

## Chapter 2

# Triterpenoids as Anticancer Drugs from Marine Sponges

Yong-Xin Li and Se-Kwon Kim

**Abstract** Natural products provide an important source of new therapeutic drugs and biochemical tools. In the last decades researchers of natural products chemistry focused their research in a wide variety of bioactive compounds from marine species. Marine sponges have been considered as a very fertile field for the discovery of bioactive natural chemical substances with respect to the diversity of their primary and secondary chemical components and metabolites. Triterpenoids are the most abundant secondary metabolite present in marine sponges. A large number of triterpenoids are known to exhibit cytotoxicity against a variety of tumor cells as well as anticancer efficacy in preclinical animal models. Therefore, triterpenoids from marine sponges leads to be used in the pharmaceutical industry as new chemical classes of anticancer agents.

**Keywords** Triterpenoids · Anticancer agents · Marine natural products · Marine sponges

## 2.1 Introduction

Natural products have served as important chemical prototypes for the discovery of new molecules, and continue to be the most promising source of drug leads, especially in the anticancer field [1]. In the last decades researchers of natural products chemistry focused their research in a wide variety of bioactive compounds from marine species. Marine sponges for the past decades have been considered as a

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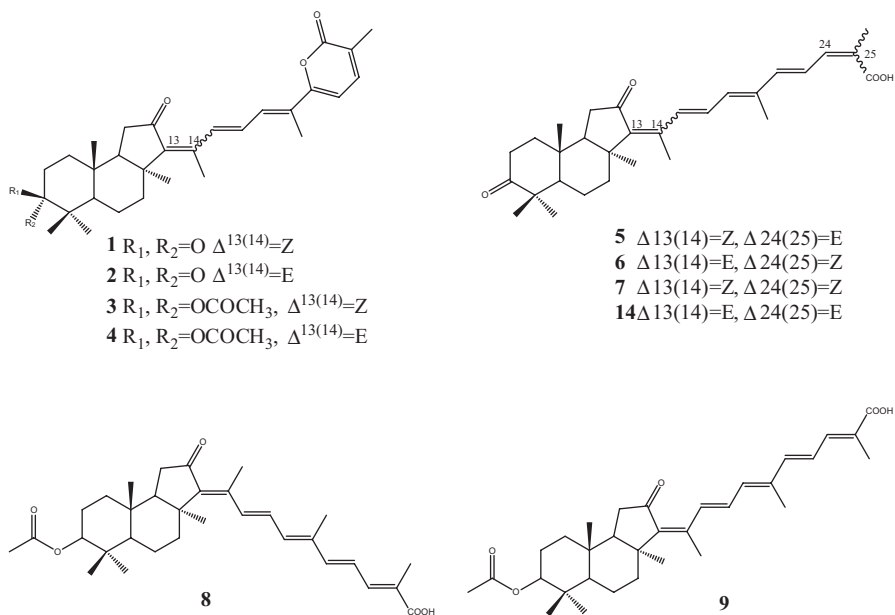
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very fertile field for the discovery of bioactive natural chemical substances with respect to the diversity of their primary and secondary chemical components and metabolites [2]. Marine sponges have a bright potential in anticancer drug discovery as they represent a major source of new antitumor and anticancer drugs [3]. Triterpenoids are structurally diverse organic compounds, characterized by a basic backbone modified in multiple ways, allowing the formation of more than 20,000 naturally occurring triterpenoid varieties. Several triterpenoids, including ursolic and oleanolic acid, betulinic acid, celastrol, pristimerin, lupeol, and avicins possess antitumor and anti-inflammatory properties [4]. Triterpenoids are terpenoid derivatives of natural products containing about thirty carbon atoms, and their structures are considered to be derived from acyclic precursor squalene [5, 6]. Triterpenoids are the most abundant secondary metabolite present in marine sources, such as marine sponges [7, 8]. During a last few years, great number of biologically active triterpenoids is found to have cytotoxicity against a variety of tumor cells [9, 10]. More than 20,000 triterpenoids has been isolated and identified from nature, which belongs to chemical groups such as, squalene, lanostane, dammarane, lupane, oleanane, ursane, hopane [11, 12]. This chapter summarizes the anti-cancer triterpenoids isolated from marine sponge, that includes isomalabaricane-type triterpenoids (stellettins, stelliferins, and geoditins), and their potential anti-cancer activity. Therefore, this chapter brings insights to marine triterpenoids as potent candidates to be developed as pharmaceuticals against tumor progression.

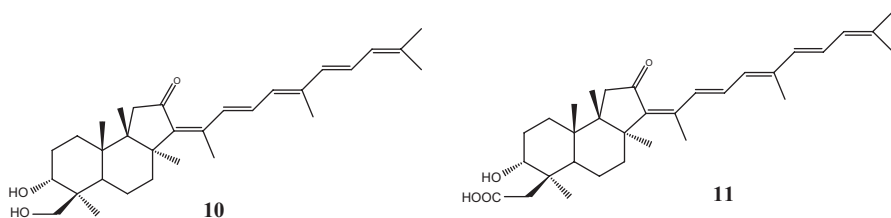
## 2.2 Triterpenoids from marine Sponge

Isomalabaricane-type triterpenoids are a rare group of triterpenoids with unique skeleton, often found in marine sponges. Isomalabaricane-type triterpenes were first reported from a Fijian collection of the sponge *Jaspis stellifera* and the Somalian marine sponge *Stelletta* sp. Since then, they have been isolated from several genera of marine sponges belonging to the order Astrophorida including members of the genera *Rhabdastrella*, *Stelletta*, *Jaspis*, and *Geodia* [13]. The cytotoxic isomalabaricane-type triterpenoids stellettins A–K (1–13) have been reported from the marine sponge species of the genus *Jaspis* [14], *Stelletta* [15–17], and *Rhabdastrella* [18]. Stellettin A (1) and B (2), were isolated from the sponge *Stelletta tmuis* collected from Hainan Island, China in 1994. Stellettin A was significantly toxic to P388 leukemia cells, exhibiting an  $ED_{50}$  value of  $0.001 \mu\text{g/ml}$  [19]. Furthermore, Liu et al. have demonstrated that stellettin A and stellettin B induce cytotoxicity in HL-60 cells treated for 24 h at  $3 \mu\text{M}$  concentration [20]. The cytotoxic isomalabaricane triterpenoids stellettins A–G (1–7) have been examined at the National Cancer Institute (Australia) against 60 cell lines. Stelletin C (3) and D (4) were the most potent derivative with a mean panel  $GI_{50}$  of  $0.09 \mu\text{M}$ . The stellettin E (5) and F (6) pair was approximately 10-times less potent (mean  $GI_{50}$  of  $0.98 \mu\text{M}$ ) [13, 15].

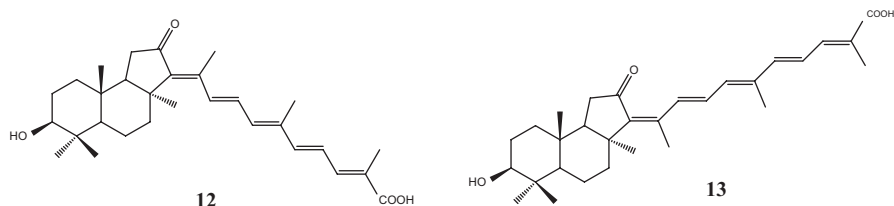
The isomalabaricane triterpenes, Stelletin A-D (**1–4**), stellettin H (**8**) and stellettin I (**9**) with and rhabdastrellic acid-A (**14**), have been isolated from the marine sponge *Rhabdastrella globostellata*, collected from the Philippines. These compounds have shown selective cytotoxicity towards p21<sup>WAF1/Cip1</sup>-deficient human colon tumor (HCT-116) cells [21].



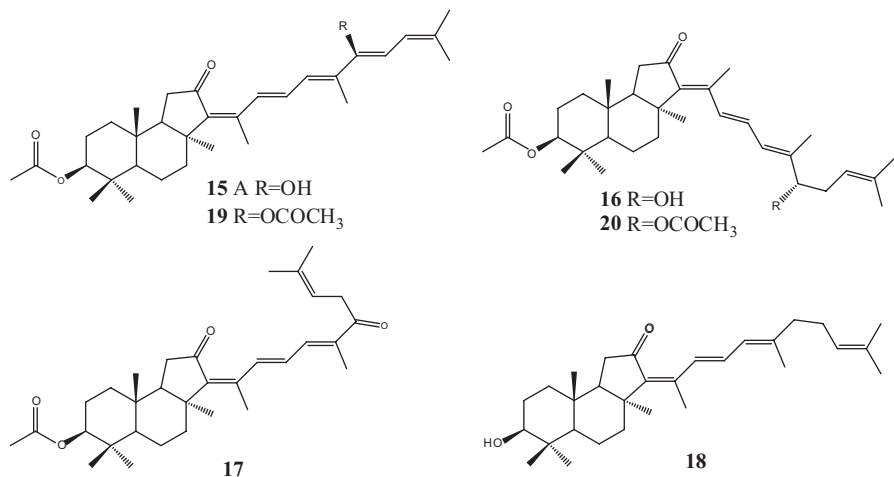
The cytotoxic isomalabaricane triterpenoids Stellettin J (**10**) and K (**11**) from *Rhabdastrella globostellata* has shown activity in an assay measuring stabilization of the binding of DNA with DNA polymerase  $\beta$ . However, stellettin J (**10**) and K (**11**) displayed varying levels of activity toward the A2780 ovarian cancer cell line, revealing structure-based effects on both the level of cytotoxicity and DNA-polymerase  $\beta$  binding [22].

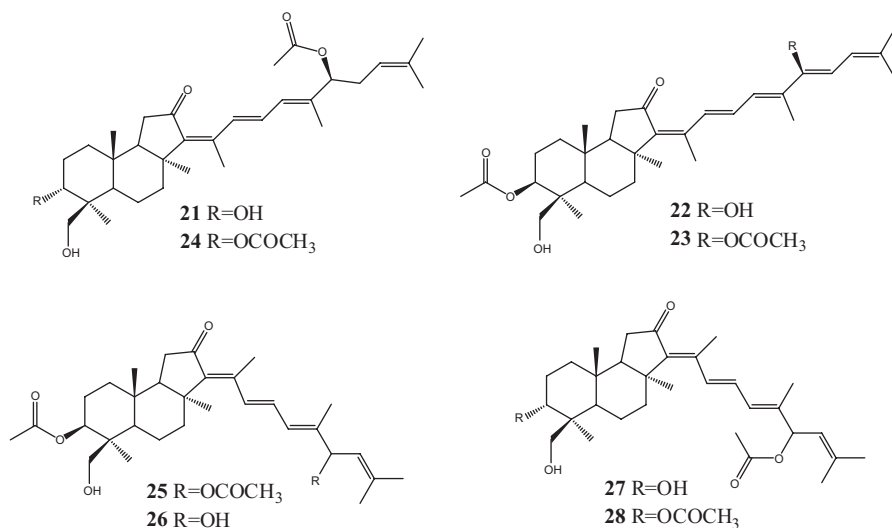


Stelletin L (**12**) and M (**13**) were isolated from the marine sponge *Stelletta tenuis* collected in the South China Sea and both compounds exhibited significant cytotoxic activity against stomach cancer cells (AGS) *in vitro* [17].

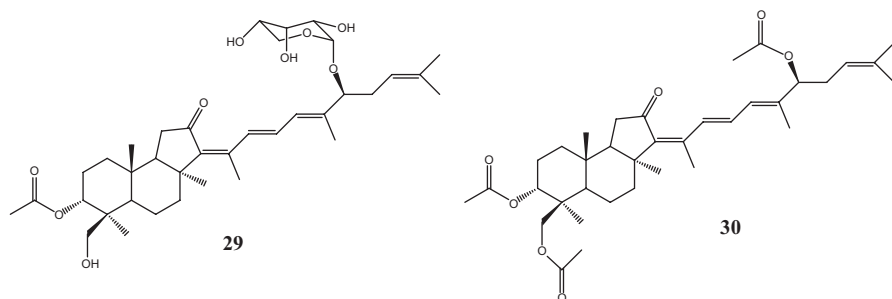


Stelliferins A–F (**15–20**), antineoplastic isomalabaricane triterpenes were isolated from the Okinawan marine sponge *Jaspis stellifera* [23]. The isomalabaricane triterpenes, stelliferin G (**21**), 29-hydroxystelliferin A (**22**), 29-hydroxystelliferin E (**23**) together with the known triterpene 3-*epi*-29-hydroxystelliferin E (**24**), 13*E*-29-hydroxystelliferin E (**25**), 29-hydroxystelliferin B (**26**), 13*E*-stelliferin G (**27**), and 13*E*-3-*epi*-29-hydroxy-stelliferin E (**28**), were isolated from the organic extract of the sponge *Jaspis sp.* collected in the South Pacific ocean. All compounds were tested against melanoma (MALME-3M) and leukemia (MOLT-4) cells. The mixtures of 29-hydroxystelliferin B (**26**) and 13*E*-stelliferin G (**27**) have shown highest growth-inhibitory [(IC<sub>50</sub>) 0.11, 0.23 µg/mL, respectively] activities against MALME-3M [24].



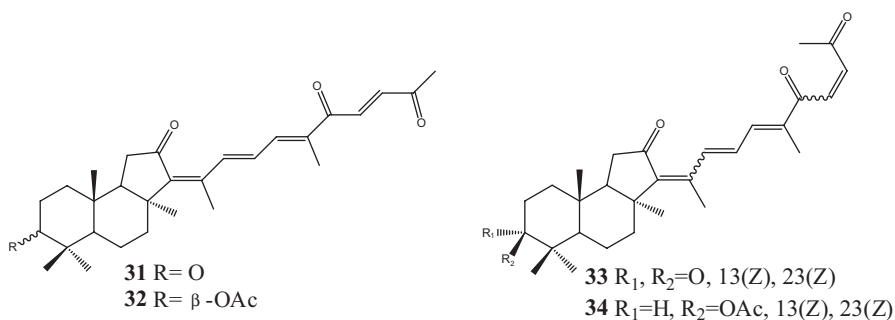


Moreover, stelliferin riboside (**29**) and 3-*epi*-29-acetoxystelliferin E (**30**) isomalabaricane triterpenoids were isolated from an extract of the sponge *Rhabdastrella globostellata* which was active in an assay measuring stabilization of the binding of DNA with DNA polymerase  $\beta$ . Two compounds have shown to induce 29 and 23 % binding, respectively [22].

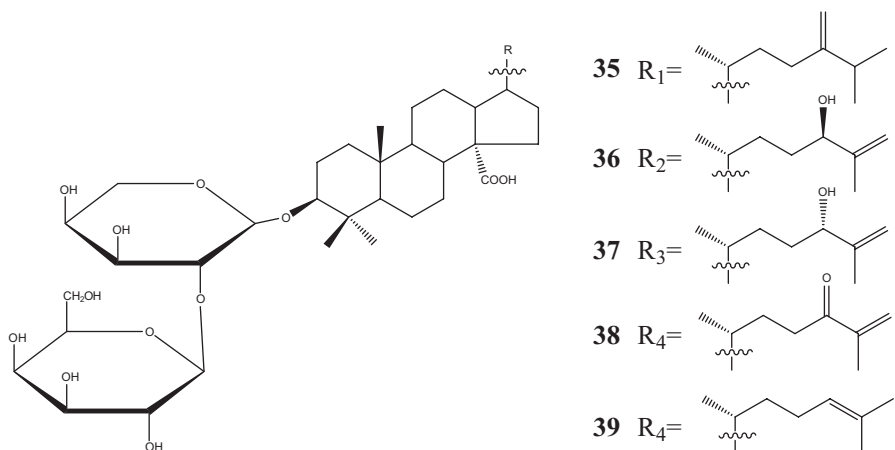


Four isomalabaricane triterpenes, geoditin A (**31**), geoditin B (**32**), isogeoditin A (**33**), and isogeoditin B (**34**) were isolated from marine sponge *Rhabdastrella aff. distincta*. All compounds were tested against a small panel of human tumor cell lines [18]. Geoditin A (**31**) and geoditin B (**32**) have also been isolated from marine

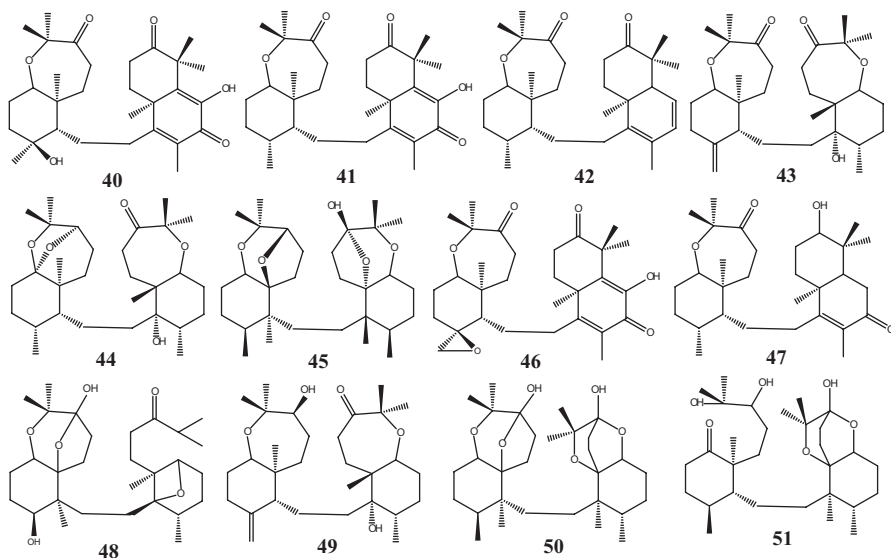
sponge *Geodia japonica*. Geoditin A was the most cytotoxic to HL60 cells [IC 50 Z3 mg/ml (<6.6 mM)], and geoditin B exhibited relatively weak cytotoxicity [25].

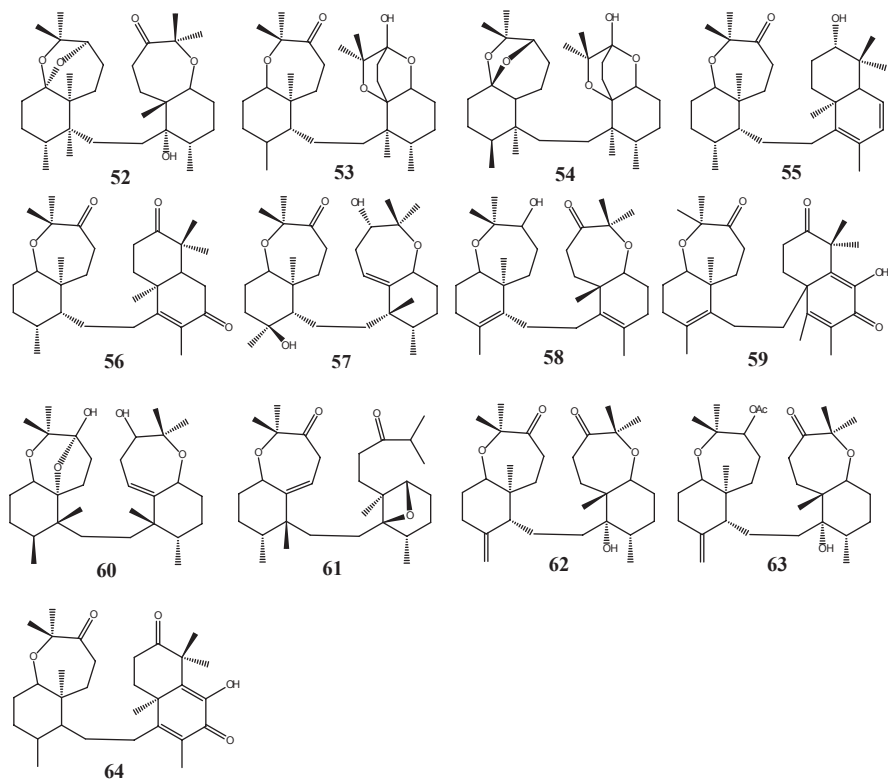


Five cytotoxic triterpene glycosides, erylosides F1-F4 (**35–38**), and erylosides F (**39**) were isolated from the sponge *Erylus formosus* collected from the Mexican Gulf (Puerto Morelos, Mexico). Four compounds induced the early apoptosis of Ehrlich carcinoma cells, where erylosides F3 have shown the highest activity at a concentration of 100  $\mu$ g/mL [26].



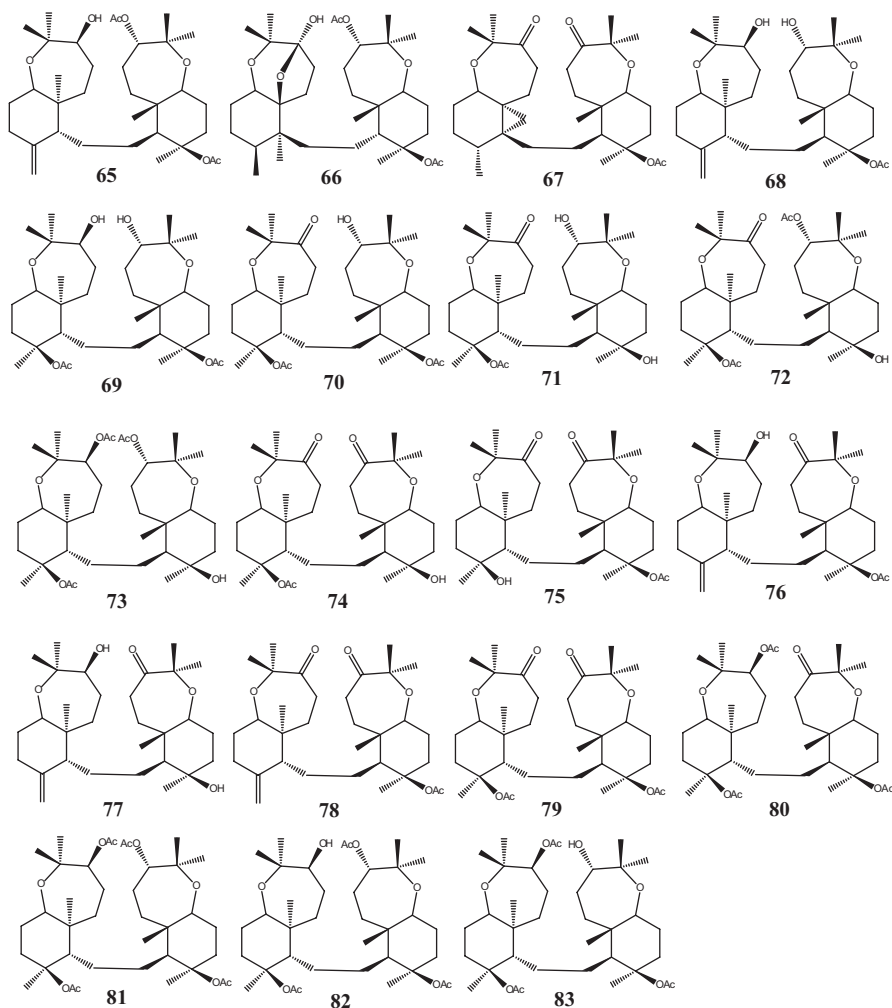
The special group of triterpenoids named sodwanones, sodwanones A-I (**40–48**) and sodwanones K-W (**49–61**), have been isolated from the Indo-Pacific sponge *Axinella wltneri* [27]. Sodwanones G (**46**), H (**47**), and I (**48**) have been found to have cytotoxic activity. The compounds have shown cytotoxicity activity against cell cultures of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human melanoma. Sodwanones G (**46**), H (**47**), I (**48**) showed high specificity towards human lung carcinoma cell line A-549, where the specificity of sodwanone G was prominent (**46**) [28]. The cytotoxic triterpenes, sodwanones K(**49**), L (**50**), and M (**51**) were found to be cytotoxic to P-388 murine leukemia cells [29]. The biological activity of sodwanone S (**57**) was evaluated against 13 human tumor cell lines [30]. Sodwanone V (**60**) inhibited both hypoxia-induced and iron chelator (1, 10-phenanthroline)-induced HIF-1 activation in T47D breast tumor cells ( $IC_{50}$  15  $\mu$ M), and sodwanone V (**60**) was the only sodwanone that inhibited HIF-1 activation in PC-3 prostate tumor cells ( $IC_{50}$  15  $\mu$ M). Sodwanone A (**40**) and sodwanone T (**58**) inhibited hypoxia-induced HIF-1 activation in T47D cells ( $IC_{50}$  values 20–25  $\mu$ M), and sodwanone V (**60**) showed cytotoxicity to MDA-MB-231 breast tumor cells ( $IC_{50}$  23  $\mu$ M). Sodwanone derived compounds, 3-epi-sodwanone K (**62**), 3-epi-sodwanone K 3-acetate (**63**), 10,11-dihydrosodwanone B (**64**) have been isolated from *Axinella sp.*, and **62** and **64** also inhibited hypoxia-induced HIF-1 activation in T47D cells ( $IC_{50}$  values 20–25  $\mu$ M) and **63** was cytotoxic to T47D cells ( $IC_{50}$  22  $\mu$ M) [31].



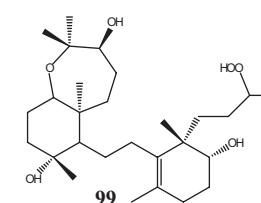
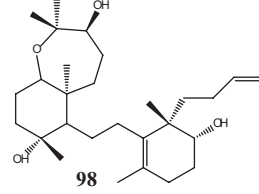
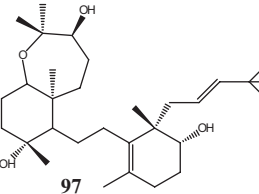
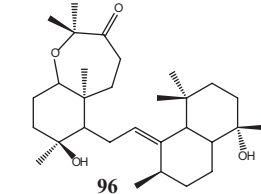
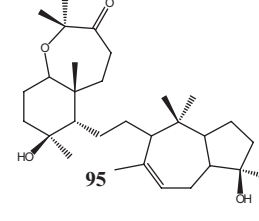
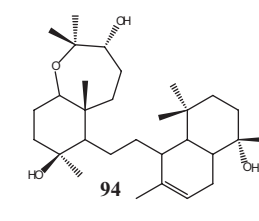
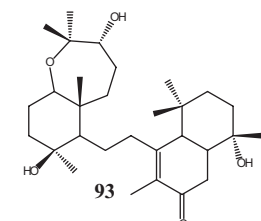
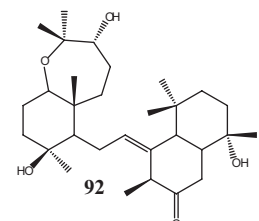
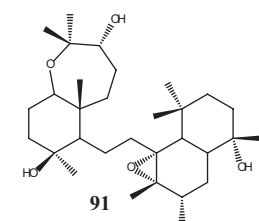
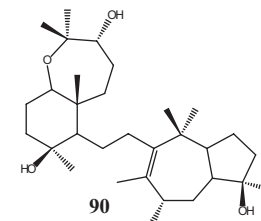
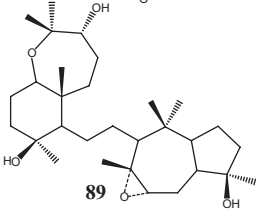
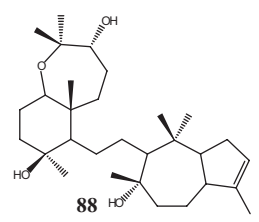
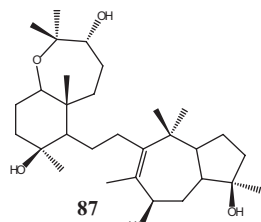
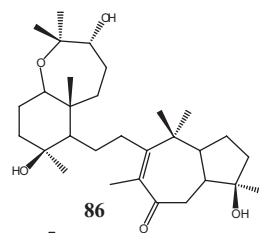
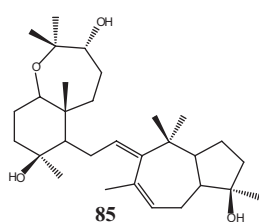
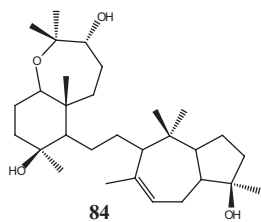


Raspacionin triterpinoids (**65–83**), raspacionin (**65**), raspacionins A (**66**), raspacionins B (**67**), 21-Deacetyl-raspacionin (**68**), 10-Acetoxy-21-deacetyl-28-hydroraspacionin (**69**), 10-Acetoxy-21-deacetyl-4-oxo-28-hydroraspacionin (**70**), 10-Acetoxy-15,21-dideacetyl-4-oxo-28-hydroraspacionin (**71**), 10-Acetoxy-15-deacetyl-4-oxo-28-hydroraspacionin (**72**), 10-Acetoxy-4-acetyl-15-deacetyl-28-hydroraspacionin (**73**), 10-Acetoxy-15-deacetyl-4-21-dioxo-28-hydroraspacionin (**74**), 10-hydroxy-4,21-dioxo-28-hydroraspacionin (**75**), 21-oxo-raspacionin (**76**), 15-deacetyl-21-dioxo-raspacionin (**77**), 4,21-dioxo-raspacionin (**78**), 10-acetoxy-4, 21-dioxo-28-hydroraspacionin (**79**), 10-acetoxy-4-acetyl-21-oxo-28-hydroraspacionin (**80**), 10-acetoxy-4-acetyl-28-hydroraspacionin (**81**), 10-acetoxy-28-hydroraspacionin (**82**), 10-acetoxy-21-deacetyl-4-acetyl-28-hydroraspacionin (**83**), have been isolated from red sponge, *Raspaciona aculeuta* Johnston (family *Raspailiidae*), and from the Mediterranean sponge *Raspaciona aculeata*. All the compounds have showed cytotoxicity against MCF-7 tumor cell line with  $IC_{50}$  values between 4 and 8  $\mu M$  [32–34].





The Red Sea sponge *Siphonochalina siphonella* is a rich source of sipholane triterpenoids including sipholenols (A, C-L) (**84**, **85–94**), sipholenones (A, E) (**95**, **96**), and siphonellinols (C, D, E) (**97**, **98**, **99**). Sipholenol A (**84**) and sipholenone A (Sipholenol B) are the major sipholane triterpenoids [35]. Sipholenol A was found to have increased the sensitivity of resistant KB-C2 cells [36]. Sipholenol A (**84**), sipholenol I (**91**), sipholenol L (**94**), sipholenone A (**95**), sipholenone E (**96**), siphonellinol C (**97**), and siphonellinol D (**98**) have found to show potent reversal of multidrug resistance in cancer cells that over expressed P-glycoprotein. These compounds enhanced the cytotoxicity of several P-glycoprotein substrate anticancer drugs, and significantly reversed the multidrug resistance phenotype in P-glycoprotein-overexpressing multidrug resistant cancer cells KB-C2 and KB-V1 in a dose-dependent manner [37, 38].



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