

## **Significance of investigating allelopathic interactions of marine organisms in the discovery and development of cytotoxic compounds**

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### **Abstract**

Marine sessile organisms often inhabit rocky substrata, which are crowded by other sessile organisms. They acquire living space via growth interactions and/or by allelopathy. They are known to secrete toxic compounds having multiple roles. These compounds have been explored for their possible applications in cancer chemotherapy, because of their ability to kill rapidly dividing cells of competitor organisms. As compared to the therapeutic applications of these compounds, their possible ecological role in competition for space has received little attention. To select the potential candidate organisms for the isolation of lead cytotoxic molecules, it is important to understand their chemical ecology with special emphasis on their allelopathic interactions with their competitors. Knowledge of the ecological role of allelopathic compounds will contribute significantly to an understanding of their natural variability and help us to plan effective and sustainable wild harvests to obtain novel cytotoxic chemicals. This review highlights the significance of studying allelopathic interactions of marine invertebrates in the discovery of cytotoxic compounds, by selecting sponge as a model organism.

**Keywords:** Marine sessile organisms; Competition for space; Allelopathic interactions; Allelochemicals; Cytotoxic compounds.

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## 1. Introduction

Living space is one of the basic requirements of any organism. In regions such as coral reefs and rocky intertidal areas, diverse sessile marine organisms share a limited space. Most of these organisms require space on hard substrata for the settlement and metamorphosis of their larvae. In the harsh intertidal environment, the space they occupy should be suitable in terms its exposure to water currents carrying food and sufficient irradiance in the case of phototrophic sessile organisms. Thus, suitable space on shallow marine substrata often is a limiting resource for the settlement, growth, and reproduction of tropical marine organisms [1-4]. Spatial competition among sessile marine invertebrates is a major process, which not only controls the patterns of diversity and abundance of these organisms, but also zonation in intertidal organisms and structure of an ecosystem [5, 6]. Thus, spatial competition has gained the attention of several investigators, who are interested in understanding community structure [1, 7, 8]. The competitive interactions among sessile organisms are mediated by 1) their relative growth rates and 2) release of toxic chemicals. Growth-mediated interactions are well documented in literature [9-11] whereas chemically-mediated interactions have not received enough attention. These chemically-mediated interactions are the source of novel bioactive metabolites [12]. A wide range of natural products have been obtained from marine invertebrates [13-23]. However, only a few have been explored for their ecological role in spatial competitions [12, 24-26]. To the best of our knowledge, there is no report so far where the understanding of the ecological function of the compound has been utilized for its development as a potential drug. This review includes 1) examples of chemically-mediated spatial competition of sponges with other sessile invertebrates, 2) various factors affecting the production of chemicals involved in spatial competition and 3) significance of studying chemically-mediated interactions to utilize the knowledge in the discovery and development of drug molecules. This paper emphasizes the need of linking chemical ecology to drug discovery for sustainable utilization of marine natural resources with special reference to the marine sponges.

## 2. Strategies to compete for space

Marine invertebrates acquire living space by using various offensive and defensive strategies like (1) growth interactions (e.g. overgrowth by corals) [27], (2) aggressive behaviour (e.g., induced development of sweeper tentacles by bryozoans [28], (3) feeding interactions (e.g., extracoelenteric digestion via mesenteries filaments by scleractinian corals) [29] and (4) allelopathy [12]. Allelopathy may be defined as the direct inhibition of one species by another by using toxic chemicals [30]. These allelochemicals belong to the class of secondary metabolites which are not directly involved in growth and reproduction of the organisms. However, these allelochemical provide interspecies defences in terms of occupied space by affecting metabolic and physiological processes in the competitors. The

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allelochemicals can either be released into the water column or transferred by direct cell to cell contact between donor and recipient [31]. Chemically-mediated interactions are often difficult to notice. Standoff interactions, where no clear outcome, such as a win or loss is observed, are very common in marine hard substratum communities [32]. Amongst above four defensive strategies discussed, allelopathy or chemical defence is the most important in case of soft-bodied sessile invertebrates such as sponges, octocorals and ascidians which lack proper physical defences [33]. The knowledge of chemical defences of these organisms is very useful for obtaining novel bioactive compounds (secondary metabolites) of therapeutic value. However, the production of secondary metabolites in the organisms does not occur continuously and is subjected to spatio-temporal variation [34]. Various reports have postulated two prominent hypotheses to explain variability in the production of secondary metabolites: 1) growth-differentiation balance hypothesis (GDBH) and 2) optimal defence theory (ODT). The GDBH assumes that an organism maintains a balance between resources invested in primary and secondary functions, whereas ODT postulates that allelochemical production is primarily restricted to areas that are under threat (e.g. outer surfaces) or areas of higher importance (e.g. reproductive organs) [35, 36]. The ODT is applicable to various marine invertebrates, including sponges [37]. According to ODT, the production of allelochemical is a costly process. The total energy reservoirs of the organisms are limited and the production of any secondary metabolites takes place at the expense of other primary functions such as growth and reproduction [38].

### **2.1. The sponge as a model organism**

Most of the ecologists have investigated 'sponge-coral interactions' to understand the mechanism of spatial competition in sessile invertebrates [31], factors affecting the competitive outcomes [39] and chemicals involved in defending the occupied space or acquiring new space [12]. The use of allelopathy to occupy substrata has been reported in several other groups of sessile marine organisms like anemones, soft corals (Coelenterata, Alcyonacea), tunicates etc. [32, 40]. Several bioactive compounds have been detected in a variety of cnidarians including soft corals, zoanthids and sea anemones [41, 42]. Besides the chemical defences, cnidarians, tunicates and bryozoans employ a variety of alternative mechanisms (faster growth rate, early sexual maturity, high fecundity, presence of sweeper polyps, sweeper or marginal tentacles) to protect their occupied area [43-45]. Among all above soft-bodied sessile organisms, the sponges are noteworthy because they inhabit multiple, diverse ecosystems, from equator to poles and from shallow waters to the highest depths [46]. Most of the sponges have siliceous spicules which provide an advantage over other calcareous organisms, subjected to problems of ocean acidification and global warming [47]. These soft-bodied sponges lack any specialized organs (or physical defence) and mostly depend on their secondary metabolites

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(chemicals) for various ecological interactions such as spatial competition [48], avoiding epibiosis [49] and predation deterrence [49, 50]. A large number of compounds with lethal or growth inhibitory properties have been isolated from sponges [51]. However, only a few have been studied for their ecological role in the benthic ecosystem [52]. Sponges are important components of the benthic ecosystem [53-55]. Although sponges are normally slow growing; their morphological plasticity enables them to adjust the overall shape and size to grow along with other fast-growing sessile organisms [56]. They fall in the list of longest living animals [57] which make them persistent competitors for other sessile invertebrates. In short, the remarkable allelopathic behaviour along with longevity, plasticity, siliceous skeletal framework makes the sponges an ideal model to study competitive interactions for the exploration of novel lead compounds.

## **2.2. How do the sponges acquire and maintain space?**

In regions with limited substratum availability, the sponges acquire living space via growth interactions and/or by producing allelochemicals. The competition for space between sponges and other organisms is highlighted in some reviews [4, 58]. In spite of the difficulties in testing the effect of these chemicals in the field, the role of allelopathic chemicals of sponges in spatial competition has been recognized [59]. There have been contrasting views on the role of these chemicals in acquiring space from other organisms and from other species of sponges by controlling their overgrowth [60]. The spatial interactions among sponges are more difficult to study and most of the focus has been given to the interaction between corals and sponges. Various reports on the spatial competition of sponges recommend that these chemicals help sponges to avoid overgrowth of other organisms, instead allowing the sponge to occupy more space [60]. Sponges produce allelochemicals that can prevent larval settlement of other organisms on their surfaces. This aids in keeping their pores free from clogging and maintaining the optimal feeding rate [61]. Many reports have demonstrated that sponge crude extracts are successful in preventing the larval settlement and growth [62-64]. The importance of sponge associated- bacterial communities have also been highlighted in preventing the larval settlement on the surface of the sponge [64]. The sponges have been reported to have direct (by producing allelochemicals) and indirect (by promoting associated bacteria for allelochemical production) epibiotic chemical defence [65]. By using these techniques, sponges prevent the settlement of other organisms on their surfaces.

## **3. Allelochemical mediated interactions in spatial competition**

In dynamic environments such as rocky inter-tidal regions, marine sessile invertebrates such as sponges, bryozoans, cnidarians, and macro-algae experience constant stress due to limited substratum availability (Fig. 1).

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The ecological role of allelochemicals has been illustrated in both defending the already occupied area and dislodging the established organisms to claim the new area [12, 31]. Most of the studies depicting the role of allelochemicals in spatial competition have been carried out on crude extracts [11, 59, 66]. There is the only single report available so far that demonstrates the temporal variation in pure allelopathic compound 'Avarol' from the sponge *Dysidea avara* depending on the nature of neighbours; thereby explaining its ecological importance [67]. Monthly comparison of chemical profiles of crude extracts against the pure compound can reveal the factors that affect its production. Similar studies should be conducted in future, which will aid in designing suitable conditions of aquaculture for effective and sustainable production of the target compounds. There are only few reports on identification of pure allelochemicals from sponges; however, the temporal variations due to various abiotic and biotic factors have not been considered [12, 66, 68, 69].

### 3.1. Among sponges

There are some reports available on spatial competition among sponges. The Mediterranean sponge *Crambe crambe* does not allow other sponges to grow in the few centimetres adjacent to its borders, suggesting the possible role of allelochemicals in creating the zone of inhibition in the surroundings [24]. Similarly, the coral reef sponge *Dysidea sp.* in Guam has been demonstrated to cause necrosis in other sponge *Cacospongia sp.* by producing allelochemical '7-deacetoxyolepupane' (Fig. 2a) [68]. In contrast, some reports suggest that the spatial interactions such as over-growth/ out growth among different species of sponges are symbiotic in nature where basal sponge acts as suitable substratum and the overgrown sponge acts as epizoic [9, 70-73]. The supporting species are able to maintain their integrity and avoid suffocation/starvation by having specialized skeletal construction and canal system. In some investigations, epizoic sponges showed increased survival rates by adhering tightly to the supporting sponges [9, 71].

### 3.2. Sponges and corals

Most of the studies were conducted on the interaction between sponges and corals. The bio-eroding sponge *Siphonodictyon sp.* was reported to produce an allelochemical 'siphonodictidine' (Fig. 2b) to reduce growth and respiration rates of adjacent coral polyps by boring deeply into living coral heads [66]. The sponge secretes mucus that acts as a carrier for this allelochemical which inhibits coral growth around the base of the oscular chimneys of these sponges [66]. The Caribbean sponge *Plakortis halichondroides* was tested for the production of allelochemicals that inhibited the metabolic processes in 14 different species of corals even those which were not in direct contact with the sponge [31]. Allelochemically mediated interactions are highly specific as demonstrated by in situ effects of four species of Indonesian sponges on their neighbours [74]. Necrosis effect was reported in 85% of corals

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which were in contact with the sponges, but less than 25% of overgrown sponges were necrotic. Interestingly, it was found that the same sponge individual could cause necrosis in one adjacent species, while other species remained unaffected, suggesting that these interactions are highly specific. The sponge *Haliclona* sp. 628, bearing nematocysts and zooxanthellae (might be acquired from its coral substrate) secretes the allelochemical 'halichonacyclamine A' (Fig. 2c) that causes necrotic killing of the coral *Acropora nobilis* within a 1 to 2 cm radius of this sponge. The disproportionate dead patches of *A. nobilis* were observed due to settlement of the larvae of the sponge *Haliclona* sp. 628 [69, 75]. Recent work on 'halichonacyclamine A' showed that this compound can act as an efficient anti-plasmodial agent against plasmodium falciparum strain FcB1 and chloroquine-resistant 3D7 strain with  $IC_{50}$  of 0.052 - 0.33  $\mu\text{g mL}^{-1}$  respectively [76]. In the same report, the compound was also found to be cytotoxic when tested against breast cancer cells MCF7 ( $IC_{50} = 2.6 \text{ mg mL}^{-1}$ ) [76].

Another encrusting and excavating sponge *Cliona tenuis* releases the toxin 'clionapyrrolidine A' (Fig. 2d) that can kill live coral tissue in 1-4 days [12]. In one experiment, the intact sponge released allelochemicals that displaced corals at the rate of 20 cm per year, but live fragments of *C. tenuis*, placed in direct contact with corals are killed by coral defences within 24 h. This showed that allelopathy occurs during sub-dermal *C-tenuis*-coral contact rather than superficial external contact [10]. In reefs under stress conditions, the biomass of corals and non-aggressive sponges (lacking chemical defence) are found to be negatively correlated [77, 78]. Thus, the sponges compete with corals by releasing active metabolites that can undermine the skeletal integrity of corals and reduce their photosynthetic efficiency and respiration, leading to reduced coral growth [59, 66].

### 3.3. Sponges and micro-algae associated with corals

Several Caribbean sponges cause bleaching of the massive coral *Diploria labyrinthiformis* by inhibiting photosynthesis of microalgal symbionts. When corals were exposed to the crude extract of the sponge *Agelas clathrodes*, there was a reduction in both, their baseline fluorescence (correlated with the production of chlorophyll a), and potential quantum yield (measure of photosynthetic efficiency) as revealed by in situ pulse amplitude modulated (PAM) fluorimetry [59]. The sponge was found to affect the microalgal symbionts (zooxanthellae) of corals in two ways: a) impairing photosynthesis with bleaching and b) impairing photosynthesis without any significant amount of bleaching. The sponge *A. clathrodes* contained allelochemicals 'pyrrole-imidazole alkaloids' which resulted in the failure of symbiosis between coral and zooxanthellae [59].

### 3.4. Sponges and other cnidarians

The soft corals, zoanths, sea anemones are also reported to compete with sponges by means of their

aggressive organs such as sweeper tentacles [43] or allelochemicals [41, 42, 79]. Recent evidence suggests that several species of zoanthids such as *Palythoa* sp. and *Zoanthus* sp. are ubiquitous in coastal areas near Brazil [80] and Venezuela [81] where nutrient concentrations often are high, thus these zoanthids take advantage of nutrient loading on reefs and gain a competitive edge over other sessile organisms such as sponges [80]. In intertidal regions of the Indian west coast, the sponge *Cinachyrella cavernosa* demonstrated competition for space with *Zoanthus sansibaricus*. This standoff competition seems to be mediated through allelochemicals released by both the species to maintain their occupied space (Singh and Thakur, unpublished data).

### **3.5. Sponges and bryozoans**

Chemical-mediated interactions were also observed within a diverse group of encrusting coral reef bryozoans and sponges where the allelochemical present in sponge extracts caused the mortality in bryozoans [82, 83]. The effect of crude extracts from nine sympatric sponges was examined on four bryozoan species. Five sponges exhibited species-specific chemical responses [82]. However, the results did not help to estimate the natural concentrations of allelochemicals released during such competitions due to the use of whole organisms extracts. It was hypothesized that the toxic chemicals might be stored inside the sponges and released at different concentrations depending on the intensity of competitive interactions [82]. Allelochemicals were found to be advantageous for sponges allowing them to overgrow competitively dominant bryozoan species in a space-limited environment [84, 85]. Later, it was demonstrated that density-dependent growth and survival in bryozoans was limited by space as well as nutrients; thus suggesting the possible role of food and space in determining the competitive ability of the organisms [84].

## **4. Factors affecting allelochemical production in marine sponges**

The production of allelochemicals, in any organism, is a costly process and influenced by the overall biology and ecology of the organism. The biological factors include growth and reproduction, which are in turn, influenced by the environmental conditions. The competitive environment consists of abiotic (e.g. temperature, nutrient availability, physical disturbances etc.) and biotic (e.g. natural enemies) factors that determine the organism's ability to exploit space or resource [67].

### **4.1. Nutrient availability**

One of the major limiting factors for sessile invertebrates is the low availability of nutrients that affect their primary functions (growth and reproduction) and secondary function (production of defensive chemicals). The high level of nutrients in coral reefs at Eilat in the northern Red Sea increased the abundance of filter-feeding invertebrates that outcompete the corals in these regions [86]. However,

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there is no report on the direct effect of nutrient availability on the production of allelochemicals in the sponges. Interestingly, the abundance of a particular sponge can increase depending on its efficient filtration rate and nutrient availability, which may result in loss of other types of sponges [87]. This signifies the importance of availability of food as energy source for various energy driven processes such as overall growth and production of allelochemicals. The various studies done on phytoplankton have shown that the deficiency in nutrient supply leads to low production of allelochemicals [88, 89].

#### **4.2. Temperature**

Global climate change such as elevated sea temperature and high UV radiation have been reported to cause bleaching and mortality of corals in the Tanzania and Maldives reefs [90]. Increased temperature caused the stress condition and influenced the production of heat shock proteins among cnidarians [91]. Various studies on marine plants, phytoplankton and micro-organisms have revealed that temperature is the most important factor regulating the production of allelochemicals [92-94]. In a study on the New Zealand sponge *Mycale hentscheli*, the production of three cytotoxic compounds: mycalamide A, pateamine, and peloruside A demonstrated temporal and spatial variations. The reasons behind the variability in these cytotoxic compounds were attributed to differences in temperature and various other biotic and abiotic factors such as sponge size, morphology, depth and geographical locations [95].

#### **4.3. Wave action**

Water motions can significantly affect the nature of interaction among various species, thus affecting the chemicals produced by them as a result of these interactions. Strong wave action can allow corals to grow in close proximity by deflecting their aggressive organs as documented in case of coral *Galaxea fascicularis* and its neighbouring coral species [96]. Moreover, strong water movement dilutes the effect of allelochemicals produced by the sponge against its neighbouring fauna [12]. In contrast, weak water currents have been reported to enhance the competitive ability of some species of macroalgae [97]. In spite of this, the effect of strong wave on the allelochemical production of marine organisms, including sponges has been ignored so far. It will be interesting to note how the nature of water currents affects the distribution and enhances the reactivity of some allelochemicals.

#### **4.4. Light**

It is another major factor that regulates the outcome of competitive interactions by affecting the production of allelochemicals. The sponges which contain the broad spectrum allelochemicals have been found to occur in open habitats (i.e. in full sunlight) where a defensive mechanism mediated by light would seem to operate most effectively. This light-related variation in toxicity was demonstrated in

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photophilous and sciophilous environments of the sponge *Crambe crambe* [98]. In well illuminated regions, the sponge *C. crambe* allocates its energy in production of allelochemicals owing to the presence diverse forms of neighbouring species. On the other hand, in shaded regions, the sponge has a natural selective advantage over other sessile organisms which require proper illumination for their survival [98]. The resources allocated to structural material (collagen, fibres, spicules) of the sponge was higher in the shaded habitat, suggesting inverse relation between chemical and physical defences [98]. In well illuminated regions, the sponge *Verongia arrophoha* which contained symbiotic cyanobacteria showed a higher growth rate and production of allelochemical as compared that in darker areas where it lacked the ability of producing the allelochemical due to decrease in symbiotic cyanobacteria [99].

#### **4.5. Shape, size and life forms**

The shape and morphology of the species can determine its competitive output by modifying the direction of water currents and sediment deposition, which can indirectly influence the transport of waterborne allelochemicals to its target. The small and medium- sized individuals of the encrusting sponge *Crambe crambe* showed higher toxicity, as compared to that of larger sized individuals [98]. In Curacao and Colombia reefs, aggressive sponge species *Desmapsamma anchorata* and *Niphates erecta* were abundant in regions with high diversity of other competitors such as regions with more than 25% coral cover [78]. The rapid growth rate and efficient regeneration capacity were found to be main contributing factors for the competitive success of these two sponges over other sessile organisms. These sponges were also found to contain toxic that deter predators, but the possible role of their toxins in space competition was not considered [78]. However, *D. anchorata* showed irregular and unpredictable growth, which leads to the speculations that there might be trade off between primary function (faster growth rate) and secondary function (productions of toxic compounds) in this sponge species. Different life forms also determine the ability of the organisms to produce toxic compounds. The larval forms of the encrusting sponge *Crambe crambe* were non- toxic, whereas two week old recruits were able to deter predators [98]. This depicts the strategy employed by the sponges to wisely allocate the resources towards their life -history functions (growth, reproduction and defence) for their overall survivalship.

#### **4.6. Predators**

The production of allelochemicals against predators is reported in several sponges as a major strategy of survivorship [100]. The sponges use allelochemicals not only for spatial competition but also for deterring predators, showing that the chemicals have multiple ecological roles [98, 100]. In the regions where fish predation and grazing are intense, the soft –bodied organisms such as sponges, soft corals

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or ascidians show either higher toxicity or unusually hardened body as compared to areas which are devoid of any stress due to spatial competition and predation [26, 48, 82, 101]. In short, the production of allelochemicals is also affected by the types and abundance of predators.

## 5. Production of allelochemicals

The involvement of genetic machinery in the production of allelochemicals by the marine organism is not fully understood. Differential display of transcripts in LPS-treated tissue and untreated tissue of the sponge *Suberites domuncula* showed molecular machinery that enables the sponge to shield itself from its anti-bacterial toxic compounds [102]. Some of the sponge' immune molecules have been reported to show an adaptive response on the level of cytokines to xenogenic material and it was further found that some low-molecular weight, non-proteinaceous defence molecules (e.g. lyso-PAF) were also produced in an adaptive manner. Spatial competition causes a stress condition for both the participating organisms. This was observed in the laboratory experiment conducted to study competition for space among temperate corallimorpharians and actinarian sea anemones [91]. In symbiont hypothesis, microbial symbionts are reported to be the original producers of secondary metabolites, isolated from their hosts. In view of this, several sponge secondary metabolites are found to be products of complex symbiont bacterial associations [103]. Biosynthetic pathways of the molecules produced by associated microorganisms have been well studied. The anti-tumour molecules 'onnamides' have been reported from the bacterium-associated with the marine sponge *Theonella swinhoei*. The biosynthetic pathway of onnamides has been identified and it was shown that onnamides are encoded by the onnamide (*onn*) gene cluster, consisting of *trans*-AT polyketide synthases (PKS) and non-ribosomal peptide synthases (NRPS) genes [103]. Unfortunately, biosynthetic pathways of the production of allelochemicals in marine invertebrates, including sponges have not been explored much. This information will not only be useful for sustainable therapeutic use of marine allelochemicals but also for investigating ecological implications of allelopathic interactions. Recently, the genetic machinery and the pathway for the cellular responses have been studied in the coral *Acropora millepora* in response to direct contact with four different macroalgae (*Chlorodesmis fastigiata*, *Dictyota bartayresiana*, *Galaxaura filamentosa* and *Turbinaria conoides*) for 20 days [104]. The initial response of the coral to the exposure of macro-algal extracts was the differential expression of genes involved in signalling pathway, which led to other cellular responses. Within 24 h of exposure, several genes involved in regulation of cell cycle were down-regulated whereas the genetic machinery involved in antioxidant activity and removal of damaged and misfolded proteins became active; thus maintaining the oxidative damage caused by allelochemicals [104]. The oxidative imbalance occurred when accumulation of damaged proteins exceeded the cell's proteolytic capacity leading to rapid protein degradation and

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eventually to apoptosis and/or necrosis in corals. The allelochemicals released by the macro-algae were observed to affect the genetic components (such as genes involved in cytoskeletal organization, photosynthesis and antioxidant activity) of the coral and its symbionts (zooxanthellae) [104].

## **6. Importance of studying allelochemically mediated spatial competition**

Marine invertebrates are well known for production of novel bioactive compounds. However; there are major hurdles in the isolation of these compounds from marine invertebrates (for instance sponges) for three primary reasons: 1) target organisms are difficult to identify and maintain under laboratory conditions, 2) the ecological role of the compounds is not known, 3) these compounds show temporal variation which is not understood well. In such a scenario, understanding of allelopathic interactions discloses the ecological role of these compounds and the factors that can affect their production in a natural environment. The cytotoxic compounds involved in spatial competition vary according to the ecological need of the organisms. Recently, it was illustrated for the first time in a long term study for two years on the sponge *Dysidea avara* [67]. The aim of the research was to check the variation in the production of well known anti-cancer compound 'Avarol' (Table 1) in terms of ecological (seasonality, interactions of producing organism with neighbours) and biological (reproductive stages) factors. The results showed that the production of Avarol is directly related to the presence of competitive species, demonstrating a possible role of Avarol in controlling the growth of neighbours by cytotoxic activities. The other parameters such as temperature and reproductive stages did not show a significant correlation with the metabolite production. The authors have emphasized the role of understanding the main factors responsible for the production of the target molecule as a way to solve the supply issue, thus enhancing the yield of compound for drug development. In the same study, it was observed that the increased production of this allelochemical 'Avarol' at the surface of contact directly depends on the nature and type of the neighbours. It was also proposed that more experimental and observational studies should be undertaken on a long term basis to understand the mechanisms behind these factors and contribution of ecological as well as biological parameters. The need to study the allelochemically mediated interaction was further supported by the study on spatiotemporal variation of cytotoxic compounds in the same sponge *Mycale hentscheli*, collected from two different sites in central New Zealand [95]. Although the ecological role of these metabolites in *M. hentscheli* was not studied, the variation in metabolite concentrations between sites as well as within sites implied the presence of site-specific ecological factors such as presence of aggressive or non-aggressive competitors for the variability in the production of cytotoxic compounds. These reports support the importance of biological and ecological factors involved in triggering the production of specific metabolites. Ecological studies to understand these chemico-biological interactions can satisfy the need of bulk amount of compounds

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required for drug discovery and development. In nutshell, such studies will aid in selection of target or source organisms, understanding the ecological functions of allelochemical compounds and factors affecting their production. The knowledge of the factors contributing to the optimal production of these compounds in nature can allow us to choose the best harvest time and location for the discovery of novel compounds. This approach for the acquisition of novel bioactive metabolites through such chemically mediated interaction studies can be well understood by the schematic flowchart (Fig. 3). The presence of a healthy sponge species in a highly competitive and diverse environment signifies that such sponge species must be producing bioactive compound worthy of testing for its anti-proliferative potential. However, allelochemical will be subjected to temporal variation depending on the abiotic (such as temperature, salinity, etc) and biotic factors (such as abundance of neighbouring fauna). The above example the cytotoxic compound 'Avarol' signifies the importance of understanding the ecology of the target organisms to account for its natural variability. This step will serve as a tool to unravel the mechanism of production of secondary metabolites and advance toward the discovery and development of therapeutic molecules of marine origin.

## **7. Link between allelochemical and cytotoxic compounds**

During spatial competition, marine sessile invertebrates produce allelochemicals which serve as a chemical offence to combat competitors for space and resources [105]. These compounds hinder the growth of the competitors by impairing the cell division. Such compounds show three types of cellular mechanisms to kill the neighbouring cells: 1) apoptosis or programmed cell death 2) autophagy (or autophagocytosis) 3) necrosis [106]. Due to their cytotoxic properties, these can be used as genotoxic, carcinogenic, mutagenic and teratogenic agents. The anti-cancer compounds which are available in the market, have been shown to act via apoptosis or autophagy [106] whereas the cytotoxicity reported in spatial competition showed necrosis as their mode of action. Unfortunately, out of around 4000 compounds isolated from sponges during the last three decades, only a few have successfully passed the clinical trials and are available in the market [107]. Those compounds whose ecological roles have been studied, but they are not tested as anticancer drugs are listed in Fig.2 a-d. Non-utilization of the knowledge gained from ecological studies of the secondary metabolites in the discovery and development of drug molecules is due to poor interactions between chemists and ecologists. There is a need to link the chemical ecology with the drug discovery for sustainable utilization of marine resources and advancement in natural products based drug development. Some of the anti-cancer compounds from marine sponges which are facing serious supply problems and whose ecological roles are not yet studied are discussed below.

### **7.1. Salicylihalamides A and B**

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This is a novel cytotoxic macrolide isolated from an unidentified species of *Haliclona* sp. [108]. This genus *Haliclona* has received considerable attention due to the presence of a variety of active metabolites such as bioactive alkaloids. The organic extract of this sponge was found highly active against NCI 60-cell lines (human tumour assay) [108]. Bioassay-guided fractionation led to the discovery of salicylihalamide A and B (Table 2a), novel salicylate macrolides with a highly unsaturated amide side chain. Salicylihalamide A was reported to possess a unique chemical scaffold not commonly present in other antitumour compounds [108]. It acts by inhibiting the ATPase activity in mammalian vacuole [109, 110]. This strategy is used in the treatment of several tumours, HIV, bone and kidney diseases [109]. This compound is currently under pre-clinical trials; however, it faces another challenge of limited supply [111]. Although, the chemical synthesis of salicylihalamide A is possible, but the process is not cost effective [112]. The only possible option for meeting the commercial demand is through wild harvest (which is a threat to the natural population) or mariculture (which has not been successful so far). The salicylihalamide A was produced only by *Haliclona* sp. having green morphology and its production was significantly correlated with sea surface temperature (SST) [112]. Similar to other reports on the temporal variation in concentration of secondary metabolites [34, 95, 113-115]; the concentration of salicylihalamide A was found to be higher in warmer months. An understanding of the ecological function of this compound can aid in formulating the optimal conditions for its production by mariculture [112, 116].

## 7.2. Peloruside A

This peloruside A (Table 2b) is a 16-membered macrolide ring containing compound which was isolated from a New Zealand marine sponge, *Mycale hentscheli* [117]. It showed cytotoxic activity at nanomolar concentrations [118]. Due to its microtubule-stabilizing activity, it can arrest cells in the G<sub>2</sub>-M phase of the cell cycle and induces apoptosis [119]. It has a relatively less complex structure because of which the structure elucidation and synthesis of analogues have been made possible to some extent. However, the chemical synthesis pathways of analogues are not feasible for industrial scale-up due to the high cost of the methods involved. It was estimated that a final yield of merely 2 g pure peloruside A is possible from extraction and purification of 200 kg of raw sponge [120]. The main obstacle for the clinical trials is its insufficient supply from wild stocks. Recent efforts in mariculturing of sea sponges have shown promising outcomes [120]. However, the reports suggest that only *Mycale hentscheli* sponges present in a short stretch of Pelorus Sound, New Zealand have the ability to produce peloruside A [95]. This signifies the role of abiotic and biotic factors of a geographical location in determining the type of secondary metabolite produced. Although, the initial efforts in mariculture of this species have been successful, a higher population density of the *Mycale* sponges is not achieved

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through mariculture due to fouling organisms especially the ascidians [95]. These weeds are to be removed on a regular basis using divers, which is time consuming and labour intensive.

### 7.3. Laulimalide and Isolaulimalide

The marine macrolide compounds Laulimalide (Table 2c) and Isolaulimalide (Table 2d) were originally obtained from the Pacific Ocean sponge *Cacospongia mycofijiensis* [121]. Its mode of action is to stabilize microtubules and inhibit the proliferation of various human carcinoma cell lines, including multidrug and paclitaxel resistant cells, at low nanomolar concentrations [121]. A number of alternative synthetic routes to laulimalide are available in the literature [122]. Despite the progress in chemical synthesis of the compound, there is still a supply problem, which has slowed down the development of this compound as an anti-cancer drug. The efforts are being made to obtain an analogue with similar anti-cancer properties. This drug has the potential to enter clinical trials in the near future. However, its chemical ecological investigation would help in solving the supply problem.

The major hurdle faced in drug development from natural sources is often referred to as an insufficient supply of raw material. Large harvests of wild marine organisms can cause serious impact on their natural population and the community structure [123]. To avoid the over exploitation of wild specimens, three major alternatives are followed: 1) chemical synthesis of the bioactive compound 2) mariculture 3) development of sponge cells using tissue culturing techniques [124, 125] and 4) gene transfer technology [126]. However, there are various setbacks faced by each of these solutions. Chemical synthesis has been more promising for relatively simple compounds rather than for complex compounds. Moreover, not all the chemical synthesis pathways are cost effective. In such a scenario where chemical synthesis of an active compound is not feasible, mariculture has been considered as the best possible option [113]. Mariculture of invertebrates requires a proper understanding of their life cycle and ecological role of the compounds. Many authors have highlighted that the difficulties in indoor or outdoor mariculturing of sponges for production of bioactive compounds [127-129]. Therefore, for successful production of bioactive metabolites from an organism, we need to simulate conditions, similar to those present in its natural habitat. With the advancement of cell and molecular biology techniques, modern day solutions (such as cell culturing and gene transfer technology) seem to be the best possible alternatives in future. However, till today, cell culturing of sponges for the production of secondary metabolites have not been successful. Similarly, gene transfer technology is still infancy. This is because most of the genes encoding for secondary metabolites comprise of multi-gene clusters which are differentially controlled by a complex set of regulatory proteins [130]. At present, it is the need of the hour to make every possible effort to avoid the indiscriminate wild harvest of marine invertebrates. The significance of understanding the ecological role of the lead molecule can aid in 1)

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planning the wild harvest time, 2) simulating the proper conditions in an indoor or outdoor aquarium for production of desired compounds, 3) determining the proper nutrient conditions and growth factors for the development of continuous cell lines and 4) advancement in the field of gene transfer technology to some extent.

## 8. Present status of allelochemicals in drug development

At present, there are no reports on the ecological role (as allelochemicals) of marine derived -lead molecules which are currently in clinical trials. Most of these drug molecules have been harvested from marine organisms through random collection without prior information about their ecological role. Recent review on cyanobacterial toxins has provided evidence of their role as allelochemicals and potential applications in market as algaecides, herbicides and insecticides [131]. However, the marine natural products have been reported to have multiple ecological roles [132-134] which is suggestive of multiple targets/ receptors that might result in some undesirable side effects during clinical trials. This problem can be solved by chemically modifying the functional groups of existing lead molecule which are responsible for side effects or undesirable properties. The structure-activity studies and semi-synthetic approach will result in development of structural analogues with greater bioactivity and lesser or no side effects. Nevertheless, the sponges are among the topmost contributors of marine derived drug molecules [135, 136]. It is interesting to note that the first marine-originated drug 'Ara-C' was obtained from the marine sponge *Tectitethya crypta* (formerly *Cryptotethya crypta*) after derivatization of its nucleosides spongothymidine and spongouridine [137, 138]. It is among the only three FDA approved marine-derived drugs in the United States and available in under the trade name cytarabine (Cytosar-U<sup>®</sup>, Depocyt<sup>®</sup>) for the treatment of leukemia [139, 140]. There are various reviews on the marine derived lead molecules which are at various phases of drug development [51, 116, 136, 139-144]. Table 3 lists out the sponge derived drug molecules which are currently in clinical trials.

## 9. Future trends in therapeutically important allelochemicals

Aquatic systems provide higher number of species and chemical diversity than terrestrial ecosystems [13, 145]. The chemically mediated interactions occurring in aquatic systems have not been well understood and quantified. Most of the studies on chemically mediated interactions are based on the field observation and manipulative experiments (such as removal of one or more competitors, gel assay etc.) [25, 26, 31, 82, 105, 146-148]. In very few studies, the compounds responsible for these interactions have been identified and their mechanism of action have been investigated [12, 66, 68, 69, 82, 149]. A recent line of research is focusing on localization of allelopathic agents, their mechanism of action and ecological factors affecting their production [34, 67, 95, 150]. Many of the secondary metabolites from sponges have been reported to be originated from their symbionts [151]. However,

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most of these microbial symbionts are non-culturable due to involvement of some host specific factors in their proliferation [152]. Using metagenomics approach, it is possible to identify these microbial associates and carefully design the suitable culture media for production of desirable compounds [153]. Apart from production of metabolites by microbial fermentation, future challenges include the understanding of biosynthetic pathways and signal transduction, responsible for the production of allelochemicals. Knowledge of biosynthetic pathway will help in expression of genes coding for targeted metabolite in another host by gene transfer technology. However, in various cases, the transgenic production of secondary metabolites is not possible due to involvement of several genes and regulating factors [154]. In such a scenario, chemoenzymatic synthesis which is cell-free, enzyme-based system can act as an alternative approach for production of secondary metabolites [155]. In this context, recent developments in genomics, proteomics and metabolomics studies are very promising.

## **10. Conclusion**

This review highlights the competitive ability of sponges to occupy space from other sessile invertebrates using chemical weapons. Many authors have demonstrated the use of secondary metabolites from sponges against predators, but only a few have investigated the role of allelochemicals in defending the substratum. These allelochemicals hinder the growth of the competitors by impairing their cells; thereby they can also be applied as cytotoxic agents. The outcome of competitive interactions in any organism depends on environmental factors (e.g., levels of nutrients, temperature, irradiance etc.) which alter its relative growth rates. Production and secretion of allelochemicals by the organisms depends on their necessity. In such a scenario, understanding the ecological roles of the allelochemicals and the factors regulating their production will aid in sustainable wild harvest of target organisms.

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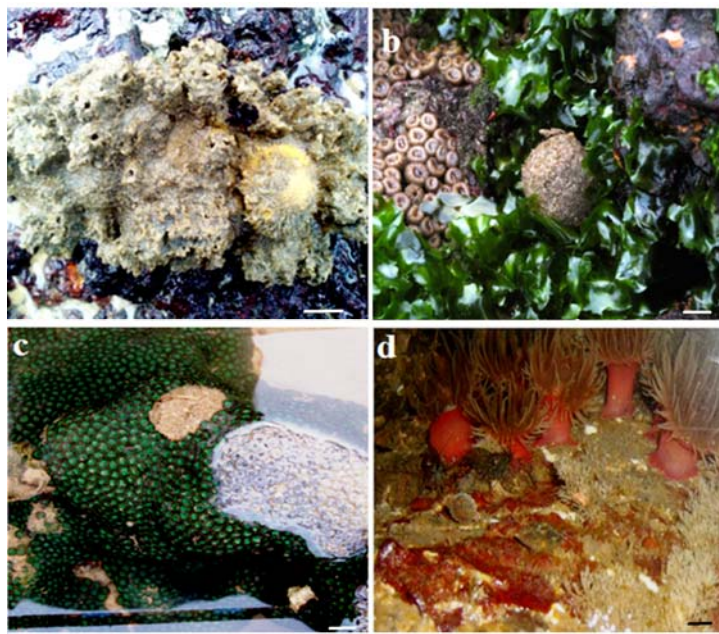


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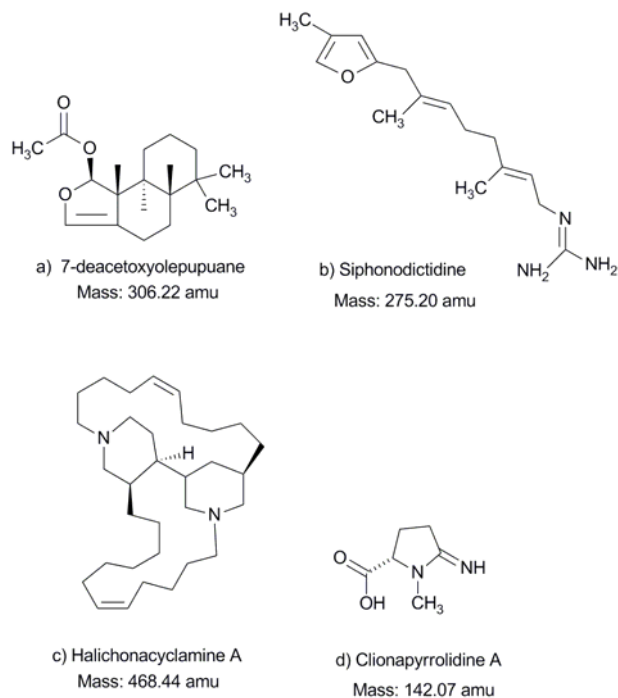
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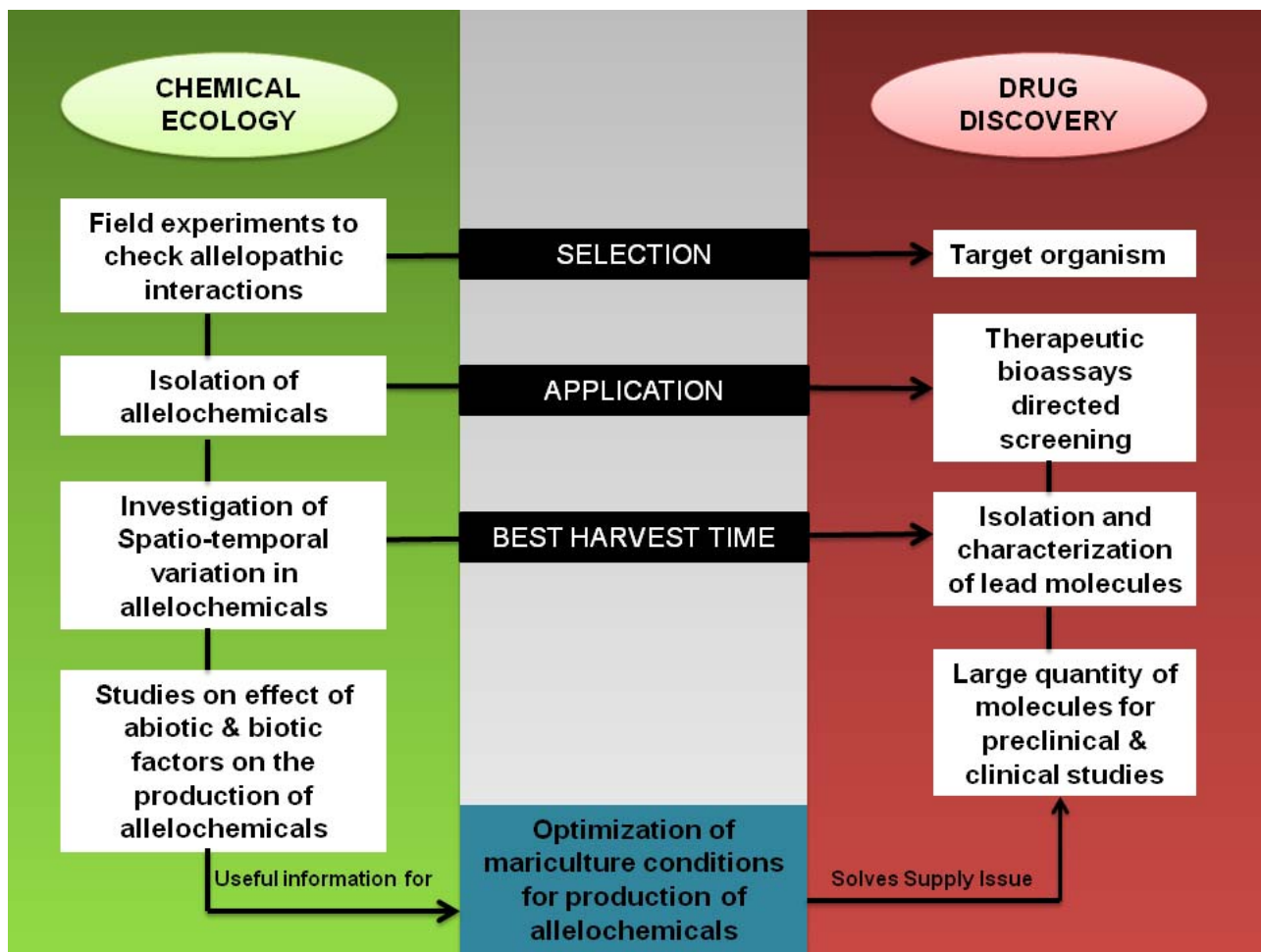
## Figures and Tables



**Fig.1.** Examples of competitive interactions of sponges with other sessile invertebrates from intertidal regions of Indian west coast a) Spherical shaped sponge *Cinachyrella cavernosa* growing on the encrusting sponge *Biemna fortis*, Mhapan (b) Sponge *C. cavernosa* overgrowing on macroalgae *Ulva fasciata* (Delite), Mhapan (c) Sponge *C. cavernosa* facing tough competition from cnidarian *Zoanthus sansibaricus* on rocky intertidal Anjuna beach (d) Bryozoans *Bugula* sp. growing over sheet of red sponge (unidentified), Ratnagiri (Photographs by N.L.Thakur (b,d) and Anshika Singh (a,c) Scale: 1 cm)



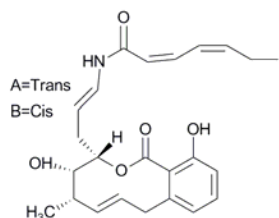
**Fig.2.** Examples of sponge-derived cytotoxic compounds, having role in competition for space in natural environment.



**Fig.3.** Flow chart highlighting the importance of understanding chemical ecology, while exploring marine natural products.



## a) Salicylilalamides A and B



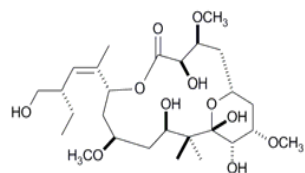
411.20

*Haliclona* sp.Cytotoxicity in NCI 60-cell lines  
(LC50=0.40-0.62 nM)Vascular type (H<sup>+</sup>)-  
ATPase Inhibitor

Preclinical

[51, 108, 109,  
111]

## b) Peloruside A



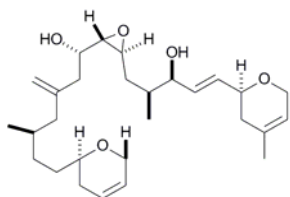
548.32

*Mycale  
hentscheli*Inhibition of cell cycle (G2-M phase) and  
induces apoptosis in murine (32D) and human (HL-60)  
myeloid cell lines cell lines  
(LC50= 4 to 15 nM )Microtubule-stabilizing  
activity

Preclinical

[51, 111, 118,  
119, 159,  
160]

## c) Laulimalide



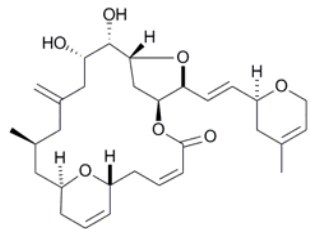
460.32

*Cacospongia  
mycofijiensis*Inhibition of rat aortic smooth muscle cell line and  
various human carcinoma cell (eg. multidrug and  
paclitaxel resistant cells)  
(Laulimalide, LC50=0.006-1.2 μM)Microtubule-stabilizing  
activity

Preclinical

[51, 111, 121,  
122]

## d) Isolaulimalide



514.29

*Cacospongia  
mycofijiensis*Inhibition of rat aortic smooth muscle cell line and  
various human carcinoma cell (eg. multidrug and  
paclitaxel resistant cells)  
Isolaulimalide, LC50=1.97-2.65 μM)Microtubule-stabilizing  
activity

Preclinical

[51, 111, 121,  
122]

Table 3 List of sponge derived drugs in clinical trials.

Compound	Mode of action	Application	Status	Company	Refs.
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Cytarabine (Ara-C)	DNA Polymerase Inhibitor	Anti-cancer drug	Approved	Bedford, Enzon	[140]
Vidarabine (Ara-A)	DNA Polymerase Inhibitor	Antiviral drug	Approved	King Pharmaceuticals	[140]
Eribulin Mesylate (E7389)	Microtubule interfering agent	Anti-cancer drug	Phase III	Eisai Inc.	[161, 162]
Gemcitabine (GEM) (Gemzar)	Ribonucleotide reductase inhibitor Replaces cytidine during DNA replication	Anti-cancer drug	Phase II	Eli Lilly and Company	[163]
IPL576,092 (Contignasterol derivativel)	Inhibition of leukocyte infiltration and hypersensitivity during allergy	Anti-inflammatory drug	Phase II	Aventis Pharma	[164]
PM-10450 (Zalypsis®)	Transcription inhibitor	Anti-cancer drug	Phase I/II	PharmaMar	[165]
Discodermolide	Microtubule interfering agent	Anti-cancer drug	Phase I/II	Novartis	[142]
HT1286 (Hemiasterlin derivative)	Microtubule interfering agent	Anti-cancer drug	Phase I	Wyeth	[142]
LAF389 (Bengamide B derivative)	Methionine aminopeptidase inhibitor	Anti-cancer drug	Phase I	Novartis	[142]
Hemiasterlin (E7974)	Microtubule interfering agent	Anti-cancer drug	Phase I	Eisai Inc.	[142]
KRN7000 (Agelasphin derivative)	Immunostimulatory (Va24 + NKT cell activation)	Anti-cancer drug	Phase I	Kirin	[142]
PM-060184	Microtubule interfering agent	Anticancer drug	Phase I	PharmaMar	[143]
NVP-LAQ824 (Psammaplin derivative)	Histone deacetylase (HDAC) inhibitors or DNA methyltransferases (DNMT) inhibitor	Anticancer drug	Phase I	Novartis Pharma	[166]