CHAPTER 10

Sea-Originated Cytotoxic Substances

Norihito Maru and **Daisuke Uemura**[1]

Contents

Abstract

Cancer accounted for huge number of deaths, which represents about 13% of all deaths worldwide, and the number of the deaths due to cancer is increasing. Natural products and their synthetic analogs are widely used as antitumor drugs. As represented by these drugs, many anticancer drugs originated from cytotoxic compounds. Marine natural products are a gold mine of strong bioactive compounds with unique structures created in evolution of organisms over hundred million years. However, in the field of drug discovery, most studies have focused on plant essences and bacterial metabolites, and candidate compounds from marine origin are still remaining relatively unexplored.

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I. INTRODUCTION

Important anticancer drugs are not found without the tremendous effort of scientists. In 2008, cancer accounted for nearly 7.6 million deaths, which represents about 13% of all deaths worldwide (Ferlay *et al.*, 2010). Further, the number of the deaths due to cancer is increasing, and has been projected to reach to 11.5 million in 2030. Therefore, there is a constant need for new compounds that can serve as leads for new anticancer drugs. Currently, natural products and their synthetic analogs are widely used as antitumor drugs, including paclitaxel, vinblastine, and etoposide. As represented by these drugs, many anticancer drugs originated from cytotoxic compounds. Cytotoxicity is ambiguous concept that is also paraphrase of recasting of cell death (necrosis and apoptosis) or arrest in cell division. Mechanisms of action are huge diverse modes, such as membrane integrity losing, metabolic enzyme inhibition, signal-transfer defection, apoptosis induction, DNA replication inhibition, mitosis inhibition, and so on. Due to wide variety of mode of action, cytotoxic compounds could also contribute to the discovery of new type drugs.

Marine natural products are a gold mine of strong bioactive compounds with unique structures created in evolution of organisms over hundred million years. However, in the field of drug discovery, most studies have focused on plant essences and bacterial metabolites, and candidate compounds from marine origin are still remaining relatively unexplored. This review shows cytotoxic compound of an antitumor drug lead and compounds with potential for use for drug discovery that isolated from marine phenomena.

II. HALICHONDRINS, ANTITUMOR COMPOUNDS FROM *HALICHONDRIA OKADAI*

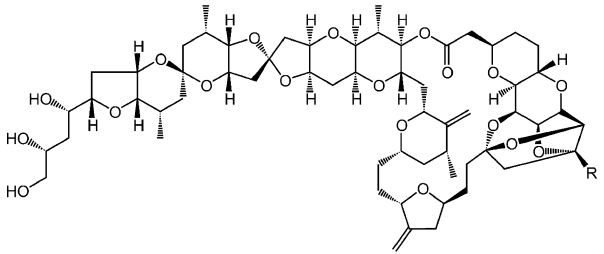
H. okadai Kadota (Fig. 10.1) is a sponge that is abundant in the tidal zone in the Pacific Ocean south of the Boso Peninsula in Japan. Sponges take seawater into their bodies, gather food by filtration, and coexist with symbiotic microorganisms, which account for about 40% of the sponge's volume (Vogel, 2008). Thus, sponges might be aggregates of marine microorganisms. Since sponges have existed for about 500 million years without being able to physically move, they must possess some hidden capability for endurance. After the oil crisis in the 1970s, Gorgonians were shown to contain large quantities of prostaglandins, and this increased the level of interest in natural marine resources. This represented a shift from mass chemicals to fine chemicals. Under these circumstances, the level of interest in marine organisms, and particularly sponges, increased,

FIGURE 10.1 Black sponge *Halichondria okadai*.

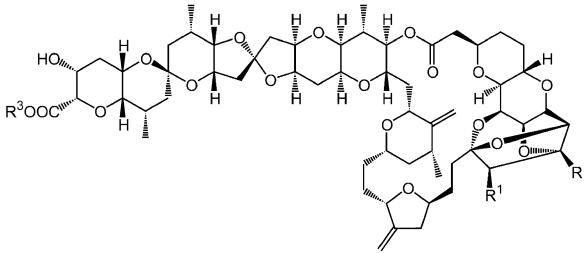
and research on antitumor compounds in *H. okadai* Kadota was started (Uemura, 2010). The inhibitory effects of the constituent compounds were closely examined based on the proliferation of B16 melanoma cells *in vivo*, and eight halichondrin homologues (Fig. 10.2) were identified (Hirata and Uemura, 1986).

Based on the name of this particular sponge, the antitumor substances were named halichondrins. However, 600 kg of the sponge gave <15 mg of the most active homolog, halichondrin B. Fortunately, useful experience was gained by determining the structure of palytoxin, and we concluded that its structure could not be determined based solely on detailed NMR data. In particular, halichondrin B was very fragile and was obtained in small quantities, which made our task very difficult. Thus, norhalichondrin A, which was present in greater quantities, was purified in the form of a *p*-bromophenacyl ester, and a high-quality crystal was obtained. X-ray crystal structure analyses were performed, and extremely complex and specific structures were seen (Uemura *et al.*, 1985). The 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane ring system inside the molecule was the most complex. Both ends of the molecule were diverse: at one end, the number and length of the carbon chains varied, and at the other end, the number and oxidation state of the hydroxy groups varied.

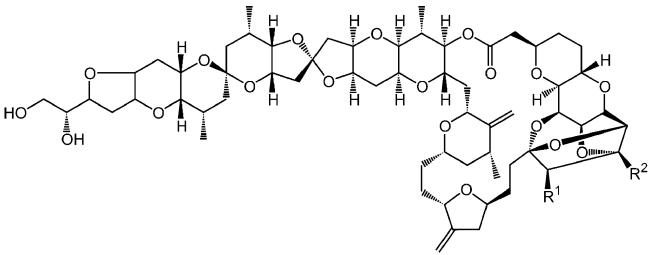
While we suspected that there are a total of nine variations in halichondrin A, we have not identified all of them, mostly due to issues regarding limited quantities. The antitumor activities of halichondrin B have been clarified by *in vivo* experiments, and it appears to be a promising compound. However, toxicity has always been an issue. In a joint Japan–US science seminar on cancer research held in Hawaii in 1987, B. A. Chabner at NCI and G. R. Pettit at Arizona State University were



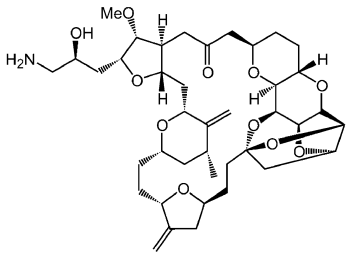
Halichondrin B: R = H
Halichondrin C: R = OH



Norhalichondrin A: $R^1 = R^2 = OH$, $R^3 = H$
Norhalichondrin B: $R^1 = R^2 = R^3 = H$
Norhalichondrin C: $R^1 = R^3 = H$, $R^2 = OH$
p-Bromophenacyl derivative: $R^1 = R^2 = OH$, $R^3 = CH_2COC_6H_4Br$



Homohalichondrin A: $R^1 = R^2 = OH$
Homohalichondrin B: $R^1 = R^2 = H$
Homohalichondrin C: $R^1 = H$, $R^2 = OH$



Eribulin

FIGURE 10.2 Halichondrins and eribulin.

very excited by our research. In fact, Pettit and M. Munro at Canterbury University in New Zealand had obtained halichondrin B from different sponges. However, they had not been able to determine its structure.

Once the framework of a complicated natural product has been elucidated, the overall structure can be determined using various analytical techniques. Therefore, it is extremely important to elucidate the skeleton, and only researchers can appreciate the joy at being the first to reveal this information. In 1992, Y. Kishi, a leading researcher in the total synthesis of complex natural products, who had already successfully synthesized palytoxin carboxylate (Armstrong *et al.*, 1989), synthesized halichondrin B (Aicher *et al.*, 1992). Based on these findings, the antitumor activities of the intermediates were tested at Eisai's US laboratory, and the results clarified that the right half of the molecule was active (Towle *et al.*, 2001). While these results were expected, they were very encouraging because this meant that such compounds could be produced at total synthesis laboratories. Subsequently, many researchers studied the molecule and fine-tuned its structure to develop eribulin mesylate (Newman, 2007). With the help of process chemistry, which is at the center of modern organic synthesis chemistry, they succeeded in mass production, and there are high expectations for its application in breast cancer therapy (Jarvis, 2007). Eribulin has been approved by the US Food and Drug Administration, the European Medicines Agency, and the Japan Ministry of Health, Labour, and Welfare for locally advanced or metastatic breast cancer.

It is not easy to obtain halichondrin B from living organisms. Munro's group planned and implemented sponge cultivation and has conducted studies, but the process has not always gone smoothly. As mentioned above, sponges coexist with many microorganisms and filter food from their environment. At this point, we do not yet know which organism actually produces halichondrins, although many laboratories have isolated and cultured microorganisms from inside sponges. However, only <1% of the microorganisms can be cultured (Rouhi, 1999). Subsequently, with the use of a metagenome technique, gene groups were viewed as compound sources, and fosmid libraries have been prepared. Overall, about 150,000 libraries have been made, and research is currently focused on compound production and genomic information (Abe *et al.*, unpublished work). In the near future, we believe that a new biosynthesis system will be elucidated.

III. CYTOTOXIC COMPOUNDS RELATED TO THE CORAL COMMUNITY

Coral reefs are rich resources as primary producers in tropical and subtropical areas. However, coral is being destroyed by many different external factors, including overgrowth by organisms that cover coral

and feeding by coral predators. The discovery of new ecologically active compounds often triggers the development of basic scientific concepts in the field of biological sciences, since such compounds have direct physiological and behavioral effects on other living organisms (Uemura *et al.*, 2009).

Recently, we encountered a catastrophic change in the Nakijin coral reef in Okinawa Prefecture: the coral's surface was covered with the black sponge *Terpios hoshinota* (Fig. 10.3). This sponge emits compounds that kill corals and cover the dead bodies, which suggest that the sponge might be injecting a toxin into the corals. Guided by cytotoxicity assays, nakiterpiosin (IC_{50}=16nM; Teruya *et al.*, 2003), nakiterpiosinone (IC_{50}=16nM; Teruya *et al.*, 2004), and terpiodiene (Fig. 10.4; Teruya *et al.*, 2002) were isolated from the sponge *T. hoshinota*. Notably, nakiterpiosin and its analog have a unique highly oxidized ring that corresponds to the steroid A-ring and contain bromine and chlorine atoms. Its steroidal skeleton, consisting of C-nor and D-homo components, can be found on land, but this is the first example to be found in the marine environment. Nakiterpiosin and nakiterpiosinone were recently synthesized and their stereostructures have been revised (Gao *et al.*, 2009). The mode of action was also considered. Chen and coworkers found that synthetic nakiterpiosin arrests cell cycle in the G2/M phase. However, in *in vitro* tubulin polymerization assays, nakiterpiosin did not show any activity, in contrast to taxol and nocodazole (Gao et al., 2010a,b). On the other hand, another study by Seemann indicated that nakiterpiosin interacted with tubulin directly and inhibits microtubule polymerization in an *in vitro* assay, and suggested that it may decrease the polymer mass in cells (Wei and Seemann, 2010). In any event, nakiterpiosins are promising compounds that have potential for use as antitumor agents.

FIGURE 10.3 Corals overgrown by black sponge *Terpios hoshinota*.

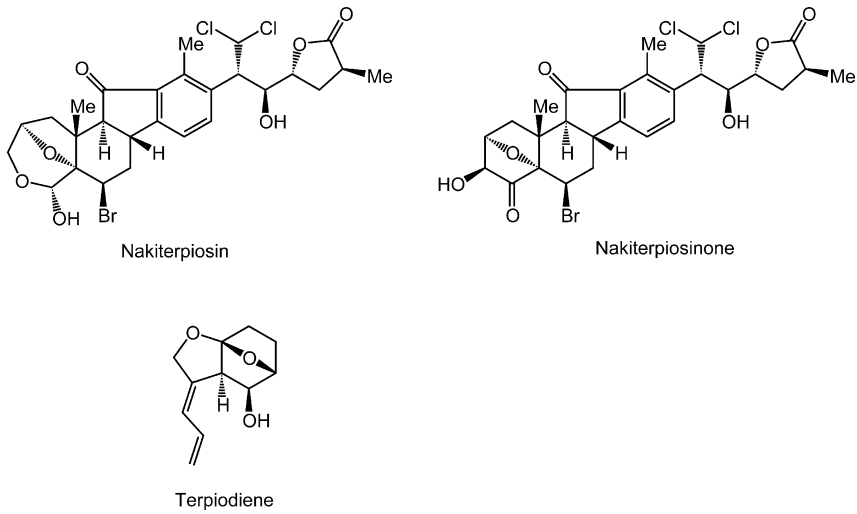
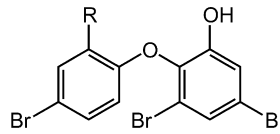


FIGURE 10.4 Cytotoxic compounds from *Terpios hoshinota*.

FIGURE 10.5 White sponge *Dysidea* sp.

In addition to the sponge Terpios, many other kinds of sponges, soft corals, and algae cover corals compete for survival, including the sponges *Dysidea* sp. and *Aplysina* sp.

White sponge, *Dysidea* sp. (Fig. 10.5), has been observed to overgrow members of the family Poritidae at Okinawa Island. Extracts from this sponge have been shown to contain brominated diphenyl ethers, which show potent cytotoxicity against P388 cells. Two known compounds, 3,6-dibromo-2-(2′,4′-dibromophenoxy) and 3,6-dibromo-2-(4′-dibromophenoxy)phenol (Fu and Schmitz, 1996; Fu *et al.*, 1995; Fig. 10.6), were



3,6-dibromo-2-(2',4'-dibromophenoxy)phenol: R = Br
3,6-dibromo-2-(2'-dibromophenoxy)phenol: R = H

FIGURE 10.6 Brominated diphenyl ether from *Dysidea* sp.

FIGURE 10.7 Yellow sponge *Aplysina* sp.

isolated from this extract. Intriguingly, these bromophenols showed strong toxicity against dinoflagellates that lives in an endosymbiotic relationship with corals (Maru *et al.*, unpublished work).

Similarly, *Aplysina* sp.(Fig. 10.7), which show a dramatic change in color from yellow to black when exposed to air, contain cytotoxic compounds including bromotyrosine-derivative alkaloids, purealidins (Ishibashi *et al.*, 1991; Yagi *et al.*, 1993), aplysamine 2 (Xynas and Capon, 1989), and purpuramin G (Fattorusso *et al.*, 1970; Fig. 10.8).

Bromotyrosine-derivative alkaloids are characteristic secondary metabolites from marine sponges of the order Verongida. The structures of these metabolites are typically based on one or two spirocyclohexadienyl isoxazole moieties that are connected to diverse side chains, as seen in aerothinin (Hernández-Guerrero *et al.*, 2007) and aerophobin-1 (Cimino *et al.*, 1983). Sunabedine is a new compound in this family that was isolated from an Okinawan sponge, order Verongida (Maru *et al.*, 2010a). The structure of sunabedine contains a 1,4-disubstituted imidazole ring that is linked to two bromotyrosines via methylene chains. The biological activity of sunabedine was examined with regard to cytotoxicity against B16 mouse melanoma cells and toxicity against brine shrimp

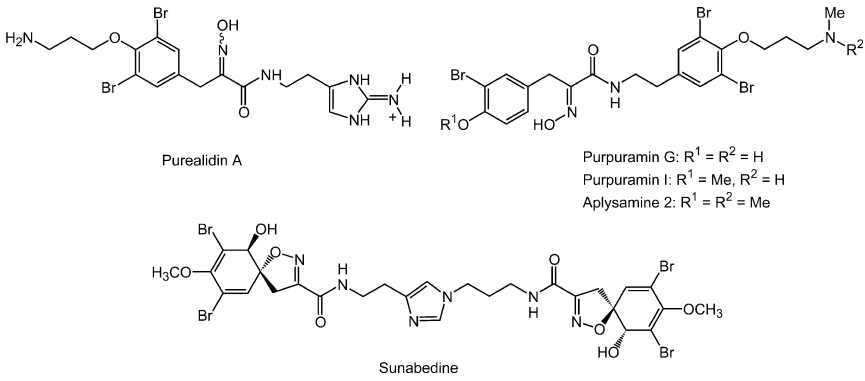
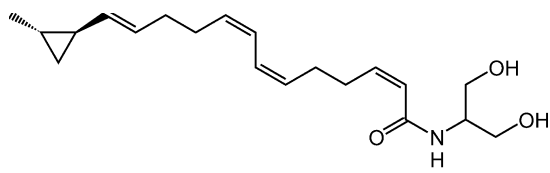


FIGURE 10.8 Bromotyrosine-derivative alkaloids.

FIGURE 10.9 Red algae *Laurencia papillosa*.

(genus *Artemia*). After incubation, sunabedine showed an IC_{50} of 39 μM against B16 cells and an LD_{50} of 110 μM against brine shrimp.

The red algae *Laurencia papillosa* (Fig. 10.9) generally grow in the intertidal zone in tropical and subtropical seas (Masuda *et al.*, 1997). Members of the genus *Laurencia* are widely distributed throughout tropical and temperate zones, and are known to be a rich source of secondary metabolites. However, there have been few phytochemical studies on *L. papillosa* (Wright *et al.*, 1996). We found that *L. papillosa* overgrew hermatypic corals of the families Acroporidae and Poritidae at Ishigaki Island, Okinawa Prefecture. The novel fatty acid amide papillamide (Fig. 10.10) was isolated



Papillamide

FIGURE 10.10 Papillamide from *Laurencia papillosa*.

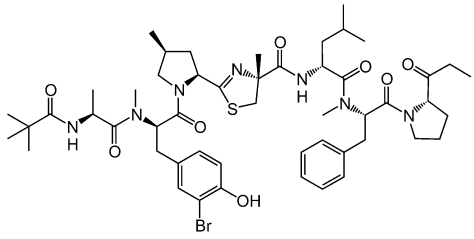
from extract of this alga (Maru *et al.*, 2010b). NMR studies showed that the structure of papillamide contained a cyclopropane ring and serinol. Despite the strong cytotoxic activity of the extract, papillamide did not show definite cytotoxic activity (IC_{50}>100 gm/L) toward P388 mouse leukemia cells or B16 mouse melanoma cells. This result shows that papillamide may have other biological activities that are not related to a toxic or predative effect, and such activities are now being investigated.

IV. CYTOTOXIC COMPOUNDS FROM CYANOBACTERIA

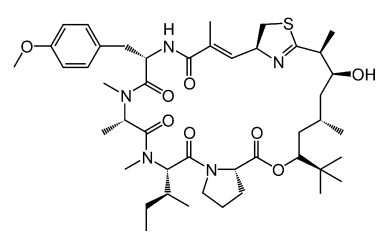
Cyanobacteria are photosynthetic prokaryotes that are widely distributed throughout marine and terrestrial environments. Members of the marine cyanobacteria genus *Lyngbya* are known to produce structurally interesting and biologically active secondary metabolites. Typically, linear/cyclic peptides and depsipeptides that include various nonproteinogenic amino acids are the major groups of these metabolites (Fig. 10.11), which can exhibit potent cytotoxicity.

Bisebromoamide is cytotoxic linear peptide isolated from the marine cyanobacterium *Lyngbya* sp. (Teruya *et al.*, 2009). Structure of bisebromoamide contains rich unusual amino acid derivatives with D-amino acids, N-methylated amino acids, a brominated tyrosine, a modified 4-methylproline, a 2-substituted thiazoline-4-methyl-4-carboxylic acid unit, and a rare 2-(1-oxopropyl)pyrrolidine moiety. Recently, stereochemistry at thiazoline ring moiety was reassigned by synthetic research (Gao et al., 2010a,b). Bisebromoamide showed strong cytotoxicity against HeLa S3 cells with an IC_{50} value of 39 nM. In observation under the microscope, bisebromoamide induced nuclear protrusion type morphological changes in HeLa cells as a result of its mode of action, actin depolymerization (Sumiya *et al.*, 2011).

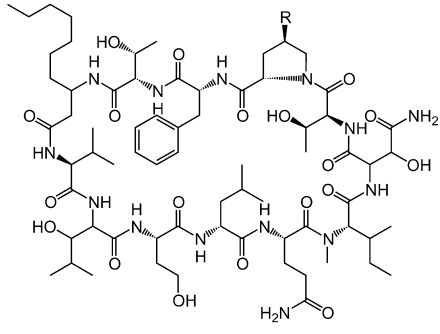
The cyanobacteria *Lyngbya* sp. was found to overgrow corals at Ishigaki Island. Apratoxin A (Luesch *et al.*, 2001) was isolated as the main toxic compound from this alga. Apratoxins were originally isolated in Guam and Palau in the *Lyngbya majuscule* known to cause swimmers' itch (Luesch *et al.*, 2002). Apratoxin A has a macrocyclic structure with parts of



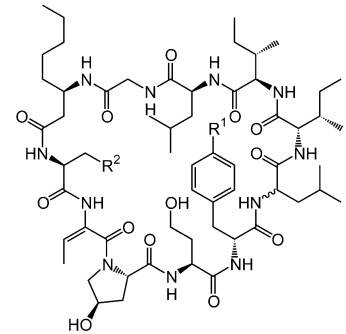
Bisebromoamide



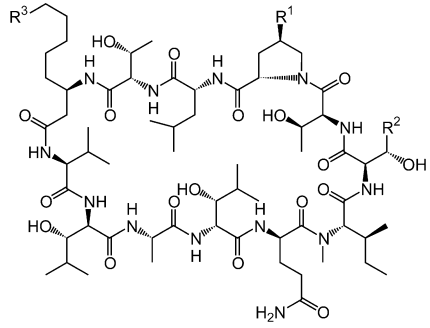
Apratoxin A



Lyngbyacyclamide A: R = H
Lyngbyacyclamide B: R = OH



Laxaphycin A: R^1 = H, R^2 = CH_2OH, $_D$-Leu
Lobocyclamide A: R^1 = OH, R^2 = OH, $_L$-Leu



Laxaphycin B: R^1 = H, R^2 = $CONH_2$, R^3 = CH_2CH_3
Laxaphycin D: R^1 = H, R^2 = $CONH_2$, R^3 = H
Lobocyclamide B: R^1 = OH, R^2 = CH_2OH, R^3 = CH_2CH_3
Lobocyclamide C: R^1 = OH, R^2 = CH_2OH, R^3 = H

FIGURE 10.11 Cytotoxic peptide from cyanobacteria.

amino acids and a polyketide unit, and shows potent cytotoxicity against P388 cells with an IC_{50} value of 0.3nM. Another *Lyngbya* sp. was also collected at Ishigaki Island, and the aqueous ethanol extract of this alga showed strong cytotoxicity against tumor cells. Two new peptides, lyngbyacyclamides A and B, were isolated via a guided bioassay

(Maru *et al.*, 2010c). The structures of these cyclic peptides were determined by spectroscopic analyses and degradation reactions. The members of the amino acid residues of lyngbyacyclamide A were assigned with the proteinogenic L-amino acids, a Val, two Thr, a Pro, a Gln, and unusual amino acids, a D-Phe, a D-Leu, an N-methyl Ile, β-hydroxy leucine and asparagine, a homoserine, and a β-amino decanoic acid. The structure of lyngbyacyclamide B only differs at a hydroxyl group on the proline residue from lyngbyacyalamide A. The biological activities of lyngbyacyclamides were examined with regard to cytotoxicity against B16 cells and toxicity against brine shrimp. After incubation, lyngbyacyclamides A and B showed an IC_{50} of 0.7μM against B16 cells. However, they did not show definite toxicity at 70μM against brine shrimp. This result suggests that lyngbyacyclamides may have a unique mode of action and could contribute to the discovery of new drugs. The structures of lyngbyacyclamides resemble those of the natural products laxaphycins (Bonnard *et al.*, 1997, 2007) and lobocyclamides (MacMillan *et al.*, 2002). Laxaphycins were originally isolated as major products from antifungal extract of cyanobacterium *Anabaena laxa* and *L. majuscule*. Isolated laxaphycins did not show antifungal effect, but especially laxaphycin B shows strong cytotoxicity against the cell line of CCRF-CEM human leukemic lymphoblasts (IC_{50}=1.1μM), CEM/VLB100 vinblastine-resistant subline (IC_{50}=1.0μM), and CEM/VM-1 subline (IC_{50}=1.4μM). Interestingly, laxaphycin A shows weak cytotoxicity against these cell lines IC_{50} over 20μM. This difference may hint studies of structure activity correlations or mode of action.

V. CONCLUSIONS

In the area of drug discovery, marine natural products comprise a rich source of cytotoxic compounds with a potential to target cancers. As shown in development of eribulin, there must be emphasized the need for the researchers in isolation chemistry, synthetic organic chemistry, biochemistry, and pharmacy to work closely together for the development of promising new molecules. Natural cytotoxic compounds of new chemotypes with novel mode of action remain of much interest as compounds that might lead to the battle against the cancer tragedy.

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