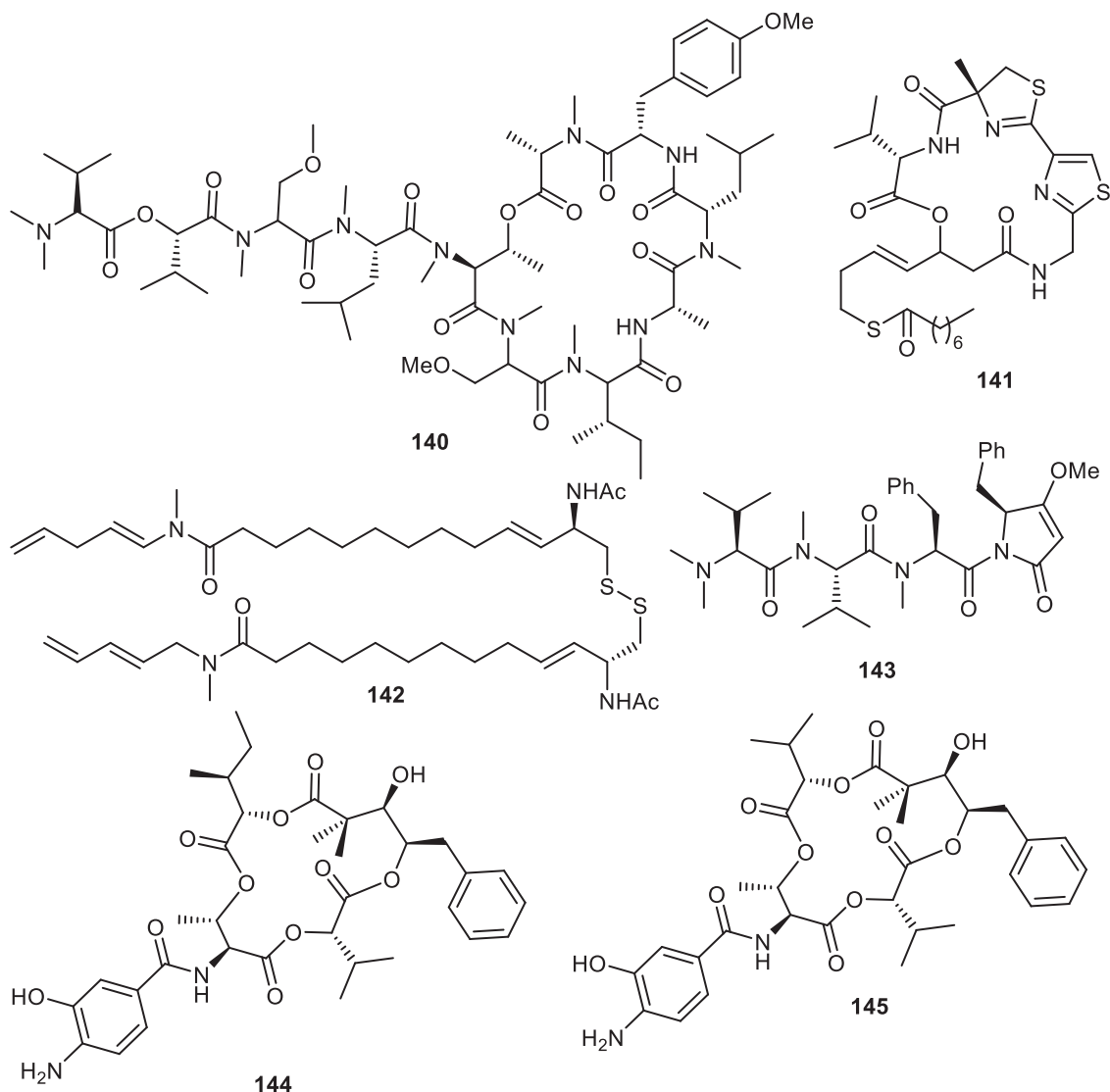


Fig. 20. Structures of peptides 140–145.

owning  $GI_{50}$  values of 0.00027 and 0.00053  $\mu\text{g}/\text{mL}$ , respectively [83].

Coibamide A (140) (Fig. 20) is a depsipeptide with antiproliferative properties isolated from the filamentous marine cyanobacterium *Lep- tolyngbya* sp. This compound was tested against a 60 cell line panel of the NCI (National Cancer Institute) and showed the highest effectiveness to the MDA-MB-231 human breast tumor cell line with a  $GI_{50}$  value of 2.8 nM [84]. Largazole (141) is a cyclodespeptide taken from a floridian marine cyanobacterium *Symploca* sp. At high concentration, compound 141 strongly prevented the growth of invasive transformed (MDA-MB-231) human mammary epithelial cells in a well regular manner ( $GI_{50}$  7.7 nM and  $LC_{50}$  117 nM). On the other hand, murine mammary epithelial cells that are nontransformed (NMuMG) were less sensitive to compound 141 ( $GI_{50}$  122 nM, and  $LC_{50}$  272 nM) [85].

Somocystinamide A (142) is a marine lipopeptide isolated from a cyanobacteria *L. majuscula/Schizothrix*. This disulfide dimer of mixed PKS/NRPS biosynthetic origin is responsible for apoptosis via the lipid partition, leading to accumulating the ceramide in treated cells. After that, it follows the colocalization pathway with caspase 8. Compound 142 efficiently showed inhibition of the MCF-7 cell line with an  $IC_{50}$  value of 210 nM [86]. Belamide A (143) isolated from the marine cyanobacterium *Symploca* sp. Pure belamide A (143) possessed cytotoxic effects towards MCF-7 cell line with an  $IC_{50}$ : 1.6  $\mu\text{M}$  [87]. Two depsipeptides, neoantimycins D (144) and E (145) were isolated from

*Streptomyces* sp. and both compounds possessed cytotoxicity towards MCF-7 with an inhibition rate of 91% and 90.5% respectively [88].

#### 4.2. Alkaloids

ZHD-0501, dimeric indole alkaloid (146) (Fig. 21) is a staurosporine derivative reported from the marine actinomycete *Actinomadura* sp. 007. This compound showed the ability to reduce the proliferation of the temperature-sensitive FT210 (*tsFT210*) mouse breast cancer cell line [89]. Streptokordin (147) is a methyl pyridine alkaloid isolated from the *Streptomyces* sp. KORDI-3238, which illustrated cytotoxicity towards MDA-MB-231 with an  $IC_{50}$  value of 7.5  $\mu\text{g}/\text{mL}$  [90]. Diazepinomicin (148) is a dibenzodiazepine alkaloid, obtained from cultures of the marine actinomycete strain *Micromonospora* DPJ12. This compound showed a cytotoxic effect towards the MDA-MB-231 with  $IC_{50}$ : 2.1  $\mu\text{M}$  [91] (Table 3).

Caboxamycin (149) and UK-1 (150) are benzoxazole compounds that were reported from the marine *Streptomyces* species NTK 937, isolated from deep-sea marine sediments in the Canary Basin. Compounds 149 and 150 displayed a growth efficient inhibitory activity against MCF-7 with a  $GI_{50}$ : of 7.3 and 0.65  $\mu\text{M}$ , respectively [92]. Pseudonocardian C (151) was isolated from the marine actinomycete *Pseudonocardia* sp. and showed efficient cytotoxic effects towards MCF-7 with



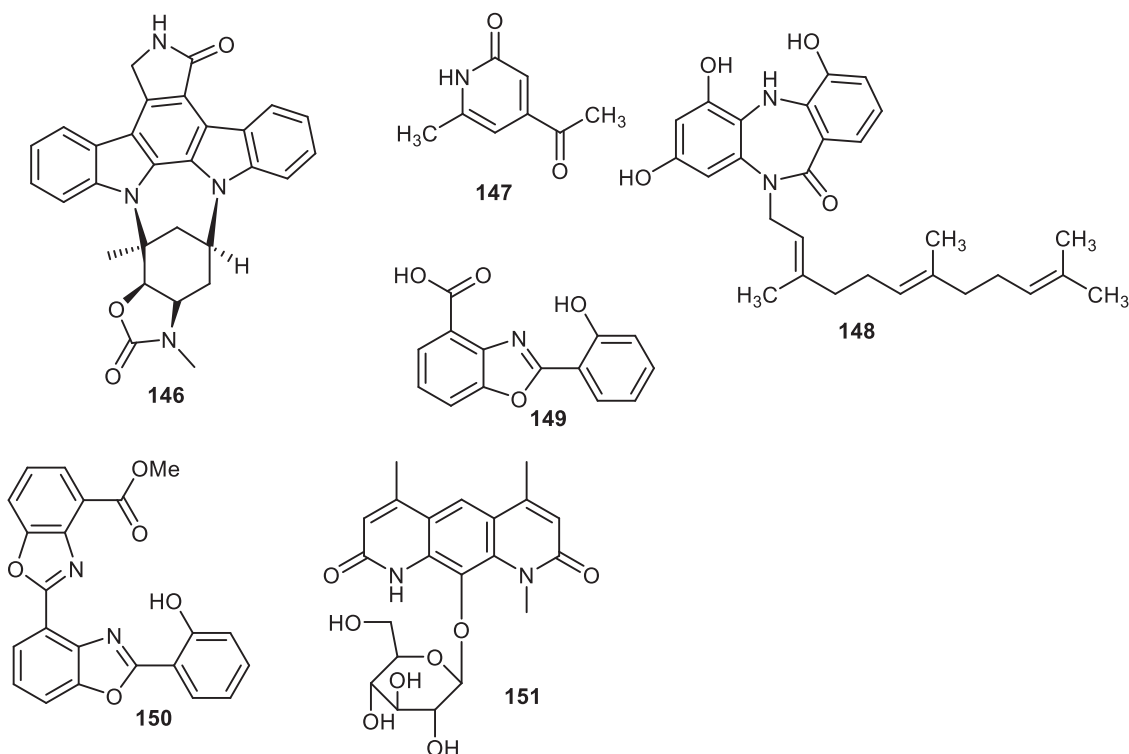


Fig. 21. Structures of alkaloids 146–151.

IC<sub>50</sub>: 8.0  $\mu$ M [93].

Pyridinium **152** (Fig. 22) was isolated and identified from the actinomycete *Amycolatopsis alba* var. nov. DVR D4 strain. It was obtained from sea sediments from the Visakhapatnam coast of the Bengal Bay, India. This compound revealed cytotoxic activity against MCF-7 with percentage inhibition of 60.4% [94]. Iodinin (**153**), 1,6-phenazinediol (**154**), questiomycin (**155**), chandrananimycins A-C (**156–158**) and phenoxazin-3-one (**159**) were obtained from *Actinomadura* sp. M048 isolates from marine sediments collected at Jiaozhou Bay, China. Both compounds **153** and **154** showed antitumor activity against breast cancer MAXF 401NL cells with IC<sub>50</sub> < 4.0  $\mu$ g/mL. On the other hand compounds **155–159** were found to be active against MCF-7 with IC<sub>50</sub> values down to 1.4  $\mu$ g/mL [95].

Aminophenoxazinones **160–162** (Fig. 23) were isolated from *Halomonas* sp. and exhibited cytotoxic effects towards MCF-7, having GI<sub>50</sub> values of 0.13, 1.6, and 2.0  $\mu$ g/mL, respectively [96]. Aqabamycin E (**163**) and vibrindole A (**164**) were isolated from certain bacteria *Vibrio* species and showed moderate cytotoxicity towards MDA-MB-231 and MCF-7 cell lines with IC<sub>50</sub> values of 25 and 20  $\mu$ g/mL and 30 and 50  $\mu$ g/mL, respectively [97].

#### 4.3. Quinones

Isoquinolinequinones, mansouramycins A-C (**165–167**) along with 3-methyl-7-(methylamino)-5,8-isoquinolinedione (**168**) (Fig. 24) were obtained from cultures of the *Streptomyces* sp. Compounds **165–168** possess cytotoxic effects towards MCF-7 and 401NL with an IC<sub>50</sub>: ranging from 0.012 to 47.7  $\mu$ M. Notably compounds **165**, **167**, & **168** were significantly more active towards MCF-7 with IC<sub>50</sub>: 2.3, 0.012 and 1.1  $\mu$ M, respectively [98]. Pseudonocardians A (**169**) and B (**170**) were isolated from the marine actinomycete *Pseudonocardia* sp. strain SCSIO 02199 collected from deep-sea sediments off the South China Sea. Compounds **169** and **170** showed efficient cytotoxic effects towards MCF-7 with IC<sub>50</sub> values of 0.027, and 0.021  $\mu$ M, respectively [93].

Parimycin (2,3-dihydro-1,4-anthraquinone) (**171**) was isolated from cultures of the marine *Streptomyces* sp. strain B8652 and possess good

effects towards MCF-7 [99]. Marmycins A (**172**) and B (**173**) are anthraquinones of the angucycline class produced by the *Streptomyces* strain CNH990. Compound **172** showed cytotoxicity towards breast cancer displaying IC<sub>50</sub>: < 0.03  $\mu$ M while marmycin B (**173**) proved to be less potent than **172** (IC<sub>50</sub>: < 0.5  $\mu$ M) [100].

Grincamycins B–F (**174–178**) and grincamycin (**179**) (Fig. 25) are classified as the C-glycoside angucycline-type metabolites. Compounds **174–179** were obtained from the fermentation of the marine actinobacteria *Streptomyces lusitanus* SCSIO LR32, collected in the South China Sea. All the compounds (**174–179**) demonstrated cytotoxicity towards MCF-7 with IC<sub>50</sub> values of 12, 11, 6.1, 8.7, 19, and 2.1  $\mu$ M, respectively [101]. Chinikomycin B (**180**) was also isolated from the *Streptomyces* sp. and showed good antitumor activity towards MAXF 401NL with IC<sub>50</sub>: 3.04  $\mu$ g/mL [102]. Kosinostatin (**181**) is a cytotoxic compound, reported from the *Micromonospora* strain TP-A0468, which showed efficient cytotoxicity in HBC-5, MCF-7, HBC-4, BSY-1, and MDA-MB-231 breast cancer cells with IC<sub>50</sub> values of 0.10, 0.05, 0.02, 0.06, and 0.21  $\mu$ M, respectively [103]. 2-hydroxyethyl-3-methyl-1,4-naphthoquinone **182** was isolated from *Actinoalloteichus cyanogriseus* and possessed cytotoxic effect towards MDA-MB-435 with IC<sub>50</sub> 10.5  $\mu$ M [104].

#### 4.4. Miscellaneous

Chinikomycin A (**183**) (Fig. 26) was isolated from the *Streptomyces* sp. and showed good antitumor activity towards MAXF 401NL with IC<sub>50</sub>: 2.41  $\mu$ g/mL [102]. Arisostatin A (**184**) is an antibiotic belonging to the tetrocarcin class and was isolated from cultures of *Micromonospora* sp. This compound, **184**, displayed cytotoxic activity against HBC-4 and HBC-5 with IC<sub>50</sub>: 0.26 and 0.059,  $\mu$ M, respectively [105]. Chromomycins A<sub>5</sub>-A<sub>8</sub> (**185–188**) were isolated from the marine bacteria, *Streptomyces* sp., collected from marine Zoanthid *Palythoa caribaeorum*. Compounds **185–188** reduced the viability of human MCF-7 tumor cells with IC<sub>50</sub> values of 3.7, 14.7, 133.0, and 10.5 nM, respectively [106]. Desertomycin G (**189**) is a member of the amino polyol polyketides containing a macrolactone ring produced by the marine-derived cyanobacteria *Streptomyces althioticus* MSM3 on the surface of the marine

**Table 3**  
Compounds 120–210 having anti-breast cancer properties.

Name	Organism	Cell line	Cytotoxicity	Ref.
Cocosamide A (120)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 30 μM	[73]
Cocosamide B (121)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 39 μM	[73]
Malyngamide 3 (122)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 29 μM	[73]
Wewakazole B (123)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 0.58 μM	[74]
Hantupeptin A (124)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 4.0 μM	[75, 76]
Hantupeptin B (125)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 0.5 μM	[75, 76]
Hantupeptins A–C (126)	<i>Moorea producens</i>	MCF-7	IC <sub>50</sub> : 1.0 μM	[75, 76]
Kailuin A (127)	<i>BH-107</i>	MCF-7	GI <sub>50</sub> : 3 μg/mL	[77]
Kailuin B (128)	<i>BH-107</i>	MCF-7	GI <sub>50</sub> : 2 μg/mL	[77]
Kailuin C (129)	<i>BH-107</i>	MCF-7	GI <sub>50</sub> : 4 μg/mL	[77]
Kailuin D (130)	<i>BH-107</i>	MCF-7	GI <sub>50</sub> : 3 μg/mL	[77]
Laxaphycins B (131)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 0.5 μM	[78]
Pitiprolamide (132)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 33.0 μM	[79]
Pitipeptolide A (133)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 13 μM	[80, 81]
Pitipeptolide B (134)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 11 μM	[80, 81]
Pitipeptolide C (135)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 73 μM	[80, 81]
Pitipeptolides F (136)	<i>Lyngbya majuscula</i>	MCF-7	IC <sub>50</sub> : 83 μM	[80, 81]
Symplostatin 1 (137)	<i>Symploca hydroides</i>	MDA-MB-435	IC <sub>50</sub> : 0.15 nM	[82]
Bacillistatin 1 (138)	<i>Bacillus silvestris</i>	MCF-7	GI <sub>50</sub> : 0.00027 μg/mL	[83]
Bacillistatin 2 (139)	<i>Bacillus silvestris</i>	MCF-7	GI <sub>50</sub> : 0.00053 μg/mL	[83]
Coibamide A (140)	<i>Leptolyngbya</i> sp.	MDA-MB-231	GI <sub>50</sub> : 2.8 nM	[84]
Largazole (141)	<i>Symploca</i> sp.	MDA-MB-231	GI <sub>50</sub> : 7.7 nM	[85]
Somocystinamide A (142)	<i>L. majuscula/Schizothrix</i>	MCF-7	IC <sub>50</sub> : 210 nM	[86]
Belamide A (143)	<i>Symploca</i> sp.	MCF-7	IC <sub>50</sub> : 1.6 μM	[87]
Neoantimycins D (144)	<i>Streptomyces</i> sp.	MCF-7	Inhibition rate: 91%	[88]
Neoantimycins E (145)	<i>Streptomyces</i> sp.	MCF-7	Inhibition rate: 90.5%	[88]
ZHD-0501 (146)	<i>Actinomadura</i> sp. 007	tsFT210	Inhibition rate: 28.3%	[89]
Streptokordin (147)	<i>Streptomyces</i> sp.	MDA-MB-231	IC <sub>50</sub> : 7.5 μg/mL	[90]
Diazebinomicin (148)	<i>Micromonospora</i> DPJ12	MDA-MB-231	IC <sub>50</sub> : 2.1 μM	[91]
Caboxamycin (149)	<i>Streptomyces</i> species	MCF-7	GI <sub>50</sub> : 7.3 μM	[92]
UK-1 (150)	<i>Streptomyces</i> species	MCF-7	GI <sub>50</sub> : 0.65 μM	[92]
Pseudonocardian C (151)	<i>Pseudonocardia</i> sp.	MCF-7	IC <sub>50</sub> : 8.0 μM	[93]
Pyridinium (152)	<i>Amycolatopsis alba</i>	MCF-7	Inhibition: 60.4%	[94]
Iodinin (153)	<i>Actinomadura</i> sp. M048	MAXF 401NL cells	IC <sub>50</sub> : < 4.0 μg/mL	[95]
1,6-phenazinediol (154)	<i>Actinomadura</i> sp. M048	MAXF 401NL cells	IC <sub>50</sub> : < 4.0 μg/mL	[95]
Questiomycin (155)	<i>Actinomadura</i> sp. M048	MCF-7	IC <sub>50</sub> : < 1.4 μg/mL	[95]
Chandrananimycin A (156)	<i>Actinomadura</i> sp. M048	MCF-7	IC <sub>50</sub> : < 1.4 μg/mL	[95]
		MCF-7	IC <sub>50</sub> : < 1.4 μg/mL	[95]

**Table 3 (continued)**

Name	Organism	Cell line	Cytotoxicity	Ref.
Chandrananimycin B (157)	<i>Actinomadura</i> sp. M048		IC <sub>50</sub> : < 1.4 μg/mL	
Chandrananimycin C (158)	<i>Actinomadura</i> sp. M048	MCF-7	IC <sub>50</sub> : < 1.4 μg/mL	[95]
Phenoxazin-3-one (159)	<i>Actinomadura</i> sp. M048	MCF-7	IC <sub>50</sub> : < 1.4 μg/mL	[95]
Aminophenoxazinone 160	<i>Halomonas</i> sp.	MCF-7	GI <sub>50</sub> : 0.13 μg/mL	[96]
Aminophenoxazinone 161	<i>Halomonas</i> sp.	MCF-7	GI <sub>50</sub> : 1.6 μg/mL	[96]
Aminophenoxazinones 162	<i>Halomonas</i> sp.	MCF-7	GI <sub>50</sub> : 2.0 μg/mL	[96]
Aqabamycin E (163)	<i>Vibrio</i> species	MDA-MB-231		
		MCF-7	IC <sub>50</sub> : 25 μg/mL	
		MCF-7	IC <sub>50</sub> : 30 μg/mL	[97]
Vibrindole A (164)	<i>Vibrio</i> species	MDA-MB-231		
		MCF-7	IC <sub>50</sub> : 20 μg/mL	
		MCF-7	IC <sub>50</sub> : 50 μg/mL	[97]
Mansouramycins A (165)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 2.3 μM	[98]
Mansouramycins B (166)	<i>Streptomyces</i> sp.	401NL	IC <sub>50</sub> : 3.5 μM	[98]
Mansouramycins C (167)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 0.012 μM	[98]
3-Methyl-7-(methylamino)-5,8-isoquinolinedione (168)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 1.1 μM	[98]
Pseudonocardian A (169)	<i>Pseudonocardia</i> sp.	MCF-7	IC <sub>50</sub> : 0.027 μM	[93]
Pseudonocardian B (170)	<i>Pseudonocardia</i> sp.	MCF-7	IC <sub>50</sub> : 0.021 μM	[93]
Parimycin (2, 3-dihydro-1, 4-anthraquinone) (171)			IC <sub>70</sub> : 0.9–6.7 μg/mL	[99]
Marmycins A (172)	<i>Streptomyces</i> strain CNH990	MCF-7	IC <sub>50</sub> : < 0.03 μM	[100]
Marmycins B (173)	<i>Streptomyces</i> strain CNH990	MCF-7	IC <sub>50</sub> : < 0.5 μM	[100]
Grincamycins B (174)	<i>Streptomyces lusitanus</i>	MCF-7	IC <sub>50</sub> : 12 μM	[101]
Grincamycins C (175)	<i>Streptomyces lusitanus</i>	MCF-7	IC <sub>50</sub> : 11 μM	[101]
Grincamycins D (176)	<i>Streptomyces lusitanus</i>	MCF-7	IC <sub>50</sub> : 6.1 μM	[101]
Grincamycins E (177)	<i>Streptomyces lusitanus</i>	MCF-7	IC <sub>50</sub> : 8.7 μM	[101]
Grincamycins F (178)	<i>Streptomyces lusitanus</i> SCSIO LR32	MCF-7	IC <sub>50</sub> : 19 μM	[101]
Grincamycin (179)	<i>Streptomyces lusitanus</i>	MCF-7	IC <sub>50</sub> : 2.1 μM	[101]
Chinikomycin B (180)	<i>Streptomyces</i> sp.	MAXF 401NL	IC <sub>50</sub> : 3.04 μg/mL	[102]
Kosinostatin (181)	<i>Micromonospora</i> strain TP-A0468	HBC-5; MCF-7; HBC-4; BSY-1; MDA-MB-231	IC <sub>50</sub> : 0.1 μM; IC <sub>50</sub> : 0.05 μM; IC <sub>50</sub> : 0.02 μM; IC <sub>50</sub> : 0.06 μM; IC <sub>50</sub> : 0.21 μM	[103]
		MDA-MB-435	IC <sub>50</sub> : 10.5 μM	[104]
2-Hydroxyethyl-3-methyl-1,4-naphthoquinone (182)	<i>Actinoalloteichus cyanogriseus</i>	MDA-MB-435		
Chinikomycin A (183)	<i>Streptomyces</i> sp.	MAXF 401NL	IC <sub>50</sub> : 2.41 μg/mL	[102]
Arisostatin A (184)				[105]

(continued on next page)

Table 3 (continued)

Name	Organism	Cell line	Cytotoxicity	Ref.
	<i>Micromonospora</i> sp.	HBC-4 and HBC-5	IC <sub>50</sub> : 0.26 and 0.059 $\mu$ M	
Chromomycins A <sub>5</sub> (185)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 3.7 $\mu$ M	[106]
Chromomycins A <sub>6</sub> (186)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 14.7 $\mu$ M	[106]
Chromomycins A <sub>7</sub> (187)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 133.0 $\mu$ M	[106]
Chromomycins A <sub>8</sub> (188)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 10.5 $\mu$ M	[106]
Desertomycin G (189)	<i>Streptomyces althioticus</i>	MCF-7	IC <sub>50</sub> : 3.8 $\mu$ M	[107]
Tartrolon D (190)	<i>Streptomyces</i> sp.	MDA-MB-231	GI <sub>50</sub> : 0.79 $\mu$ M	[108]
7-Deoxyechinosporin (191)	<i>Streptomyces albogriseolus</i> A2002	MCF-7	GI <sub>50</sub> : 0.4 $\mu$ M	[109]
Echinosporin (192)	<i>Streptomyces albogriseolus</i>	MCF-7	GI <sub>50</sub> : 6.4 $\mu$ M	[109]
Trioxacarcins A (193)	<i>Streptomyces</i> sp. strain B8652	MCF-7	IC <sub>50</sub> : < 0.0003 $\mu$ g/mL	[110]
Trioxacarcins B (194)	<i>Streptomyces</i> sp. strain B8652	MCF-7	IC <sub>50</sub> : 1.134 $\mu$ g/mL	[110]
Trioxacarcins C (195)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 0.002 $\mu$ g/mL	[110]
Trioxacarcins D (196)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 0.066 $\mu$ g/mL	[110]
Proximicins A (197)	<i>Verrucosipora</i>	MCF-7	GC <sub>50</sub> : 24.6 $\mu$ M	[111]
Proximicins B (198)	<i>Verrucosipora</i>	MCF-7	GC <sub>50</sub> : 12.1 $\mu$ M	[111]
Proximicins C (199)	<i>Verrucosipora</i>	MCF-7	GC <sub>50</sub> : 20.6 $\mu$ M	[111]
PM100117 (200)	<i>Streptomyces caniferus</i>	MDA-MB-231	GI <sub>50</sub> : 1.5 $\mu$ M	[112]
PM100118 (201)	<i>Streptomyces caniferus</i>	MDA-MB-231	GI <sub>50</sub> : 1.7 $\mu$ M	[112]
Streptomyceamide C (202)	<i>Streptomyces</i> sp. H74–21	MCF-7	IC <sub>50</sub> : 27.0 $\mu$ g/mL	[113]
Chromophore-V C-1027 (203)	<i>Streptomyces</i> strain	MDA-MB231	IC <sub>50</sub> : 0.9 $\mu$ M	[114]
ULDF4 (204)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 0.0139 mg/mL	[115]
ULDF5 (205)	<i>Streptomyces</i> sp.	MCF-7	IC <sub>50</sub> : 2.176 mg/mL	[115]
Sesbanimide A (206)	<i>Stappia indica</i>	MDA-MB-231	GI <sub>50</sub> : 6.4E-07	[116]
Sesbanimides C-F (207–210)	<i>Labrenzia aggregata</i>	MDA-MB-231	GI <sub>50</sub> : 1.6E-07–8. 6E-09	[116]

algal (*Ulva* sp.) colony which was collected from the sediment of the North Atlantic Ocean. This compound, **189**, showed a powerful reduction in the feasibility of MCF-7 cells displaying an IC<sub>50</sub>: 3.8  $\mu$ M after 96 h [107].

Tartrolon D (**190**) (Fig. 27) is a macrodiolide isolated from marine sediments of the actinomycete *Streptomyces* sp. This compound showed potent cytotoxicity towards MDA-MB-231 with GI<sub>50</sub>: 0.79  $\mu$ M [108]. 7-Deoxyechinosporin (**191**) and echinosporin (**192**) are lactones that were extracted from the microbes *Streptomyces albogriseolus* A2002 collected from sea sediment in Jiaozhou Bay, China. Compounds **191** and **192** indicated antiproliferative properties towards MCF-7 with GI<sub>50</sub>: 0.4 and 6.4  $\mu$ M, respectively [109]. Trioxacarcins A-D (**193–196**) were obtained from marine *Streptomyces* sp. strain B8652 and exhibited excellent cytotoxicity towards MCF-7 with IC<sub>50</sub>: < 0.0003, 1.134, 0.002, and 0.066  $\mu$ g/mL, respectively [110].

Proximicins A-C (**197–199**) (Fig. 28) are three furan derivatives of netropsin, isolated from the actinomycete *Verrucosipora*. These compounds differ from the previously reported heterocyclic antibiotics, such as netropsin and distamycin, by the presence of the  $\gamma$ -amino acid 4-aminofuran-2-carboxylic acid group. Compounds **197–199** have efficient cytotoxic effects against the human MCF-7 mammary tumor cell lines showing GI<sub>50</sub> values of 24.6, 12.1, and 20.6  $\mu$ M, respectively. Preliminary investigations on their mechanism of action suggested that proximicins arrest cells in the G<sub>0</sub>/G<sub>1</sub> phase [111].

PM100117 (**200**) and PM100118 (**201**) (Fig. 29) are the polyhydroxy macrolide lactones discovered from the broth cultures of the marine-derived *Streptomyces caniferus* which was obtained from the Guadeloupe Island in the Pacific Ocean. Their skeleton comprises of a 36-membered macrolide, possessing a side chain with 3 deoxy sugars and an important 1, 4-naphthoquinone chromophore. Both compounds **200** and **201** have efficient antitumor effects on MDA-MB-231 with GI<sub>50</sub>: 1.5 and 1.7  $\mu$ M, respectively [112]. Streptomyceamide C (**202**) was isolated from the *Streptomyces* sp. H74–21 isolate which in turn was derived from marine sediments present in tropical mangrove sites. Compound **202** showed anti-proliferative effects towards MCF-7 with an IC<sub>50</sub> value of 27.0  $\mu$ g/mL [113].

Chromophore-V C-1027 (**203**) belongs to the family of benzoxazine metabolites isolated from the Arctic marine actinomycete *Streptomyces* strain and showed significant cytotoxicity against MDA-MB231 cells exhibiting an IC<sub>50</sub> value of 0.9  $\mu$ M [114]. ULDF4 (**204**) and ULDF5 (**205**) resemble the chemical class of polycyclic xanthenes, were isolated from 12 diverse deposit collections of marine-derived actinomycete named as *Streptomyces bingchenggensis* ULS14. Compounds **204** and **205** showed cytotoxicity against human MCF-7 mammary adenocarcinoma cells with IC<sub>50</sub> values of 0.0139 and 2.176 mg/mL, respectively [115]. Polyketides named sesbanimide A (**206**), and sesbanimides C-F (**207–210**) were produced bacteria *Stappia indica* and *Labrenzia aggregata*. Moreover

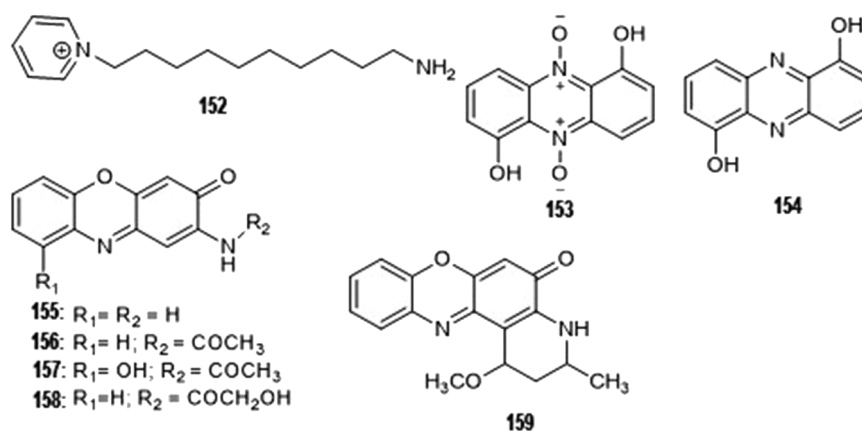


Fig. 22. Structures of alkaloids 152–159.

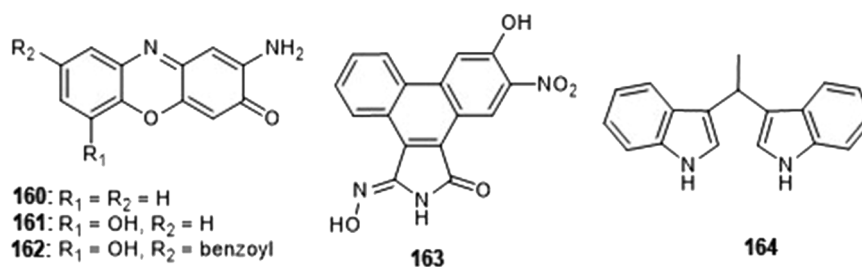


Fig. 23. Structures of alkaloids 160–164.

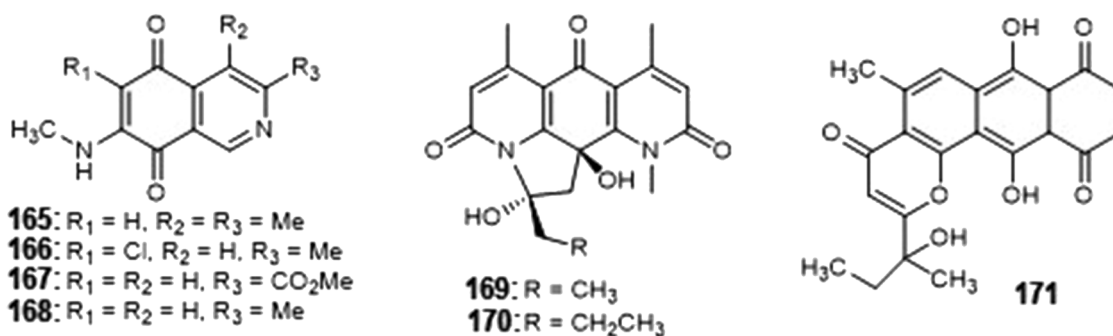


Fig. 24. Structures of quinones 165–173.

these metabolites demonstrated cytotoxic effects towards MDA-MB-231 with GI<sub>50</sub>: 1.6E-07–8. 6E-09 [116].

## 5. Marine fungi

### 5.1. Sesquiterpenes and sesterterpenes

Coriolin B (**211**) (Fig. 30) is a cyclic chlorinated sesquiterpene obtained from the marine sponge known as *Jaspis aff. Johnstoni*. This compound demonstrated cytotoxicity towards the T-47D cell lines with an IC<sub>50</sub> value of 0.7 μM [117]. Neomangicols A (**212**) and B (**213**) are sesterterpenes isolated from the derived marine fungal strain *Fusarium equiseti* CNC-477 collected from the mangroves in the Bahamas. Compounds **212** and **213** showed cytotoxicity towards MCF-7 with IC<sub>50</sub>: 4.9 and 27 μM, respectively [118]. Ophiobolin O (**214**) is a sesterterpene that was derived from the *Aspergillus ustus* fungal strain 094102, isolated from the Mediterranean sponge *Suberites domuncula*. Ophiobolin O showed IC<sub>50</sub> values of 17.8 μM towards MCF-7 cells and to arrest cell cycle progression in the G<sub>1</sub> phase, through interaction with AKT/GSK3β/cyclin D1 signaling pathway [119]. The sesquiterpenoid nitrobenzoyl ester derivative, 9α,14-dihydroxy-6β-p-nitrobenzoylcinnamamide (**215**) was identified from the algicolous fungus mycelia *Aspergillus versicolor* CNC 327 found on the external surface of the green calcareous alga *Penicillus capitatus* from the Bahamas Islands.

This compound showed inhibitory activity against the BT-549 line, an invasive ductal tumor, with an LC<sub>50</sub> value of 0.27 μg/mL [120].

### 5.2. Alkaloids

Avrainvillamide (**216**) (Fig. 31) was produced by *Aspergillus* sp. CNC358 isolate, in turn isolated from the green alga *Avrainvillea* sp. collected from an island of the Bahamas. Compound **216** exhibited inhibitory activity towards βT-549 and T-47D with IC<sub>50</sub> values of 34 and 72 nM, respectively [121]. Acetylapoaranotin (**217**), acetylaranotin (**218**), and deoxyapoaranotin (**219**) were isolated from a derived-marine fungus *Aspergillus* sp. and illustrated cytotoxicity towards MCF-7 with IC<sub>50</sub> values of 10, 36, and 31 μM, respectively [122]. Gliotoxin (**220**), another member of the sulfur-containing diketopiperazine class, was isolated from the sea-derived fungus *Aspergillus* sp. strain YL-06. Compound **220** illustrated potent cytotoxicity towards MCF-7, T47D, BT-474, ZR75-1, MDA-MB231, and MDA-MB435, with IC<sub>50</sub> value of 985, 365, 102, 158, 138, and 87, respectively [123] (Table 4).

Alkaloid fumigaclavine C (**221**) was obtained from *Aspergillus fumigatus* isolate, and it showed cytotoxicity against the MCF-7 mammary tumor cell line. At a concentration of 20 μM, this alkaloid demonstrated 93% and 89% ability of reducing the proliferation of these cancer cells after 24 and 36 h, respectively. Compound **221** has also been proven to

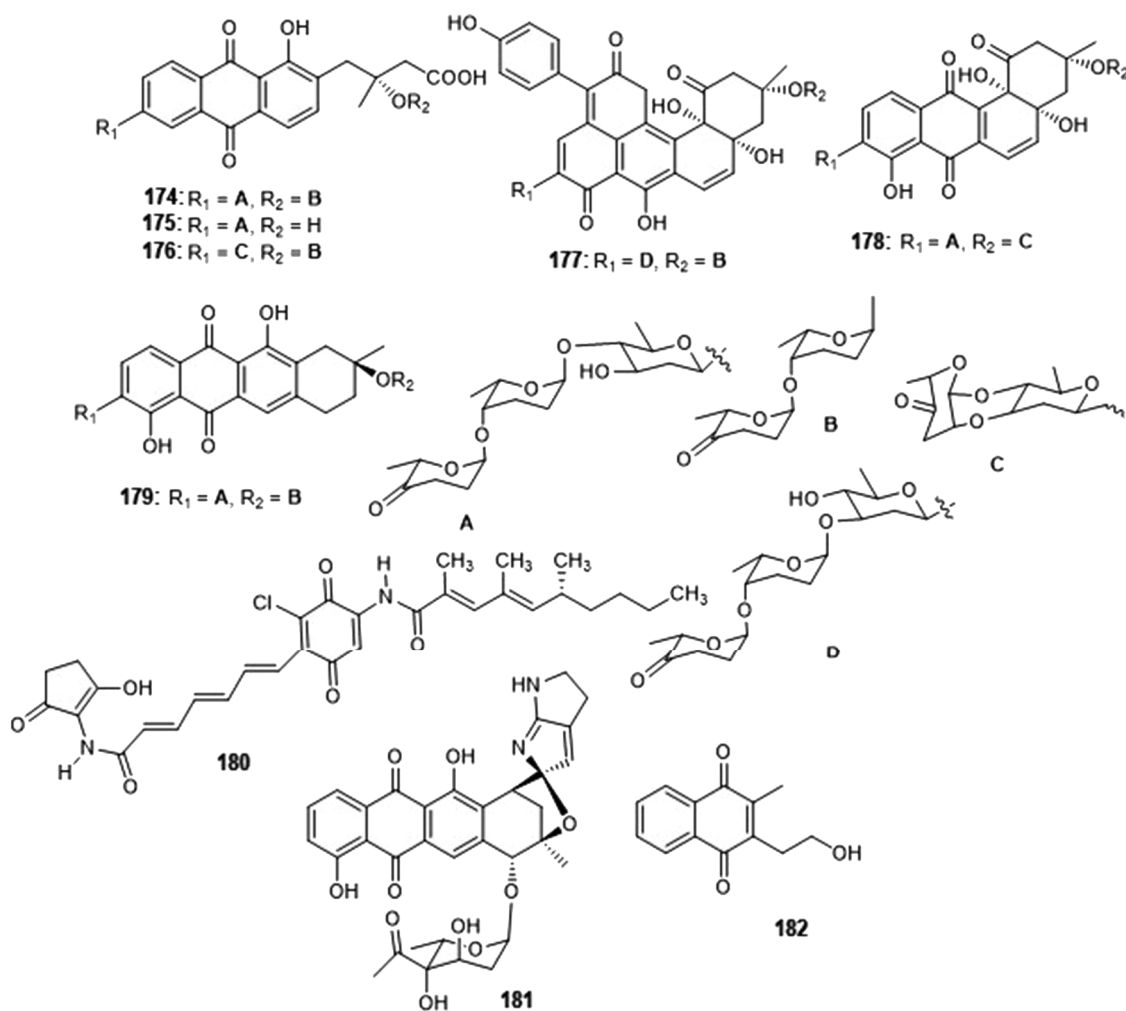


Fig. 25. Structures of quinones 174–182.

block the migration and invasion of the cancer cells by modulating the apoptotic protein expressions. Furthermore, fumigaclavine C (**221**) was revealed to down-regulate the NF-kappa-B cell survival pathway [124]. Tryprostatins A (**222**) and B (**223**) were discovered in the fermentation extract of the isolate *Aspergillus fumigatus* BM939, obtained from deep-sea sediment and demonstrated an inhibitory growth towards the mouse thermo-sensitive tsFT210 cell line [125]. In another study, alkaloid **222** revealed an ability to be a BCRP inhibitor agent. It also revealed inhibition of the human MCF-7 with an  $IC_{50}$  value of  $0.013 \pm 0.006 \mu M$  [126].

Cui and his coworkers isolated the pentacyclic-type 2, 5-diketopiperazines named cyclotryprostatins A–D (**224–227**) (Fig. 32) from the marine isolate *Aspergillus fumigatus* BM939. Compounds **224–227** showed inhibition of the cell cycle progression towards mouse tsFT210 cells in the  $G_2/M$  phase with  $IC_{50}$  values of 5.6, 19.5, 23.4, and  $25.3 \mu M$ , respectively [127]. Luteoalbusins A (**228**) and B (**229**), T988A (**230**), along with gliocladines C (**231**) and D (**232**) were isolated from the deep-sea marine fungus *Acrostalagmus luteoalbus* SCSIO F457. Alkaloids **228–232** showed cytotoxic effects towards MCF-7 exhibiting  $IC_{50}$  values ranging from 0.91 to  $0.25 \mu M$  [128]. *Arthrinium* sp., produced pyridone alkaloid arthpyrone L (**233**) and displayed cytotoxic effects towards MCF-7 and MDA-MB-231 with  $IC_{50}$ : 14.0 and  $21.3 \mu M$  respectively [129]. Penochalasin I (**234**), penochalasin J (**235**), chaetoglobosins A (**236**), C (**237**), F (**238**), G (**239**), and cytoglobosin C (**240**) were produced by *Penicillium chrysogenum* and possessed cytotoxic effects

towards MDA-MB-435 with  $IC_{50}$  ranging from 7.5 to  $38.7 \mu M$  respectively [130].

### 5.3. Quinones

2-Methoxyjuglone (**241**) and penithoketone (**242**) (Fig. 33) were isolated from *Penicillium thomii* and illustrated cytotoxic effects against MCF-7 with  $IC_{50}$ : 11 and  $21 \mu M$ , respectively. In addition, quinones **241** and **242** were active against MDA-MB-468 with  $IC_{50}$ : 15 and  $4.9 \mu M$ , respectively [131]. Alterporriol K (**243**) and L (**244**) are bianthraquinones, isolated from the marine-derived fungus *Alternaria* sp. and both natural products possessed cytotoxic effects against MDA-MB-435 and MCF-7 with  $IC_{50}$ : ranging from 13.1 to  $29.1 \mu M$  [132]. SZ-685 C (**245**) is an anthraquinone obtained from the endophytic fungus No. 1403 found in deep-sea mangroves. This compound showed inhibition of the proliferation of MCF-7 and MDA-MB-435 with  $IC_{50}$ : 7.5 and  $3.0 \mu M$  respectively [133].

### 5.4. Meroterpenes

Epoxyphomalins A (**246**) and B (**247**) (Fig. 34) are meroterpenoids, produced by marine-derived fungus *Phoma* sp. They displayed cytotoxicity against 401NL and MCF-7 cell lines with  $IC_{50}$  values of 0.010 and  $0.116 \mu g/mL$  and 0.501 and  $0.398 \mu g/mL$ , respectively [134]. Aszonapyrone A (**248**) and sartorypyrone B (**249**) were obtained from the

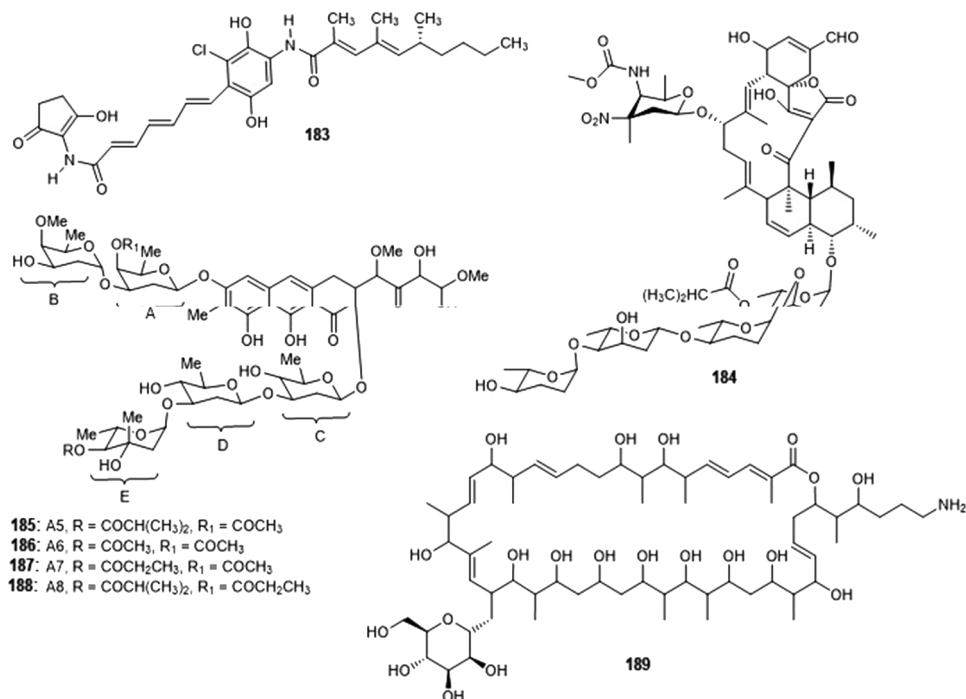


Fig. 26. Structures of compounds 183–189.

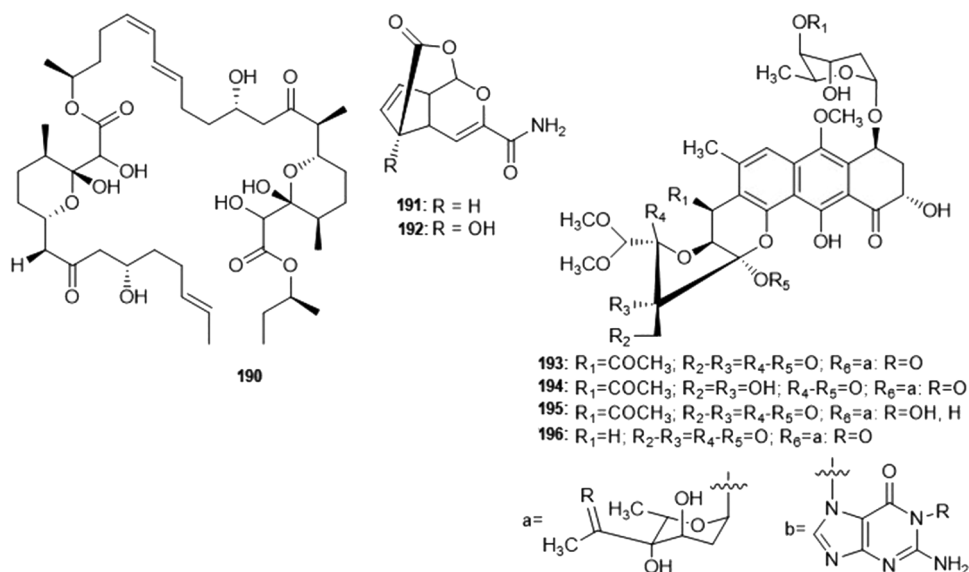


Fig. 27. Structures of compounds 190–196.

derived- marine fungus *Neosartorya laciniosa*. Both compounds revealed *in vitro* inhibitory effects towards MCF-7 with a GI<sub>50</sub> of 13.6 and 17.8  $\mu$ M, respectively [135]. Purpurogemutant (250) and purpurogemutantidin (251) are additional meroterpenoids that were reported from the marine-derived fungal strain *Penicillium purpurogenum* G59 isolated from the soil sample from Bohay Bay, Tianjin, China. Compounds 250 and 251 were active against the MCF-7 with IC<sub>50</sub>: 29.3 and 26.3  $\mu$ M, respectively [136]. Acremochlorin A (252), E-G (253–255), K-M (256–258), and meroterpenoids 259–269 were produced by fungus *Acremonium sclerotigenum*. All compounds demonstrated cytotoxicity towards MDA-MB-231 and MDA-MB-468 with IC<sub>50</sub> ranging from 0.65 to 57.0  $\mu$ M. Notably compound 252 possessed potent effects towards both cancer cells with IC<sub>50</sub> < 1  $\mu$ M [137].

### 5.5. Miscellaneous

Isosclerone (270) (Fig. 35) is a pentaketide metabolite, that was obtained from the marine-derived *Aspergillus fumigatus*. At a concentration of 60  $\mu$ M, compound 270 showed significant cytotoxic activity against the human breast malignancy MCF-7 cells after 24 h incubation and subsequently leading to apoptosis. Investigating its mechanism of action revealed that this compound blocked the MAPK pathway, inhibiting ERK, JNK, and P38 phosphorylation. It has also proven to be responsible for down-regulation of CDK and cyclin proteins and up-regulating the p53 at transcriptional level [138].

Monacolin X (271) is a polyketide isolated from the marine-derived fungus *Monascus* sp. NMK7 spores accumulated on the surface of (*Clathria frondifera*) sponge. This compound exhibited magnificent

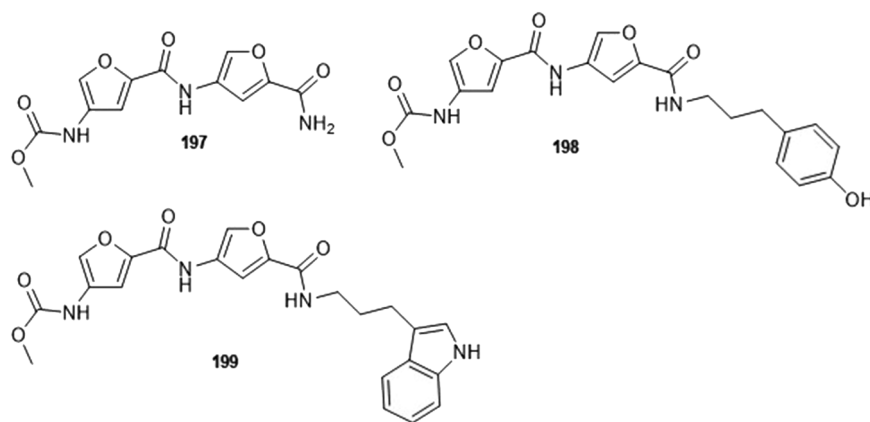


Fig. 28. Structures of compounds 197–199.

cytotoxicity effect towards MCF-7, T47D, MDA-MB-231, and MDA-MB-468 cells, displaying  $IC_{50}$  values of 42.8, 33.9, 48.7 and 26.3  $\mu\text{M}$ , respectively [139]. Pericosine A (272) is a shikimate derivative obtained from the marine fungal strain *Periconia byssoides*. Compound 272 showed potent growth inhibition towards HBC-5 with  $\log GI_{50}$ : 5.2 [140]. Terrein (273) was isolated from the diverse marine fungus *Aspergillus terreus* [141] and illustrated cytotoxicity towards MCF-7 with an  $IC_{50}$  value of 1.1 nM [142].

Marthiapeptide (274) is a cyclic peptide, containing a sequential tris-thiazole-thiazoline segment, obtained from a strain of the marine fungus *Marinactinospora thermotolerance* SCSIO 00652. Compound 274 efficiently reduced the growth of MCF-7 with an  $IC_{50}$  value of 0.38  $\mu\text{M}$  [143]. Varitriol (275), isolated from the marine fungus strain *Emericella varicolor* collected in Venezuelan waters of the Caribbean Sea, displayed a great potency towards the T-47D breast cancer cell line showing a  $GI_{50}$  value of  $2.10 \times 10^{-7}$  M [144]. Monalbidins C and D (276 and 277), monacolin K methyl ester (278), dehydromonacolin L (279), dehydromonacolin K (280), and *O*-acetylmonacolin K (283) which were reported from marine derived fungus *Monascus albidus*, possessed moderate cytotoxicity towards MDA-MB-231 with  $IC_{50}$ : 9.3–41.6  $\mu\text{M}$ . On the other hand monacolin K (282) showed better effects with 9.3–3.7  $\mu\text{M}$  [145]. In another study, ganodermasides A (284), B (285) were isolated from fungus *Pseudogymnoascus* sp. and possessed cytotoxicity towards MDA-MB-231 with  $IC_{50}$ : 30.0 and 27.0  $\mu\text{M}$  respectively [146]. Moreover, 5 R,6 S,16 R, 3E)– 5,6-dihydroxy-16-methyloxacyclohexadec-3-en-2-one (286) and bekeleylactone E (287) were produced by fungus *Aspergillus flocculosus* and showed cytotoxicity towards MDA-MB-231 with  $GI_{50}$ : 2.4 and 3.1  $\mu\text{M}$  respectively [147].

Polyketide, RF-3192 C (288) was reported from *Aspergillus niger* and showed cytotoxic effect towards MCF-7 with  $IC_{50}$ : 47  $\mu\text{M}$  [148]. Tersaphilones B (289), D (290), E (291), luteusin A (292), luteusin C (293) and RP-1551–5 (294) (Fig. 36) were isolated from fungus *Phomopsis tersa* and compounds 290–292 and 294 possessed good cytotoxicity towards MCF-7 with  $IC_{50} < 10$   $\mu\text{M}$ . On the other hand compounds 289 and 293 showed moderate and weak effects with  $IC_{50}$ : 13 and 25.5  $\mu\text{M}$  respectively [149]. Pensulfonamide (295) was produced by fungus *Penicillium aculeatum* and displayed significant cytotoxicity towards MCF-7 with  $IC_{50}$ : 2.18  $\mu\text{M}$  [150]. Three pairs of new salicylaldehyde derivative enantiomers, eurtocins F (296), I (297), and eurtirumin (298) were reported from fungus *Eurotium* sp. and demonstrated cytotoxicity towards MCF-7 with  $IC_{50}$  ranging from 20.5 to 55.5  $\mu\text{M}$  [151].

## 6. Soft coral

Pseudopterisin (299) (Fig. 37) is a glycosidic terpene isolated from the marine-derived soft coral *Pseudopterogorgia elisabethae*, collected from the Caribbean ocean [152]. It exerts its activity by hindering cytokine discharge in triple-negative breast cancer (TNBC), resulting in a delay of the NF- $\kappa$ B signal. Compound 299 revealed cytotoxicity against MDA-MB-231 with an  $IC_{50}$  value of 24.4  $\mu\text{M}$  [153]. Cembrane diterpenes 300 and 301 were isolated from the soft coral *Sarcophyton ehrenbergi* while the cembrane analog 302 was isolated from another soft coral *Nephthea* sp. Compounds 300–302 demonstrated cytotoxicity effects MCF-7 with  $GI_{50}$ : 6.1, 1.7, and 0.15  $\mu\text{g}/\text{mL}$ , respectively [154].

Sarcocrassocolides A–D (303–306) [155] and crassocolides A, B and D–F (307–311) along with lobophytolide (312) [156] (Fig. 38) are cembranoid diterpenes isolated from the marine soft coral *Sarcophyton crassocaule* collected off Taiwan. Diterpenes 303–306 exhibited cytotoxicity towards MCF-7 with  $ED_{50}$  values of 4.2, 3.2, 2.0, and 4.1  $\mu\text{g}/\text{mL}$ , respectively [155]. Compounds 307–311, which possesses a *trans*-fused  $\alpha$ -methylene  $\gamma$ -lactone moiety, displayed moderate cytotoxicity towards MCF-7 and MDA-MB-231 with  $IC_{50}$  ranging from 2.0 to 15.3  $\mu\text{g}/\text{mL}$  [156]. Lobophytolide (312) was the most active compound against MDA-MB-231 and MCF-7 with  $IC_{50}$ : 2.0 and 2.3  $\mu\text{g}/\text{mL}$ , respectively [156].

Sardigitolide B (313) (Fig. 39) represents a new biscebranoid metabolite isolated from the culture broth of the marine soft coral *Sarcophyton digitatum*. This metabolite illustrated cytotoxicities toward MDA-MB-231 and MCF-7 with the  $IC_{50}$ : 14.8 and 9.6  $\mu\text{g}/\text{mL}$ , respectively [157]. Protocenenicins A (314) and B (315) are new xenicanes (bicyclic diterpenoids featuring a cyclononane) that were isolated from the soft coral *Protodendron repens*, collected off the coast of Okuza. Compounds 314 and 315 displayed cytotoxic activities against MDAMB-231 with  $GI_{50}$  value of 2.1 and 6.3  $\mu\text{M}$ , respectively [158].

Sarcodictyins A (316) and sarcodictyins B (317) [159] are diterpenoids, isolated from the soft coral *Eleutherobia aurea* while eleutherobin (318), a glycoside analog was isolated from the soft coral *Eleutherobia* species [160]. This latter compound has proven to be more effective against MCF-7 with an  $IC_{50}$  value of 10 nM which is greater than compounds 316 and 317 which displayed  $IC_{50}$  values of 400 and 300 nM, respectively [161]. Waixenicin A (319) is a diterpenoid (aTRPM7 Inhibitor) isolated from the marine soft coral *Sarcothelia edmondsoni*, collected off the Hawaiian coast. It showed cytotoxicity towards MCF-7 cells, with an  $IC_{50}$  value of 4.6  $\mu\text{M}$  [162].

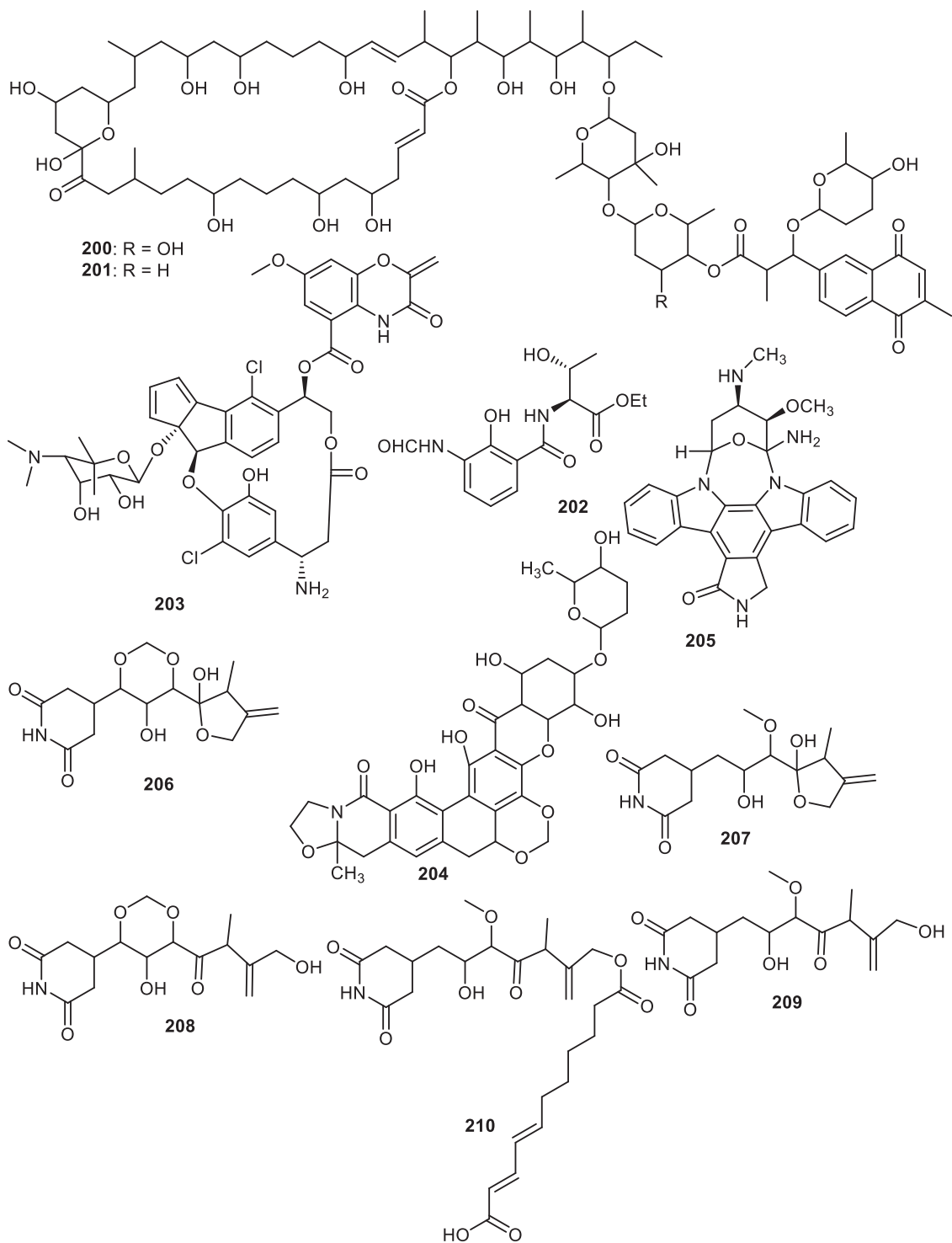


Fig. 29. Structures of compounds 200–210.



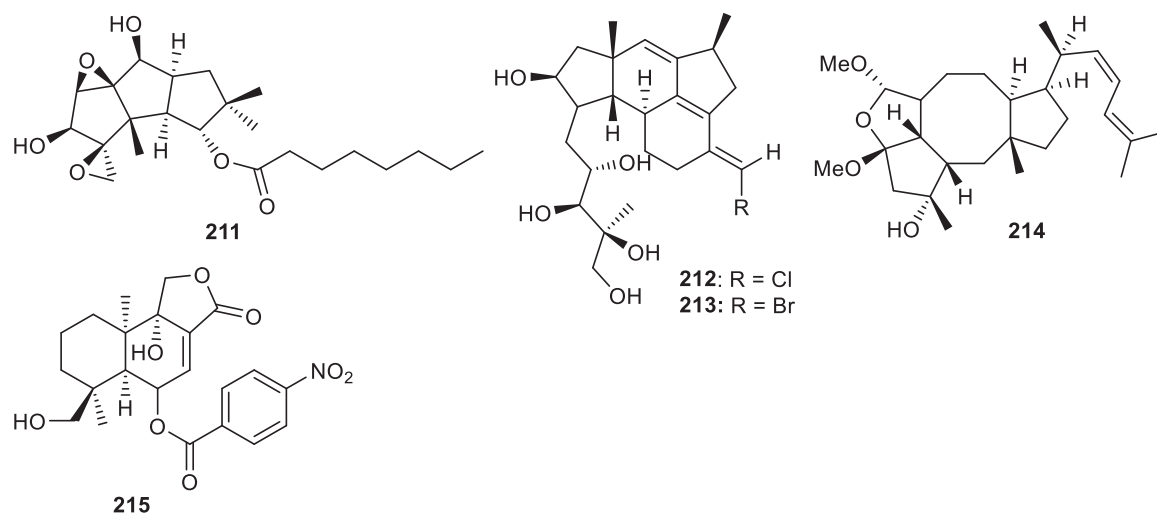


Fig. 30. Structures of sesquiterpenes and sesterterpenes 211–215.

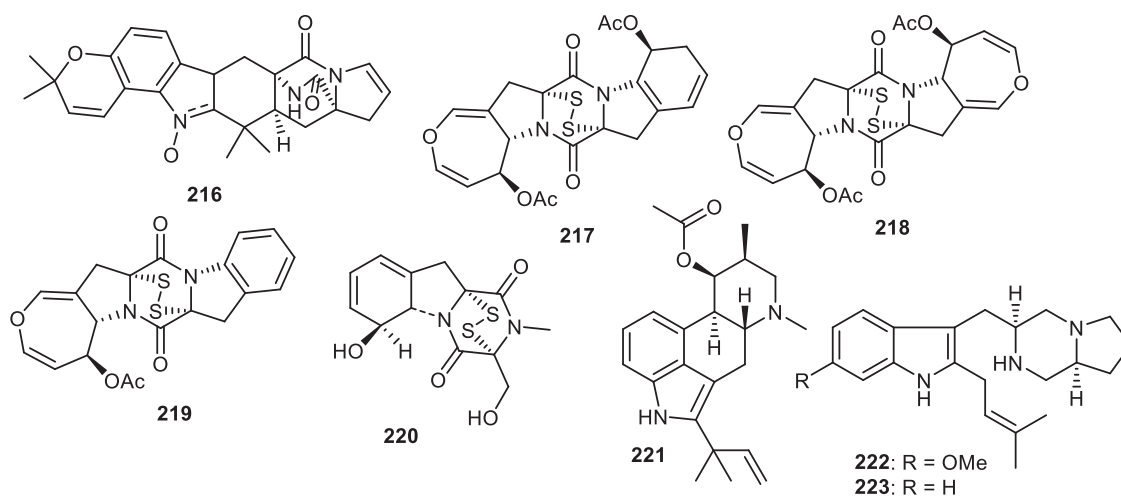


Fig. 31. Structures of alkaloids 216–223.

Three sesquiterpenes, aromadendrene (**320**), palustrol (**321**), viridiflorol (**322**), two diterpenes, xeniolide I (**323**), xeniolide O (**324**), and two steroids, 23,24-dimethylcholest-16-ene-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ,20(R)-tertol 3-monoacetate (**325**), and gorgst-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ,11 $\alpha$ ,20(S)-pentol-3-monoacetate (**326**) were reported from soft coral *Xenia umbellata*. All these compounds showed cytotoxicity towards MCF-7 with IC<sub>50</sub> ranging from 1.5 to 19.1  $\mu$ g/mL. Notably compounds 1 and 6 possessed significant cytotoxicity with IC<sub>50</sub>: 1.7 and 1.5  $\mu$ g/mL respectively [163] (Table 5).

## 7. Sea cucumbers

Argusides B-E (**327–330**) (Fig. 40) are holostane-type triterpene glycosides, isolated from the sea cucumber *Bohadschia argus* [164,165]. Compounds **327** and **328** showed potent cytotoxicity against the MCF-7 with IC<sub>50</sub>: 1.64 and 1.55  $\mu$ M, respectively [164] while argusides **329** and **330** exhibited good cytotoxicity against MCF-7 with IC<sub>50</sub>: 7.7, and 7.5  $\mu$ M (Table 6), respectively [165]. Scabraside D (**331**), fuscocineroside C (**332**) and 24-dehydrochinoside A (**333**) are also holostane-type triterpenoid glycosides isolated from the sea cucumber *Holothuria scabra*. All three compounds **331–333** showed cytotoxicity towards the

MCF-7 with IC<sub>50</sub> values of 1.80, 2.60, and 1.79  $\mu$ M, respectively [166]. Fronoside A (**334**) is triterpenoid a glycoside, found in the sea cucumber *Cucumaria frondose* and illustrated anticancer towards the MDA-MB-231 and MCF10-A, MDA-MB-435, MCF-7 with an IC<sub>50</sub> value of 1.2, 5.0, 2.5, and 2.0  $\mu$ M, respectively [167]. Holospiniferoside (**335**), a ceramide was produced by sea cucumber *Holothuria spinifera* and this molecules displayed cytotoxicity towards MCF-7 with IC<sub>50</sub>: 20.6  $\mu$ M [168].

## 8. Mollusks

Prosobranch mollusks of the genus *Lamellaria* yielded a family of pyrrole alkaloids named lamellarin D (**336**) (Fig. 41) which displayed cytotoxicity towards MCF-7 cells with an IC<sub>50</sub> value of 100 nM [169]. Pterocellins A (**337**) and B (**338**) are alkaloids isolated from the marine bryozoan *Pterocella vesiculosa*. Compound **337** possessed cytotoxicity towards MDA-MB-231 and MCF-7 with GI<sub>50</sub>: 2.6 and 1.5  $\mu$ M  $\mu$ M, respectively. Similarly compound **338** inhibited the proliferation of MCF-7, and MDA-MB-231 cells with GI<sub>50</sub>: 1.0 and 3.3  $\mu$ M, respectively [170].

Kahalalide F (**339**) (Fig. 42) is a natural depsipeptide, isolated from

**Table 4**  
Metabolites 211–298 having anti-breast cancer properties.

Name	Organism	Cell line	Cytotoxicity	Ref.
Coriolin B (211)	<i>Jaspis aff. Johnstoni</i>	T-47D	IC <sub>50</sub> : 0.7 μM	[117]
Neomangicols A (212)	<i>Fusarium equiseti</i> CNC-477	MCF-7	IC <sub>50</sub> : 4.9 μM	[118]
Neomangicols B (213)	<i>Fusarium equiseti</i> CNC-477	MCF-7	IC <sub>50</sub> : 27 μM	[118]
Ophiobolin O (214)	<i>Aspergillus ustus fungal</i>	MCF-7	IC <sub>50</sub> : 17.8 μM	[119]
9α,14-Dihydroxy-6β-p-nitrobenzoylcinnamolide (215)	<i>Aspergillus versicolor</i> CNC 327	BT-549	LC <sub>50</sub> : 0.27 μg/mL	[120]
Avrainvillamide (216)	<i>Avrainvillea</i> sp.	βT-549 T-47D	IC <sub>50</sub> : 34 nM IC <sub>50</sub> : 72 nM	[121]
Acetylpoaranotin (217)	<i>Aspergillus</i> sp.	MCF-7	IC <sub>50</sub> : 10 μM	[122]
Acetylaranotin (218)	<i>Aspergillus</i> sp.	MCF-7	IC <sub>50</sub> : 36 μM	[122]
Deoxyapoaranotin (219)	<i>Aspergillus</i> sp.	MCF-7	IC <sub>50</sub> : 31 μM	[122]
Gliotoxin (220)	<i>Aspergillus</i> sp. strain YL-06	MCF-7 T47D BT-474 ZR75-1 MDA-MB231 MDA- MB435	IC <sub>50</sub> : 985 nM IC <sub>50</sub> : 365 nM IC <sub>50</sub> : 102 nM IC <sub>50</sub> : 158 nM IC <sub>50</sub> : 138 nM IC <sub>50</sub> : 87 nM	[123]
Fumigaclavine C (221)	<i>Aspergillus fumigatus</i>	MCF-7	Inhibition: 93%	[124]
Tryprostatins A (222)	<i>Aspergillus fumigatus</i> BM939	MCF-7	IC <sub>50</sub> : 0.013 μM	[126]
Tryprostatins B (223)	<i>Aspergillus fumigatus</i> BM939	tsFT210	IC <sub>50</sub> : 12.5 μg/mL	[125]
Cyclotryprostatin A (224)	<i>Aspergillus fumigatus</i> BM939	tsFT210	IC <sub>50</sub> : 5.6 μM	[127]
Cyclotryprostatin B (225)	<i>Aspergillus fumigatus</i> BM939	tsFT210	IC <sub>50</sub> : 19.5 μM	[127]
Cyclotryprostatin C (226)	<i>Aspergillus fumigatus</i> BM939	tsFT210	IC <sub>50</sub> : 23.4 μM	[127]
Cyclotryprostatin D (227)	<i>Aspergillus fumigatus</i> BM939	tsFT210	IC <sub>50</sub> : 25.3 μM	[127]
Luteoalbusins A (228) and B (229), T988A (230), gliocladines C (231) and D (232)	<i>Acrostalagmus luteoalbus</i> SCSIO F457	MCF-7	IC <sub>50</sub> : 0.91–0.25 μM	[128]
Arthpyrone L (233)	<i>Arthrinium</i> sp.	MCF-7 MDA-MB-231	IC <sub>50</sub> : 14.0 μM IC <sub>50</sub> : 21.3 μM	[129]
Penochalasin I (234)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 7.5 μM	[130]
Penochalasin J (235)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 36.6 μM	[130]
Chaetoglobosin A (236)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 37.5 μM	[130]
Chaetoglobosin C (237)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 19.9 μM	[130]
Chaetoglobosin F (238)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 37.7 μM	[130]
Chaetoglobosin G (239)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 38.7 μM	[130]
Cytoglobosin C (240)	<i>Penicillium chrysogenum</i>	MDA-MB-231	IC <sub>50</sub> : 12.5 μM	[130]
2-Methoxyjuglone (241)	<i>Penicillium thomii</i>	MCF-7 MDA-MB-468	IC <sub>50</sub> : 11 μM IC <sub>50</sub> : 4.9 μM	[131]
Penithoketone (242)	<i>Penicillium thomii</i>	MCF-7 MDA-MB-468	IC <sub>50</sub> : 21 μM IC <sub>50</sub> : 15 μM	[131]
Alterporriol K (243)	<i>Alternaria</i> sp.	MCF-7 and MDA-MB-435	IC <sub>50</sub> : 13.1–29.1 μM	[132]
Alterporriol L (244)	<i>Alternaria</i> sp.	MCF-7 and MDA-MB-435	IC <sub>50</sub> : 13.1–29.1 μM	[132]
SZ-685 C (245)	Fungus No. 1403	MCF-7 MDA-MB-435	IC <sub>50</sub> : 7.5 μM IC <sub>50</sub> : 3 μM	[133]
Epoxyphomalins A (246)	<i>Phoma</i> sp.	MCF-7	IC <sub>50</sub> : 0.116 μg/mL	[134]
Epoxyphomalins B (247)	<i>Phoma</i> sp.	MCF-7	IC <sub>50</sub> : 0.398 μg/mL	[134]
Aszonapyrone A (248)	<i>Neosartorya laciniosa</i>	MCF-7	GI <sub>50</sub> : 13.6 μM	[135]
Sartorypyrone B (249)	<i>Neosartorya laciniosa</i>	MCF-7	GI <sub>50</sub> : 17.8 μM	[135]
Purpurogemutantintin (250)	<i>Penicillium purpurogenum</i> G59	MCF-7	IC <sub>50</sub> : 29.3 μM	[136]
Purpurogemutantintin (251)	<i>Penicillium purpurogenum</i> G59	MCF-7	IC <sub>50</sub> : 26.3 μM	[136]
Acremochlorin A (252)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 0.65 μM IC <sub>50</sub> : 0.48 μM	[137]
Acremochlorin E (253)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 45 μM IC <sub>50</sub> : 34 μM	[137]
Acremochlorin F (254)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 41 μM IC <sub>50</sub> : 15 μM	[137]
Acremochlorin G (255)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 25 μM IC <sub>50</sub> : 26 μM	[137]
Acremochlorin K (256)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 3.3 μM IC <sub>50</sub> : 1.7 μM	[137]
Acremochlorin L (257)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 12 μM; IC <sub>50</sub> : 7.5 μM	[137]
Acremochlorin M (258)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 7.4 μM IC <sub>50</sub> : 6 μM	[137]
Meroterpenoids (259–269)	<i>Acromonium sclerotigenum</i>	MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 0.65–57.0 μM	[137]
Isosclerone (270)	<i>Aspergillus fumigatus</i>	MCF-7	Inhibition %: 50–97	[138]
Monacolin X (271)	<i>Monascus</i> sp. NMK7	MCF-7 T47D MDA-MB-231 MDA-MB-468	IC <sub>50</sub> : 42.8 μM IC <sub>50</sub> : 33.9 μM IC <sub>50</sub> : 48.7 μM IC <sub>50</sub> : 26.3 μM	[139]
Pericosine A (272)	<i>Periconia byssoides</i>	HBC-5	GI <sub>50</sub> : 5.2 μM	[140]
Terrein (273)	<i>Aspergillus terreus</i>	MCF-7	IC <sub>50</sub> : 1.1 nM	[141, 142]

(continued on next page)

Table 4 (continued)

Name	Organism	Cell line	Cytotoxicity	Ref.
Marthiapeptide (274)	<i>Marinactinospora thermotolerance</i> SCSIO 00652	MCF-7	IC <sub>50</sub> : 0.38 μM	[143]
Varitriol (275)	<i>Emericella varicolor</i>	T-47D	GI <sub>50</sub> : 2.10 × 10 <sup>-7</sup> M	[144]
Compounds 276–283	<i>Monascus albidus</i>	MDA-MB-231	IC <sub>50</sub> : 9.3–41.6 μM	[145]
Ganodermaside A (284)	<i>Pseudogymnoascus</i> sp.	MDA-MB-231	IC <sub>50</sub> : 30.0 μM	[146]
Ganodermaside B (285)	<i>Pseudogymnoascus</i> sp.	MDA-MB-231	IC <sub>50</sub> : 27.0 μM	[146]
5 R,6 S,16 R,3E)– 5,6-Dihydroxy-16-methyloxacyclohexadec-3-en-2-one (286)	<i>Aspergillus flocculosus</i>	MDA-MB-231	GI <sub>50</sub> : 2.4 μM	[147]
Bekeleylactone E (287)	<i>Aspergillus flocculosus</i>	MDA-MB-231	GI <sub>50</sub> : 2.4 3.1 μM	[147]
RF-3192 C (288)	<i>Aspergillus niger</i>	MCF-7	IC <sub>50</sub> : 47 μM	[148]
Tersaphilone B (289)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 13 μM	[149]
Tersaphilone D (290)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 7.8 μM	[149]
Tersaphilone E (291)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 5.4 μM	[149]
luteusin A (292)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 2.8 μM	[149]
luteusin C (293)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 25.5 μM	[149]
RP-1551–5 (294)	<i>Phomopsis tersa</i>	MCF-7	IC <sub>50</sub> : 3.1 μM	[149]
Pensulfonamide (295)	<i>Penicillium aculeatum</i>	MCF-7	IC <sub>50</sub> : 2.18 μM	[150]
(+)-Eurotacin F (296)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 27.1 μM	[151]
(-)-Eurotacin F (296)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 28 μM	[151]
(+)-Eurotacin I (297)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 20.5 μM	[151]
(-)-Eurotacin I (297)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 23.5 μM	[151]
(+)-Eurotirumin (298)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 55.5 μM	[151]
(-)-Eurotirumin (298)	<i>Eurotium</i> sp.	MCF-7	IC <sub>50</sub> : 50.6 μM	[151]

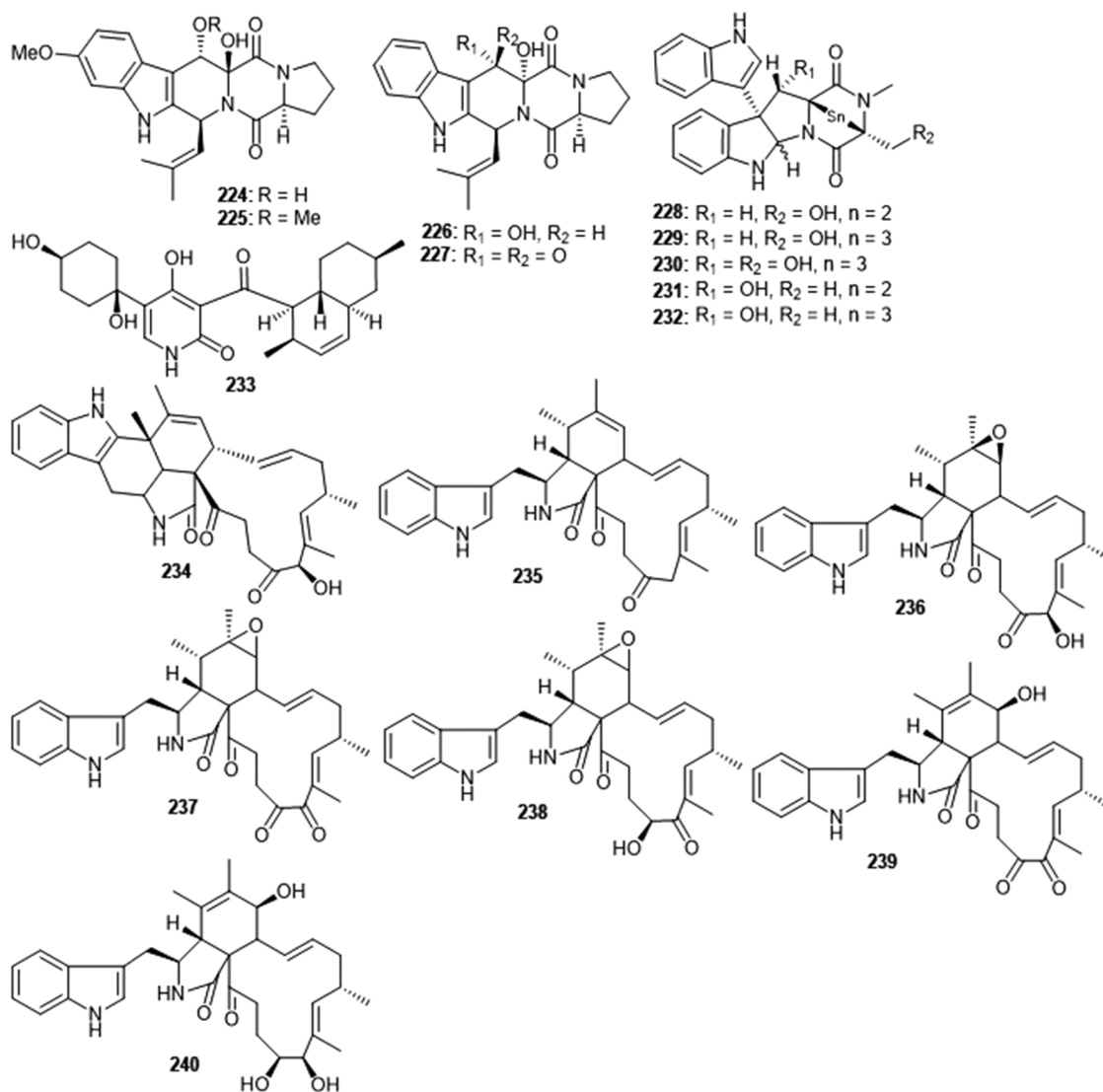


Fig. 32. Structures of alkaloids 224–240.

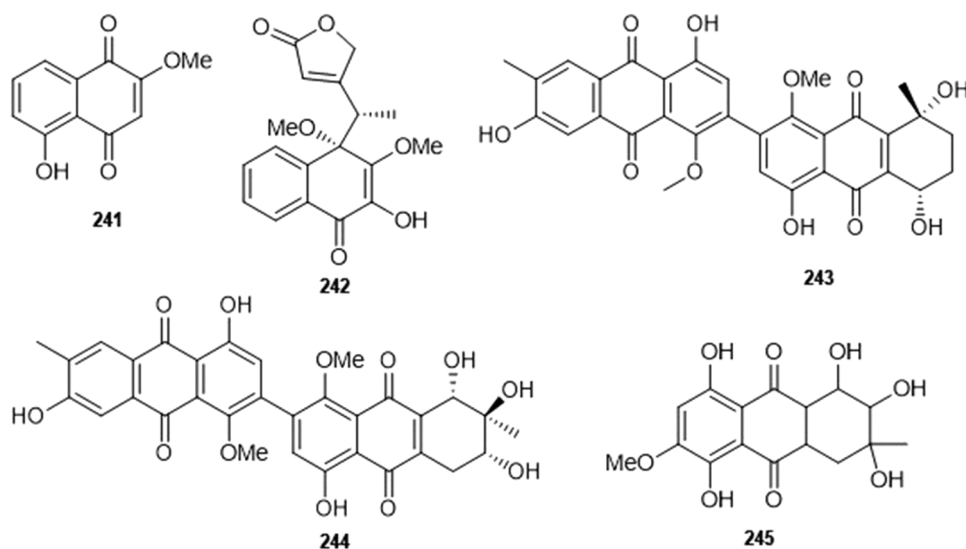


Fig. 33. Structures of quinones 241–245.

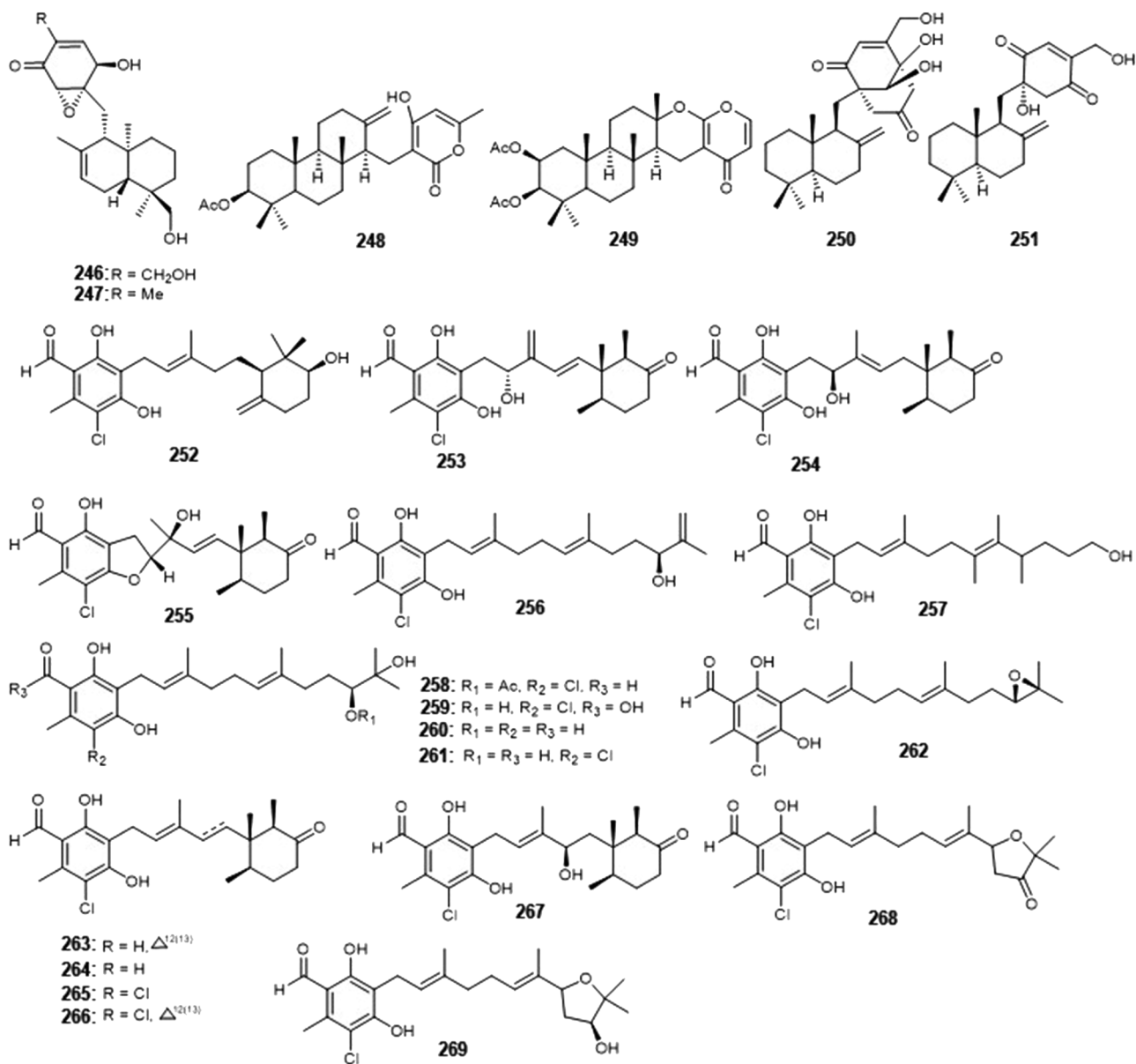


Fig. 34. Structures of meroterpenoids 246–269.

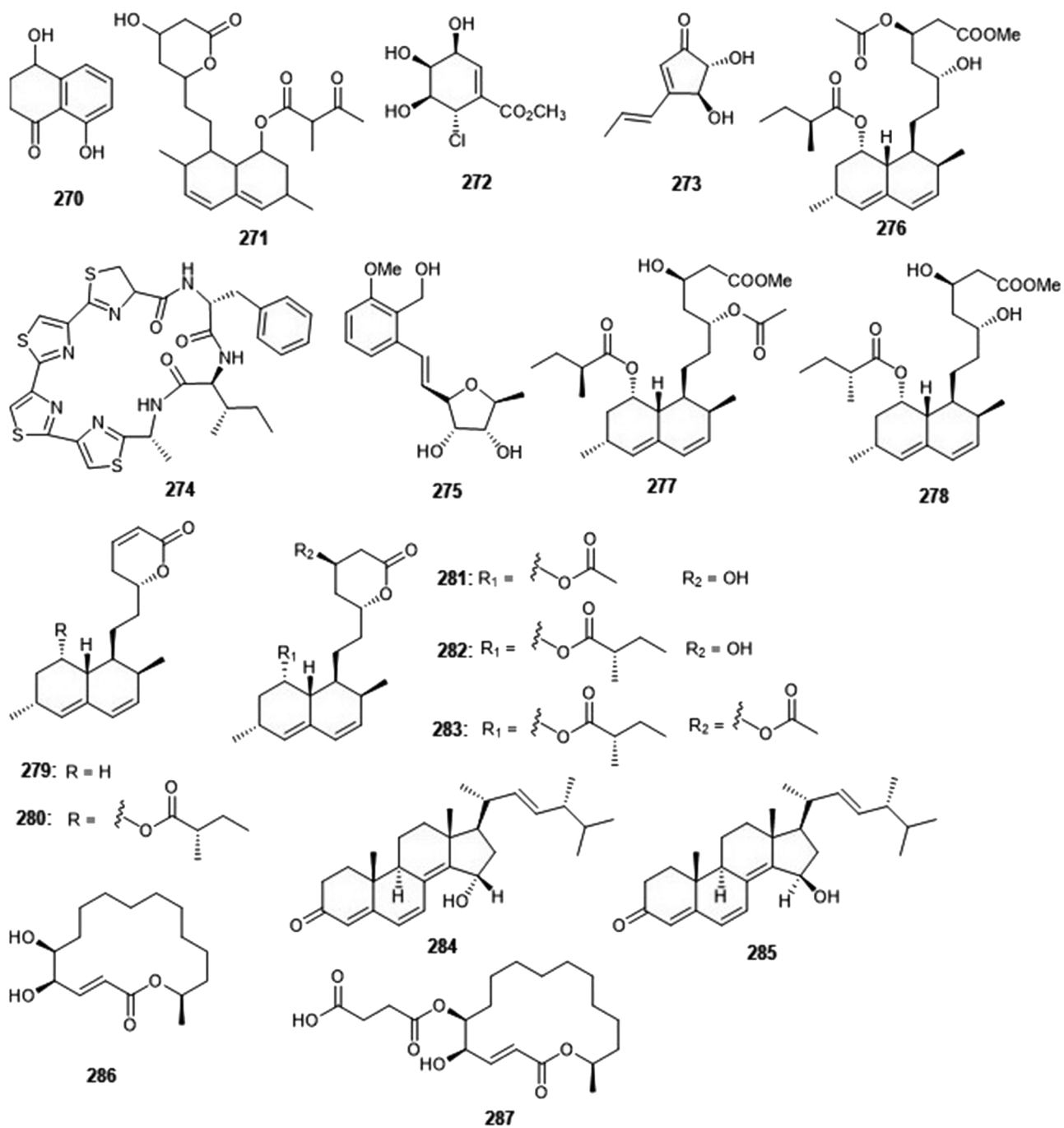


Fig. 35. Structures of compounds 270–287.

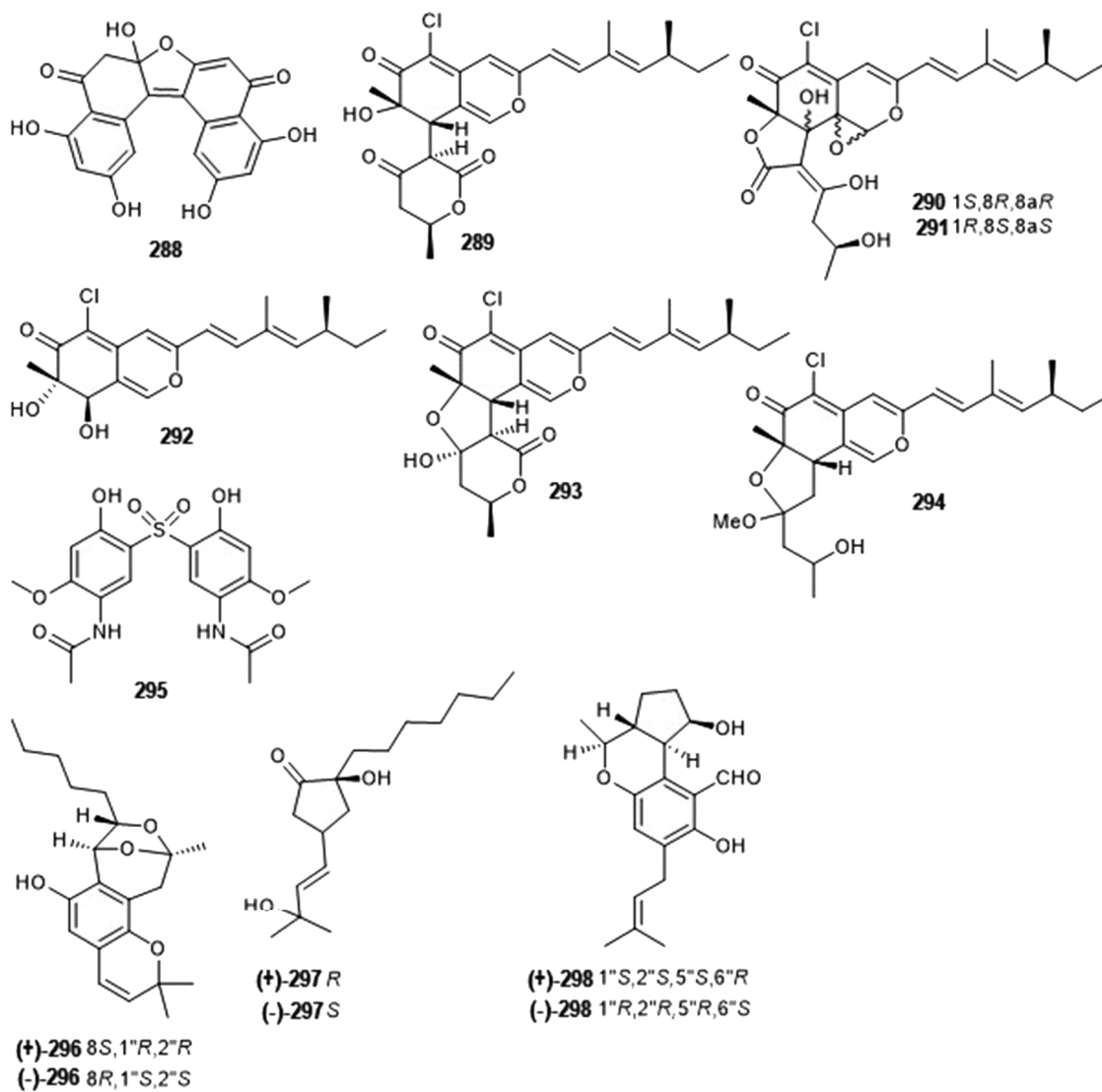


Fig. 36. Structures of compounds 288–298.

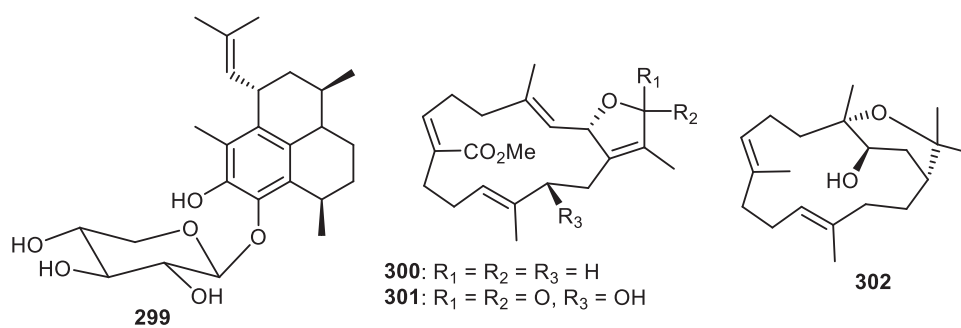


Fig. 37. Structures of compounds 299–302.

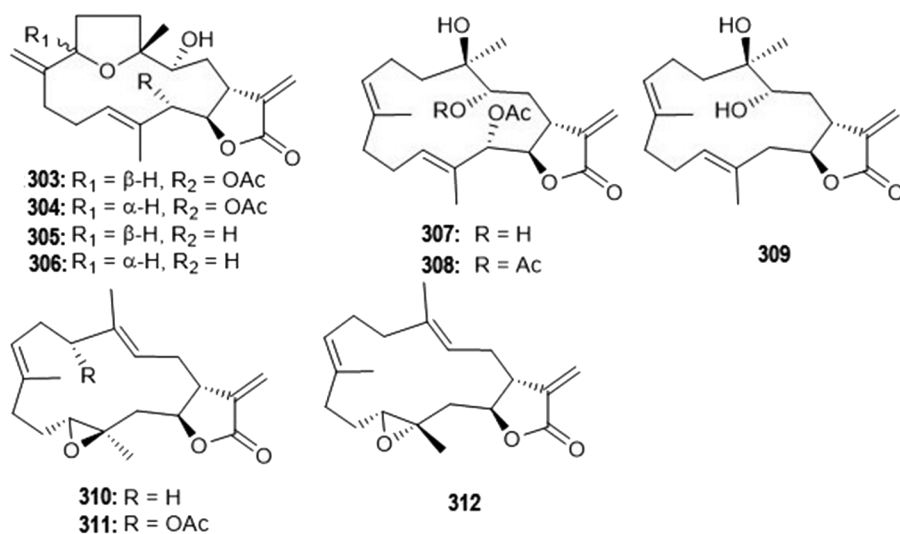


Fig. 38. Structures of compounds 303–312.

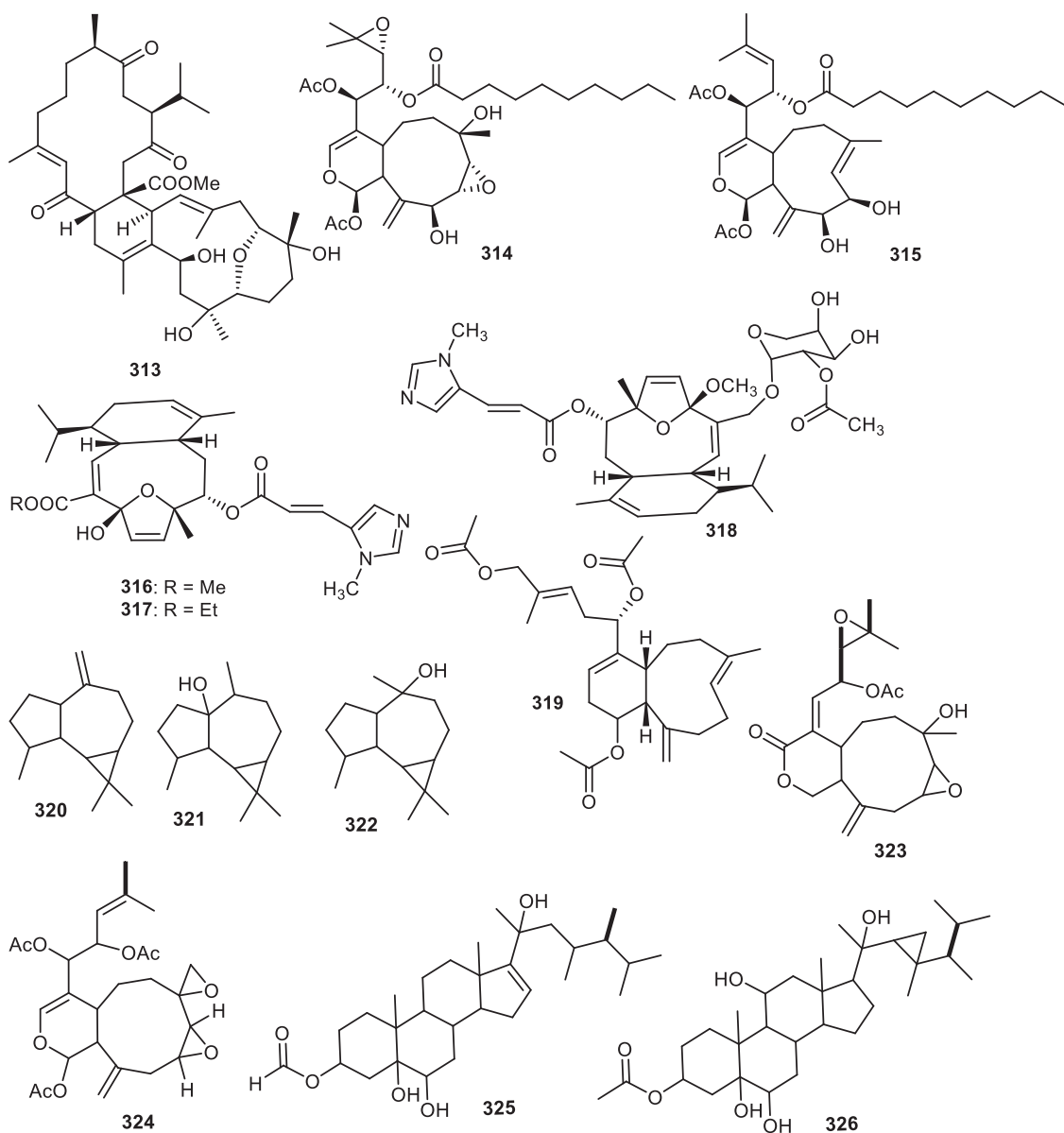


Fig. 39. Structures of compounds 313–326.

**Table 5**  
Metabolites 299–326 having anti-breast cancer properties.

Name	Organism	Cell line	Cytotoxicity	Ref.
Pseudopterosin (299)	<i>Pseudopteroqorgia elisabethae</i>	MDA-MB-231	IC <sub>50</sub> : 24.4 μM	[153]
Diterpene 300	<i>Sarcophyton ehrenbergi</i>	MCF-7	GI <sub>50</sub> : 6.1 μg/mL	[154]
Diterpenes 301	<i>Sarcophyton ehrenbergi</i>	MCF-7	GI <sub>50</sub> : 1.7 μg/mL	[154]
Cembrane diterpene 302	<i>Nephthea sp</i>	MCF-7	GI <sub>50</sub> : 0.15 μg/mL	[154]
Sarcocrassocolide A (303)	<i>Sarcophyton crassocaule</i>	MCF-7	ED <sub>50</sub> : 4.2 μg/mL	[155]
Sarcocrassocolide B (304)	<i>Sarcophyton crassocaule</i>	MCF-7	ED <sub>50</sub> : 3.2 μg/mL	[155]
Sarcocrassocolide C (305)	<i>Sarcophyton crassocaule</i>	MCF-7	ED <sub>50</sub> : 2.0 μg/mL	[155]
Sarcocrassocolide D (306)	<i>Sarcophyton crassocaule</i>	MCF-7	ED <sub>50</sub> : 4.1 μg/mL	[155]
Crassocolides A, B, D-F (307–311)	<i>Sarcophyton crassocaule</i>	MCF-7	IC <sub>50</sub> : 2.0–15.3 μg/mL	[156]
		MDA-MB-231		
Lobophytolide (312)	<i>Sarcophyton crassocaule</i>	MDA-MB-231	IC <sub>50</sub> : 2.0 μg/mL	[156]
		MCF-7	IC <sub>50</sub> : 2.3 μg/mL	
Sardigitolide B (313)	<i>Sarcophyton digitatum</i>	MCF-7	IC <sub>50</sub> : 9.6 μg/mL	[157]
		MDA-MB-231	IC <sub>50</sub> : 14.8 μg/mL	
Protoxenicin A (314)	<i>Protodendron repens</i>	MDAMB-231	GI <sub>50</sub> : 2.1 μM	[158]
Protoxenicin B (315)	<i>Protodendron repens</i>	MDAMB-231	GI <sub>50</sub> : 6.3 μM	[158]
Sarcodictyin A (316)	<i>Eleutherobia aurea</i>	MCF-7	IC <sub>50</sub> : 400 nM	[160,161]
Sarcodictyins B (317)	<i>Eleutherobia aurea</i>	MCF-7	IC <sub>50</sub> : 300 nM	[160,161]
Eleutherobin (318)	<i>Eleutherobia species</i>	MCF-7	IC <sub>50</sub> : 10 nM	[160,161]
Waixenicin A (319)	<i>Sarcotelia edmondsoni</i>	MCF-7	IC <sub>50</sub> : 4.6 μM	[162]
Aromadendrene (320)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 1.7 μg/mL		[163]
Palustrol (321)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 7.5 μg/mL		[163]
Viridiflorol (322)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 2.4 μg/mL		[163]
Xeniolide I (323)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 18.2 μg/mL		[163]
Xeniolide O (324)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 23.2 μg/mL		[163]
23,24-Dimethylcholest-16-ene-3β,5α,6β,20(R)-tertol 3-monoacetate (325)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 1.5 μg/mL		[163]
Gorgst-3β,5α,6β,11α,20(S)-pentol-3-monoacetate (326)	<i>Xenia umbellata</i>	MCF-7: IC <sub>50</sub> : 19.1 μg/mL		[163]

the Hawaiian marine mollusk *Elysia rufescens* [171] and illustrated potent cytotoxicity against SKBR-3, BT474 & MCF-7 cell lines with IC<sub>50</sub> values of 0.23, 0.26 and 0.28 μM, respectively [172]. Dolastatin 19 (340) is a macrocyclic lactone isolated from the marine mollusk *Dolabella auricularia* collected from the Gulf of California. Compound 340 inhibited the proliferation of MCF-7 with GI<sub>50</sub>: 0.72 μg/mL [173].

## 9. Tunicates and Sea pen

Lissoclinotoxins E (341) and F (342) (Fig. 43) are dimeric polysulfide alkaloids isolated from a didemnid ascidian of the genus *Lissoclinum* collected from Philippines. Compounds 341 and 342 showed cytotoxic effects towards MDA-MB-468, with IC<sub>50</sub>: 2.3 and 1.5 μg/mL, respectively [174]. Indolocarbazole alkaloids 343 and 344 were obtained from marine ascidian *Cystodytes solitus*. Both alkaloids 343 and 344 reduced the proliferation of the MDA-MB-231 with GI<sub>50</sub> 28.4 and 32.1 nM, respectively [175]. Aplidine (345) is a cyclic depsipeptide which was reported from the *Aplidium albicans* and is now in phase II clinical trials. This interesting compound displayed efficient activity towards the MDA-MB-231 human mammary cell line with an IC<sub>50</sub> value of 5 nM [176]. Metabolites 346–348 were isolated from the marine-derived Sea pen, *Virgularia gustaviana* and showed an anti-proliferative effect against MDA-MB-231 with IC<sub>50</sub> values of 0.093, 0.42, and 0.024 mg/mL, respectively [177].

Aplicyanins B (349), bromoindole alkaloids, D-F (350–352) were produced by tunicate *Aplidium cyaneum* and all compounds (except compound 351) demonstrated potent cytotoxicities towards MDA-MB-231 with IC<sub>50</sub>: 0.42, 0.41, and 0.81 μM, respectively [178]. Jimenez et al. [179] reported 2-hydroxy-7-oxostauroporine (353) and 3-hydroxy-7-oxostauroporine (354) from tunicate *Eudistoma vannamei* and mixture of these compounds possessed potent cytotoxic effects towards MDA-MB-435 with IC<sub>50</sub>: 28.6 nM.

## 10. Starfish

Triterpene glycosides, pacificosides B (355), C (356), cucumariosides C1 (357), C2 (358), and A10 (359) (Fig. 44), were reported from starfish *Solaster pacificus*. Compounds 356–359 possessed significant effects towards MDA-MB-231 with IC<sub>50</sub> of 6.4, 3.6, 4.4, and 5.5 μM, respectively. On the other hand, triterpene 355 displayed week effects with IC<sub>50</sub> of 21.5 μM [180].

## 11. Miscellaneous marine sources

Aplysqualenol A (360) (Fig. 45) is a bromotriterpene polyether, that was collected from the Caribbean sea slug *Aplysia dactylomela*, collected off the Puerto Rico coast. Compound 360 displayed a potent inhibitory activity towards the T-47D cell line, with an IC<sub>50</sub>: 0.3 μg/mL [181]. Halocynthiaxanthin (361) and fucoxanthinol (362) are two carotenoids related to fucoxanthin that were isolated from the *Halocynthia roretzi* sea squirt. Both compounds displayed a decrease in the proliferation of the MCF-7 cells and interestingly, exhibited apoptosis inducing effects [182].

## 12. Conclusion

Bearing in mind that marine world investigations are really in their infancy stages, the present review confirms that a huge diversity of the marine compounds, structurally unique have clearly illustrated their potential as new anti-breast cancer compounds. Currently, the development of new technologies, especially the new “omics” approaches, which are extremely efficient and sensitive methods to study marine secondary metabolites, combined with genome mining, should contribute to the development of new emerging bioactive compounds having a profound impact on human health, particularly in the fight against breast cancer.



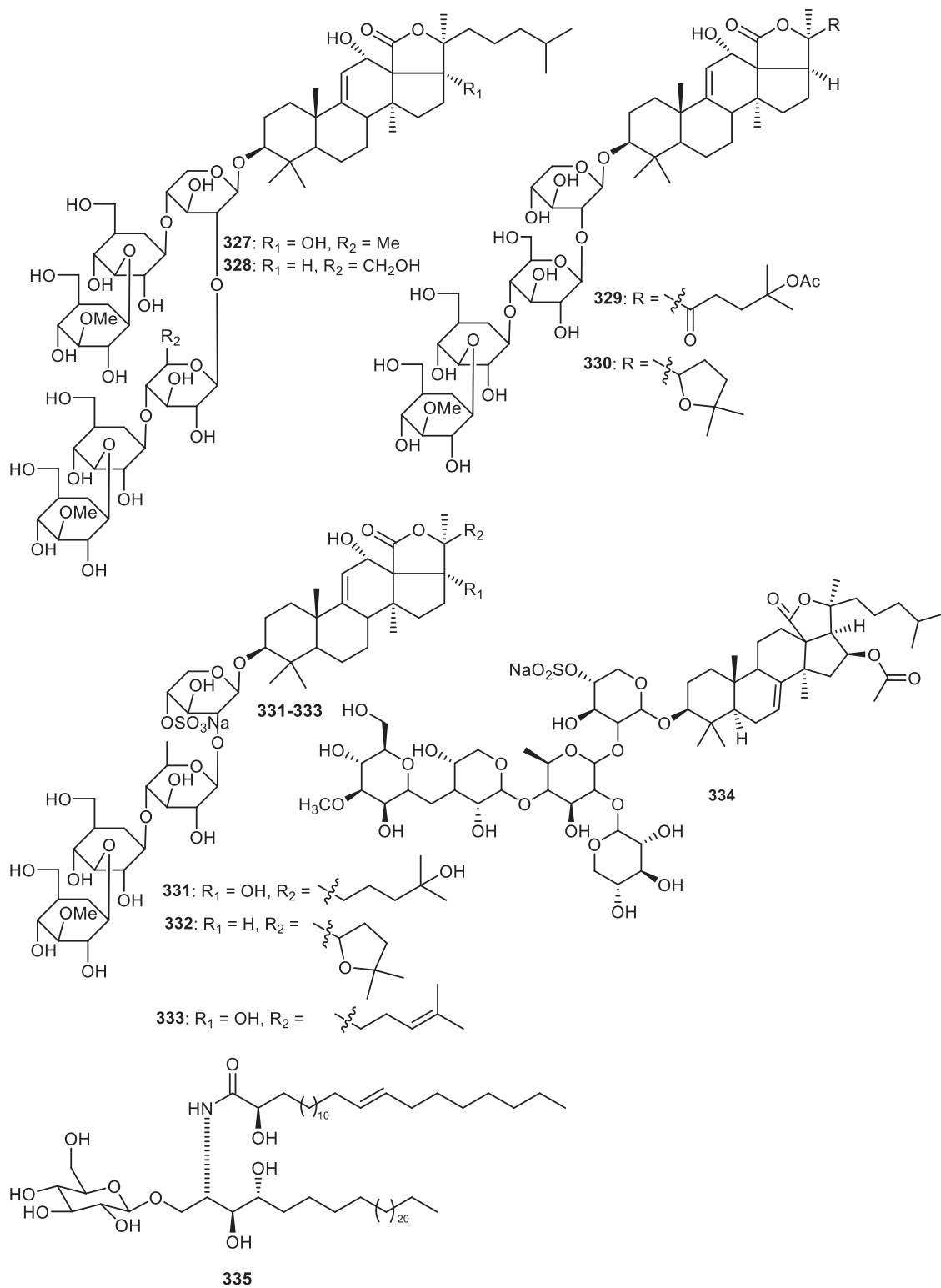


Fig. 40. Structures of compounds 327–335.

**Table 6**  
Metabolites 327–366 having anti-breast cancer properties.

Name	Organism	Cell line	Cytotoxicity	Ref.
Arguside B (327)	<i>Bohadschia argus</i>	MCF-7	IC <sub>50</sub> : 1.64 μM	[164,165]
Arguside C (328)	<i>Bohadschia argus</i>	MCF-7	IC <sub>50</sub> : 1.55 μM	[164,165]
Arguside D (329)	<i>Bohadschia argus</i>	MCF-7	IC <sub>50</sub> : 7.7 μM	[164,165]
Arguside E (330)	<i>Bohadschia argus</i>	MCF-7	IC <sub>50</sub> : 7.5 μM	[164,165]
Scabraside D (331)	<i>Holothuria scabra</i>	MCF-7	IC <sub>50</sub> : 1.8 μM	[166]
Fuscocineroside C (332)	<i>Holothuria scabra</i>	MCF-7	IC <sub>50</sub> : 2.6 μM	[166]
24-Dehydroechinoside A (333)	<i>Holothuria scabra</i>	MCF-7	IC <sub>50</sub> : 1.79 μM	[166]
Frondoside A (334)	<i>Cucumaria frondose</i>	MDA-MB-231 and MCF10-A, MDA-MB-435, MCF-7	IC <sub>50</sub> : 1.2, 5.0, 2.5, and 2.0 μM	[167]
Holospiniferoside (335)	<i>Holothuria spinifera</i>	MCF-7	IC <sub>50</sub> : 20.6 μM	[168]
lamellarin D (336)	<i>Lamellaria</i> sp.	MCF-7	IC <sub>50</sub> : 100 nM	[169]
Pterocellin A (337)	<i>Pterocella vesiculosa</i>	MCF-7; MDA-MB-231	GI <sub>50</sub> : 1.5 μM, and 2.6 μM	
Pterocellin B (338)	<i>Pterocella vesiculosa</i>	MCF-7; MDA-MB-231	GI <sub>50</sub> : 1.0 and 3.3 μM	[170]
Kahalalide F (339)	<i>Elysia rufescens</i>	SKBR-3, BT474 & MCF-7	IC <sub>50</sub> : 0.23, 0.26 and 0.28 μM	[171,172]
Dolastatin 19 (340)	<i>Dolabella auricularia</i>	MCF-7	GI <sub>50</sub> : 0.72 μg/mL	[173]
Lissoclinotoxin E (341)	<i>Lissoclinum</i> sp.	MDA-MB-468	IC <sub>50</sub> : 2.3 μM	[174]
Lissoclinotoxin F (342)	<i>Lissoclinum</i> sp.	MDA-MB-468	IC <sub>50</sub> : 1.5 μM	[174]
Alkaloid 343	<i>Cystodytes solitus</i>	MDA-MB-231	GI <sub>50</sub> : 28.4 nM,	[175]
Alkaloid 344	<i>Cystodytes solitus</i>	MDA-MB-231	GI <sub>50</sub> : 32.1 nM	[175]
Aplidine (345)	<i>Aplidium albicans</i>	MDA-MB-231	IC <sub>50</sub> : 5 nM	[176]
Compound 346	<i>Virgularia gustaviana</i>	MDA-MB-231	IC <sub>50</sub> : 0.093 mg/mL	[177]
Compound 347	<i>Virgularia gustaviana</i>	MDA-MB-231	IC <sub>50</sub> : 0.42, mg/mL	[177]
Compound 348	<i>Virgularia gustaviana</i>	MDA-MB-231	IC <sub>50</sub> : 0.024 mg/mL	[177]
Aplicyanin B (349)	<i>Aplidium cyaneum</i>	MDA-MD-231	IC <sub>50</sub> : 0.42 μM	[178]
Aplicyanin D (350)	<i>Aplidium cyaneum</i>	MDA-MD-231	IC <sub>50</sub> : 0.41 μM	[178]
Aplicyanin E (351)	<i>Aplidium cyaneum</i>	MDA-MD-231	IC <sub>50</sub> : 7.9 μM	[178]
Aplicyanin F (352)	<i>Aplidium cyaneum</i>	MDA-MD-231	IC <sub>50</sub> : 0.81 μM	[178]
2-Hydroxy-7-oxostaurosporine (353) and 3-Hydroxy-7-oxostaurosporine (354)	<i>Eudistoma vannamei</i>	MDA-MB-435	Mixture of 353 and 354: IC <sub>50</sub> : 28.6 nM	[179]
Pacificusoside B (355)	<i>Solaster pacificus</i>	MDA-MB-231	IC <sub>50</sub> : 21.5 μM	[180].
Pacificusoside C (356)	<i>Solaster pacificus</i>	MDA-MB-231	IC <sub>50</sub> : 6.4 μM	[180].
Cucumariosides C1 (357)	<i>Solaster pacificus</i>	MDA-MB-231	IC <sub>50</sub> : 3.6 μM	[180].
Cucumariosides C2 (358)	<i>Solaster pacificus</i>	MDA-MB-231	IC <sub>50</sub> : 4.4 μM	[180].
Cucumariosides A10 (359)	<i>Solaster pacificus</i>	MDA-MB-231	IC <sub>50</sub> : 5.5 μM	[180].
Aplysqualenol A (360)	<i>Aplysia dactylomela</i>	T-47D: IC <sub>50</sub> : 0.3 μM		[181]

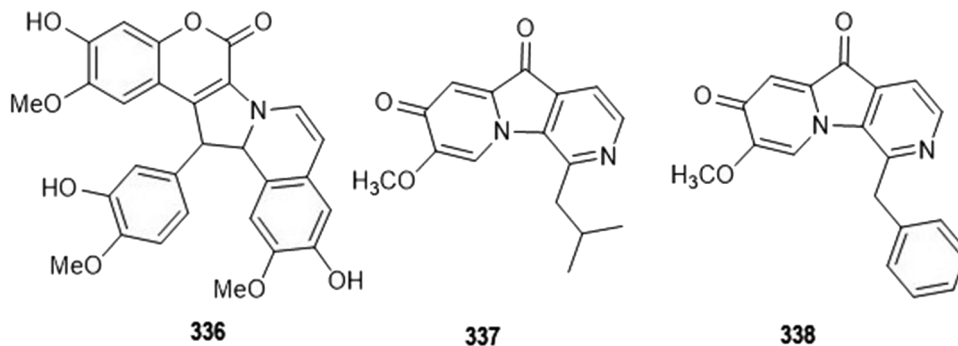


Fig. 41. Structures of compounds 336–338.

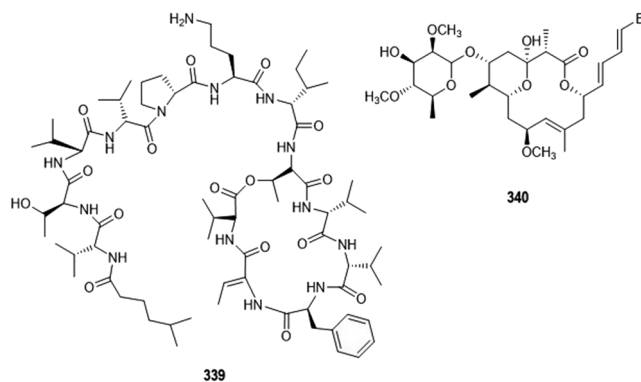


Fig. 42. Structures of compounds 339 and 340.

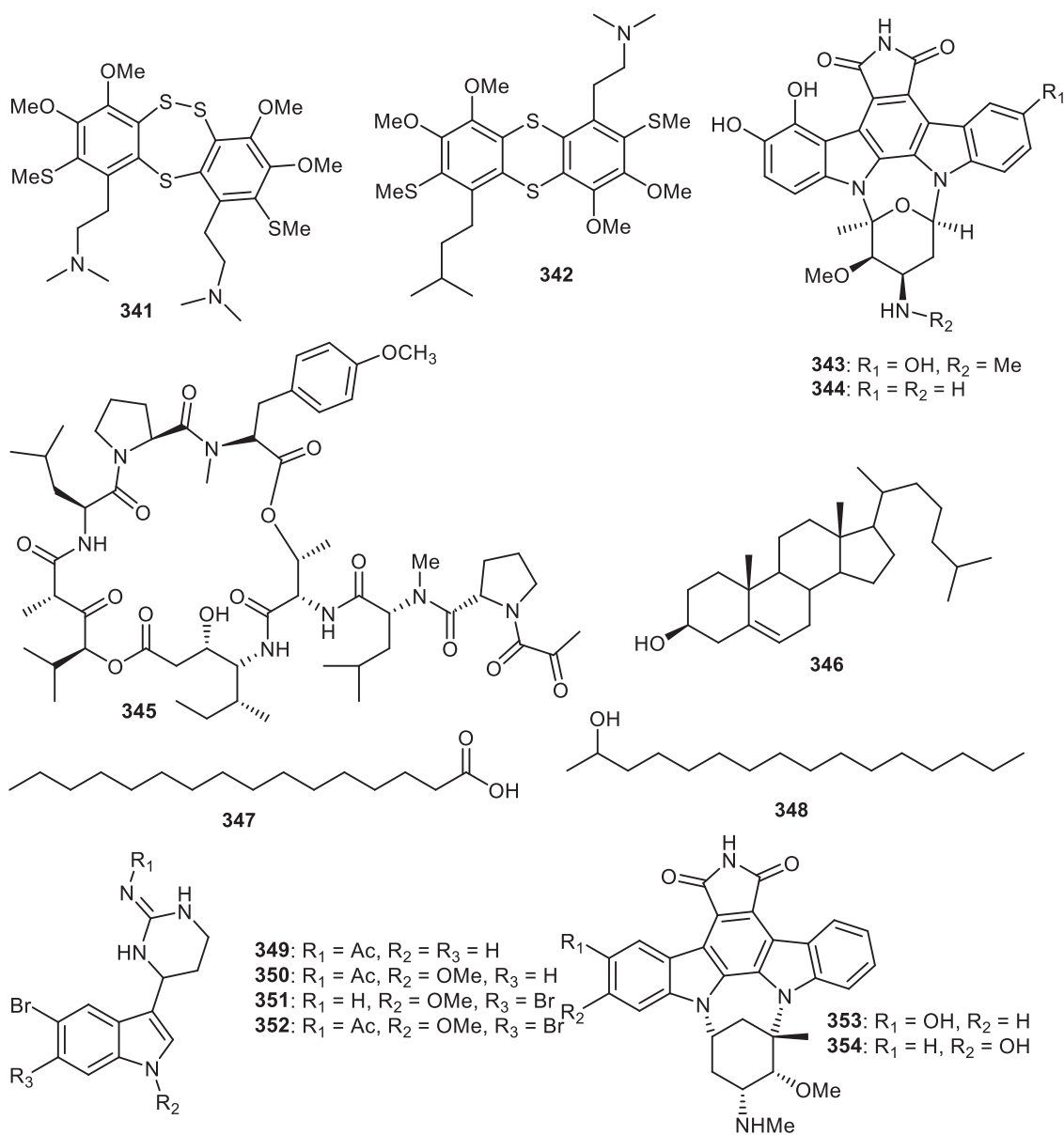


Fig. 43. Structures of compounds 341–354.

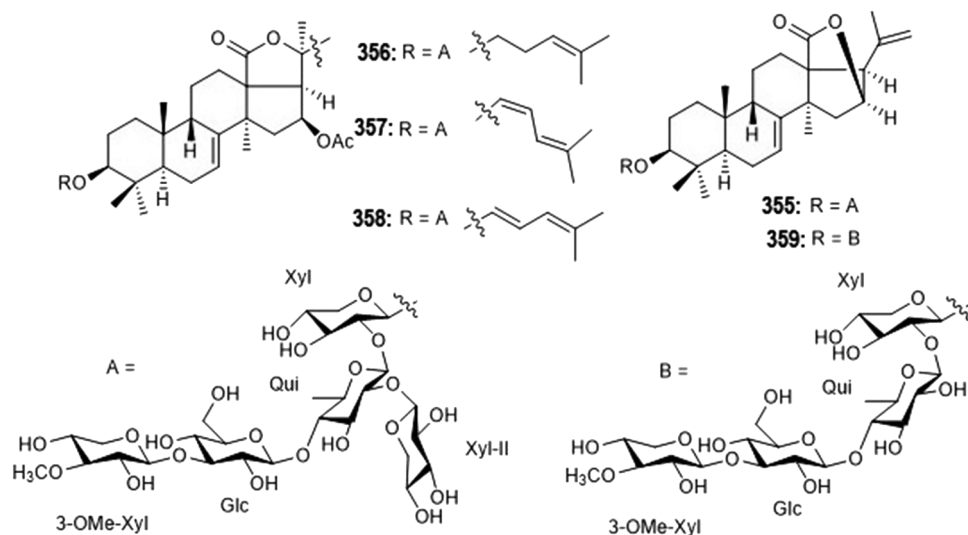


Fig. 44. Structures of compounds 355–359.

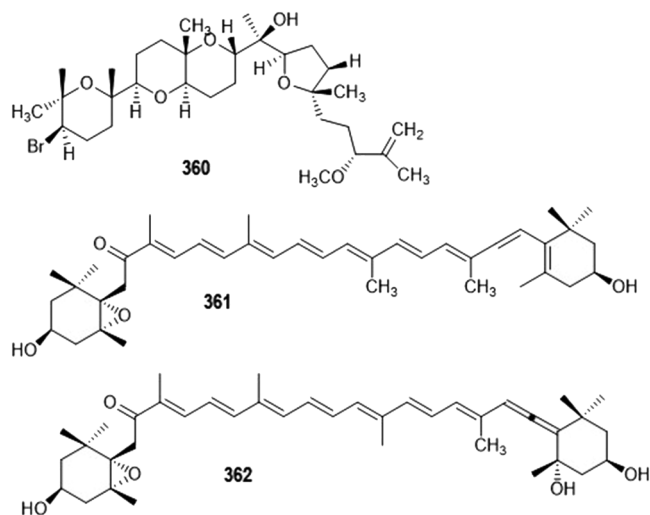


Fig. 45. Structures of compounds 360–362.

### CRediT authorship contribution statement

Amjad Hussain, Hidayat Hussain, Polrat Wilairatana: Conceptualization. X.X.: Writing – original draft preparation. Amjad Hussain, Marie-Lise Bourguet-Kondracki, Maryam Majeed, Muhammad Ibrahim, Xian-Wen Yang, Ishtiaq Ahmed, Muhammad Ibrahim, Ataf Ali Altaf, Anees Ahmed Khalil, Abdur Rauf, Polrat Wilairatana, Hassan A. Hemeg, Riaz Ullah, Ivan R. Green, Iftikhar Ali, Syed Tasadaque A. Shah Hidayat Hussain: Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

### Conflicts of interest statement

The authors declare no conflict of interest.

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