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Marine natural products: chemical and biological potential of seaweeds and their endophytic fungi

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Review

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Abstract: Marine natural products have currently been recognized as the most promising source of bioactive substances for drug discovery research. In this review, extraordinary metabolites from marine algae species are illustrated, as well as approaches for their isolation and determination of their biological properties and pharmaceutical potential. Furthermore, marine endophytic microorganisms (from marine algae) are presented as a new subject for extensive investigation to find novel natural products, which make them a potentially rich and innovative source for new drug candidates.

Introduction

Over the last five decades, the study of marine natural products has been an intriguing and fruitful field for organic chemistry research. Marine organisms are prolific producers of structurally unique bioactive metabolites, including some with unusual mechanisms of action, besides diverse biosynthetic pathways (Costa-Lotufo et al., 2009). The ability of some sessile benthic species to synthesize bioactive molecules (including Porifera, Cnidarians, Bryozoans, Tunicates and marine algae) leads to competitive benefits in an ecosystem characterized by extreme resource limitations and converts these organisms into an important source for pharmaceutical prospecting (McClintock & Baker, 2001).

The role of marine natural products in drug discovery began in the 1950s with the isolation of the nucleosides spongouridine (**1**) and spongothymidine (**2**) from the sponge *Tectitethya crypta* Laubenfels. These compounds inspired the synthesis of Cytarabine (Ara-C, **3**) and Vidarabine (Ara-A, **4**), anticancer and antiviral drugs now used for the treatment of acute myeloid leukemia and herpes virus infection, respectively (McClintock & Baker, 2001). Currently, a promising list of marine-derived compounds is in clinical trials, besides two drugs approved by the U.S. Food and Drug Administration and the EU: Yondelis (**5**) and Prialt (**6**). Ziconotide (Prialt), a peptide originally isolated from the venom of *Conus magus* Linnaeus and an analogue of the *N*-type calcium channel blocker ω-conotoxin MVIIA, is used clinically for the treatment of patients suffering from chronic pain. Trabectedin (Yondelis), a tetrahydroisoquinoline alkaloid isolated from the ascidia *Ecteinascidia turbinata* Herdman, was approved by the UE for the treatment of advanced soft tissue sarcoma (Butler, 2008; Costa-Lotufo et al., 2009; Hill, 2011).

In this context, the present work describes the main classes of compounds isolated from marine macroalgae, one of the first marine organisms to be explored for medical purposes. This report will focus on the most representative metabolites, considering the ones in clinical trials or new structures with promising pharmacological potential. In addition, we will present the intriguing metabolites isolated from endophytic fungi, fascinating microorganisms associated with marine algae, which have emerged as a new frontier for finding novel pharmaceutical candidates. Furthermore, this new productive source will be discussed on the basis of the unique structural characteristics responsible for their biological potential.

Red algae

Red algae (Rhodophyta, 98% marine) are dynamic producers of halogenated compounds, ranging

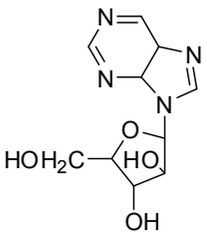
from peptides, polyketides, indoles, terpenes, acetogenins and phenols to volatile halogenated hydrocarbons (Cabrita et al., 2010; Fujii et al., 2011). Additionally, red algae synthesize large amounts of sulfated polysaccharides (cell wall constituents), as well as some shikimate and nucleic acid derivatives (Wijesekara et al., 2011; Güven et al., 2010). A wide variety of biological activities is associated with marine red algae metabolites, such as antibacterial, antifungal, antiviral, anti-inflammatory, antiproliferative, antifouling, antifeedant, cytotoxic, ichthyotoxic, and insecticidal properties.

Related to the marine red algae applications, aqueous extracts obtained from *Digenea simplex* (Wulfen) C. Agardh (Ceramiales, Rhodomelaceae) have been used as a vermifuge for centuries in the traditional medicine of East Asian countries, (Pei-Gen & Shan-Lin, 1986). Further chemical studies were carried out, leading to the isolation of Kainic acid (KA), considered to be the main active compound in this extract. The anthelmintic amino acid KA (**7**) was later re-discovered as a neuroactive compound, acting in neuronal glutamate receptors (Hopkins et al., 2000; Sakai et al., 2005). The structure of KA is strictly related to other neuronal agonist amino acids, such as domoic acid, isolated from the red alga *Chondria armata* (Kützing) Okamura, as well as an anthelmintic compound (Sakai et al., 2005). Currently, kainoids have been used in neurobiological research as a standard reagent, playing an important role in studies of neurophysiological disorders such as Alzheimer, Parkinson and epilepsy (Higa & Kuniyoshi, 2000; Smit, 2004).

Despite medicinal use, the early investigations in marine natural products focused on highly halogenated metabolites, such as the monoterpene halomon (**8**), isolated from the red algae *Portieria hornemanni* (Lyngbye) P. C. Silva (Clardy & Walsh, 2004; Fuller et al., 1992). Halomon exhibited selective cytotoxicity to brain-, renal-, and colon-tumor cell lines in a National Cancer Institute screening and was selected for preclinical drug development. Halomon (**8**) has been considered to be one of the most promising metabolites of marine algae; however, its progress as an anticancer lead has disadvantages due to its limited accessibility and solubility (Andrianasolo et al., 2006; Sotokawa et al., 2000). Another interesting bioactive halogenated compound from marine red algae is the bicyclic diterpene laurenditerpenol (**9**). Isolated by means of bioassay-guided fractionation of the lipid extract from *Laurencia intricata* J. V. Lamouroux, laurenditerpenol is the first marine natural product that inhibited the hypoxia-inducible transcription factor (IC50 0.4 μM); which has recently emerged as an key tumor-selective molecular target for anticancer drug development (Chittiboyina et al., 2007; Jung & Im, 2008; Nagle & Zhou, 2009). Moreover, Laurencia, belonging to the Rhodomelaceae family, is the most studied genus of phylum Rhodophyta and has been intensively investigated over the last fifty years. This vigorous research led to the discovery of diverse molecules with biological potential like the cytotoxic diterpene brasilenol (**10**) and the triterpene calicladol (**11**), and the antibacterial and cytotoxic C-15 acetogenines, such as laurencina (**12**), for example. Recently an overview of the taxonomy and major bioactive secondary metabolites from the *Laurencia* complex current in Brazil was published by Fujii et al. (2011).

In addition, with reference to red algae metabolites, there is a substantial amount of investigation related to the antiviral activity displayed by sulfated polysaccharides (Luescher-Mattli, 2003; Campo et al., 2009). Carrageenans (**13**) are the most common cell wall sulfo-polygalactans from Rhodophyta. The immunomodulatory effects of these polysaccharides were described as potent lectin-like T cell mitogens and polyclonal B cell activators (Luescher-Mattli, 2003). Carrageenans have been studied in the Gigartinaceae and Tichocarpacea families and also exhibited antioxidant, anticoagulant and antithrombic activities (Sokolova et al., 2011).

Although there are no drugs derived from red algae, it is clear that this phylum represents a potential source of bioactive molecules that should be explored more thoroughly. Furthermore, recently published data on marine red macroalgae describes new structures with biological potential. In *Laurencia* sp. a new brominated diterpene, 10-acetoxyangasiol (**14**), was discovered, which exhibited potent antibacterial activities against the clinical bacteria *Staphylococcus aureus*, *Staphylococcu*s sp. and *Vibrio cholerae* (Vairappan et al., 2010). One more natural product, (5S)-5-acetoxycaespitol (**15**), isolated among seven new halogenated metabolites from the Brazilian red algae *Laurencia catarinensis* Cordeiro-Marino & Fujii, demonstrated cytotoxic activity in different tumor cells lines (Lhullier et al., 2010). From the same genera, *Laurencia*, several compounds with fascinating structural diversity were recently published. This rich metabolite assortment is exemplified by the cytotoxic oxasqualenoid (**16**) (Cen-Pacheco et al., 2010), a new highly brominated aromatic compound (**17**) (Qin et al., 2010), a new tricyclic brominated diterpenoid (**18**) with *in vitro* and *in vivo* anti-inflammatory activity (Chatter et al., 2011) and a new halogenated terpenoid (**19**) and a new C15-acetogenin containing a cyclic ether (**20**) (Abdel-Mageed et al., 2010; Gutiérrez-Cepeda et al., 2011; Liu et al., 2010). Finally, a new bromophenol (**21**) with antioxidant activity was found in *Rhodomela confervoides* (Hudson) P. C. Silva (Li et al., 2011b), while lithothamnin A (**22**), a new and unique bastadin-



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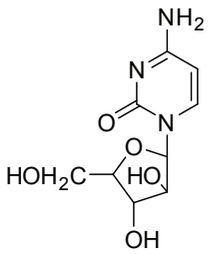

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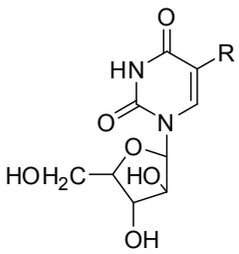
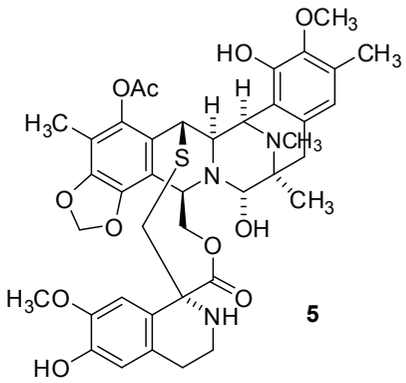


3 R=CH_3 Ara-C
4 R=H Ara-A



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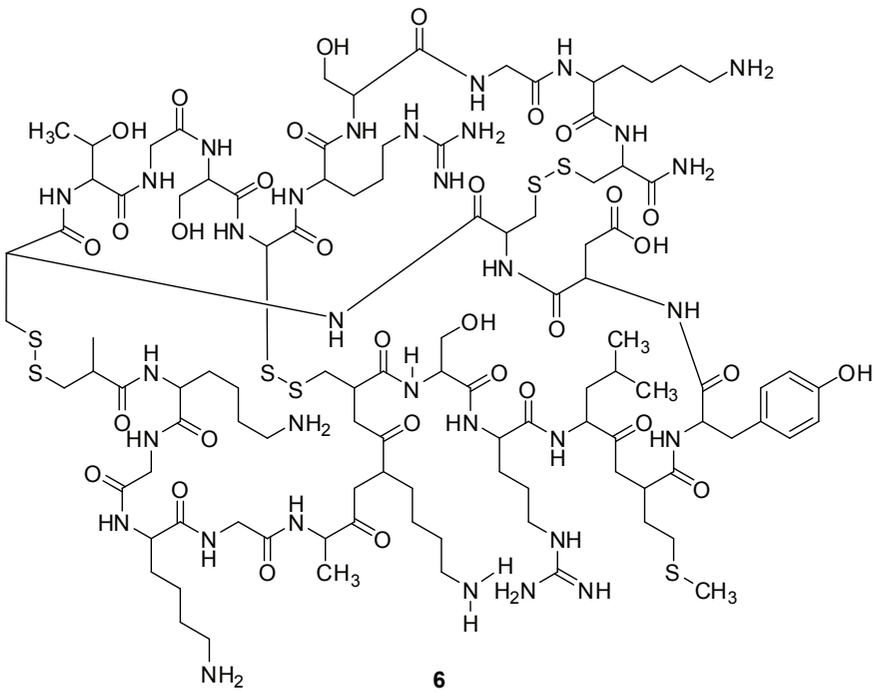

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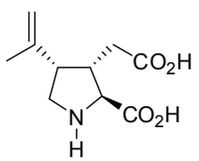

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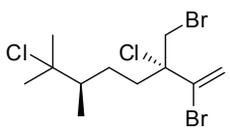

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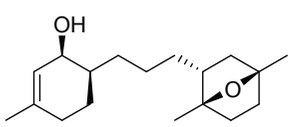

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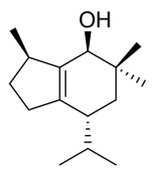

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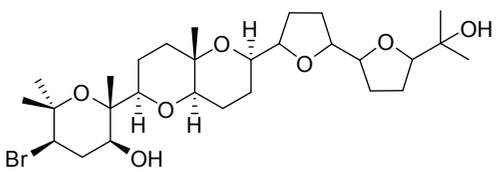

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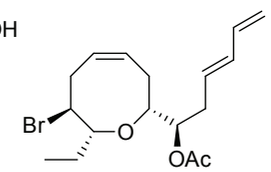

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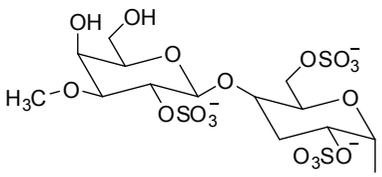

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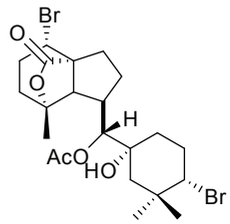

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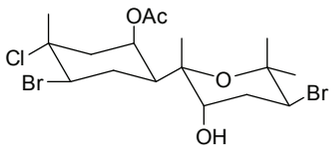

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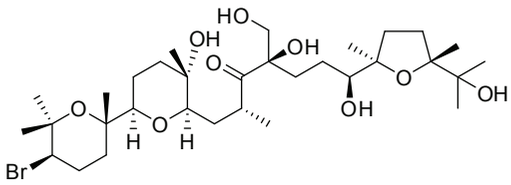

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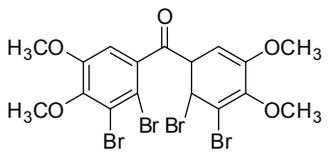

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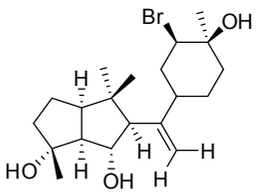

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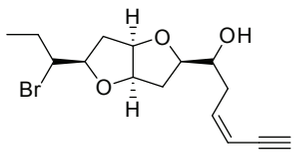

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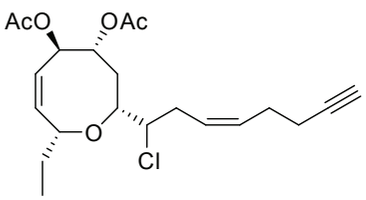

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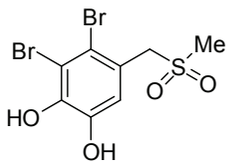

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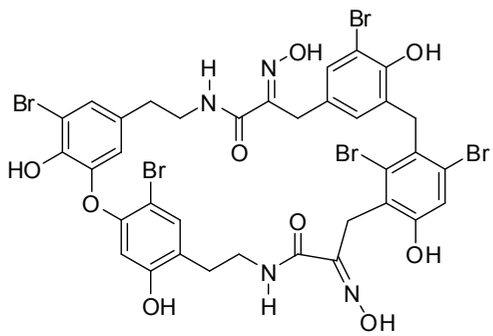

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like structure, was isolated from *Lithothamnion fragilissimum* Foslie (Wyk et al., 2011).

Brown algae

The phylum is almost exclusively marine and is known for producing major metabolites derived from isoprene (McClintock & Baker, 2001). Besides the complex diterpenoids synthesized by brown algae, volatile compounds, fucoidans, phlorotannins and fucoxanthins exhibiting antioxidant, antibiotic, antifungal, antiviral, or anti-cancer activities have been reported (Folmer et al., 2010).

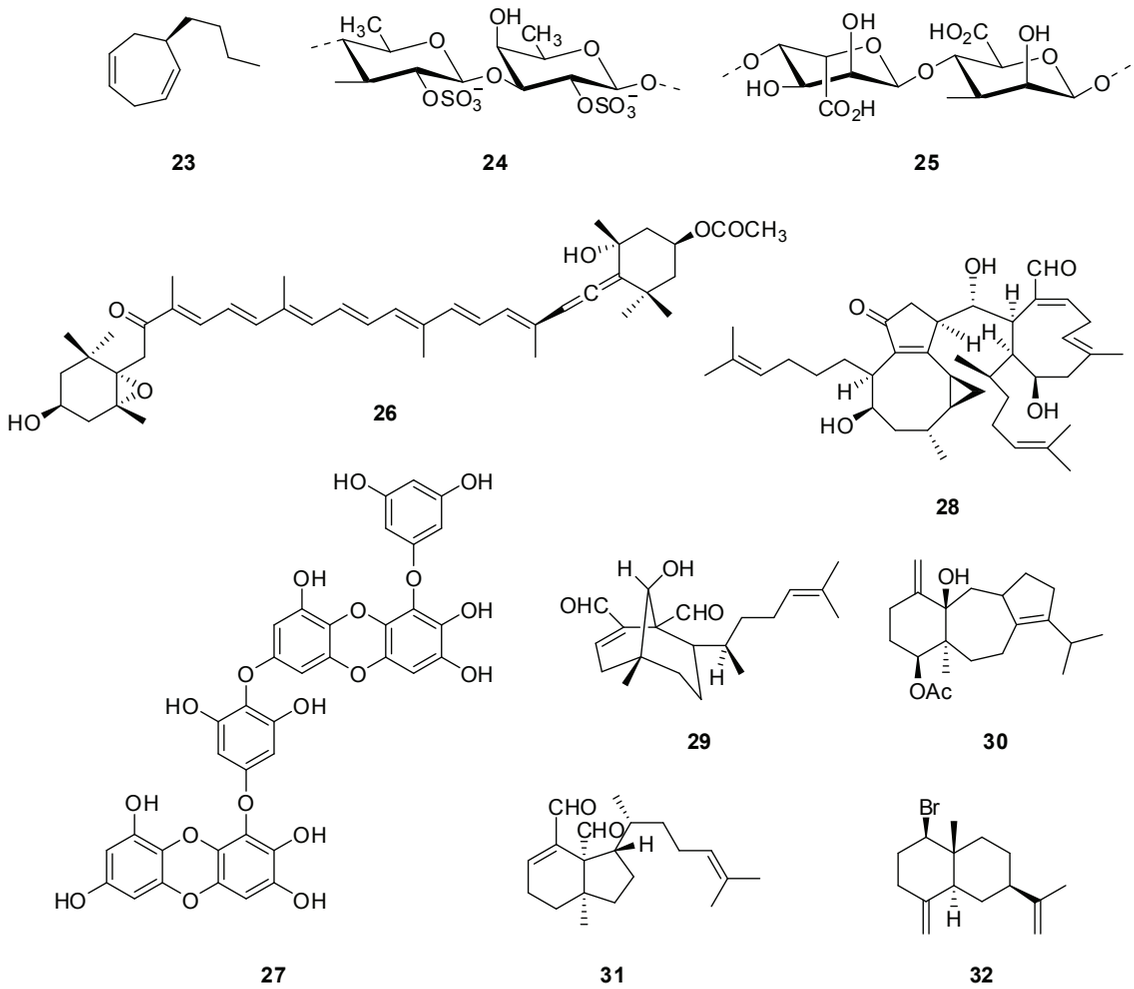
The main volatile compounds produced by marine brown algae are cyclic or acyclic short chain hydrocarbons (C8 or C11), arising from enzymatic conversion of long chain fatty acids. These compounds are used as pheromones in sexual reproduction, while the decomposition products are employed in chemical defense (McClintock & Baker, 2001; Rui & Boland, 2010). Metabolites such as dictyotene (**23**) have been isolated from varied species and are related to the complex sexual reproduction process in this phylum. However, some authors have associated the occurrence of these metabolites to restricted areas where there is a great variety of hydrocarbons due to oil pollution (Teixeira, 2009).

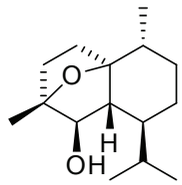
Fucoidans are sulfated polysaccharides (**24**) that have been reported to possess antiviral activity against infectious diseases, such as HIV, herpes simplex virus types (HSV-1 and HSV-2) and cytomegalovirus (Wijesekara et al., 2011). A fucoidan isolated from *Cladosiphon okamuranus* Tokida (Phaeophyceae) demonstrated strong inhibition against dengue virus type two infections. The results described by Hidari et al. (2008) indicate that fucoidan interacts directly with envelope glycoprotein on the virus. Consequently, this compound could be a candidate for development of a potential inhibitory agent against the dengue virus (Wijesekara et al., 2011).

Phlorotannins are tannin derivatives mainly isolated from brown algae, composed of several phloroglucinol units polymerized in different ways. Among all marine algae, the members of the Laminariaceae family are reported to be the richest source of phlorotannins (Thomas & Kim, 2011;

Wijesinghe & Jeon, 2011). These structures could drive the drug discovery process, since they exhibit antioxidant, anti-inflammatory, antidiabetic, antitumor, antihypertensive and anti-allergic activities (Thomas & Kim, 2011). Recently, the biological knowledge and the promising potential for cosmeceutical applications have been reviewed for phlorotannins, some alginates (**25**) and fucoxanthins (**26**) (Wijesinghe & Jeon, 2011). Dieckol (**27**) has been reported as a promising target for application in antiaging and whitening formulations due to its exceptional protective activity against photo-oxidative stress, besides its tyrosinase inhibitory activity (Heo et al., 2009; Li et al., 2009).

Recently, the isolation of a new asymmetric bis-diterpene dictyotadimer A (**28**) from the genus *Dictyota* Lamouroux was reported (Viano et al., 2011), while at the same time antiviral diterpenes (**29**) were found in *Dictyota menstrualis* (Hoyt) Schetter, Höming & Weber-Peukert (Cavalcanti et al., 2011). Ayyad et al. (2011) described the new diterpene amijiol acetate (**30**) from *Dictyota dichotoma* (Hudson) J. V. Lamouroux, very interesting not only for its potent cytotoxicity against several different cell lines, but also for its antioxidant properties. New diterpenes featuring the 2,6-cyclo-xenicane skeleton (**31**) were isolated from *Dilophus fasciola* (Roth) J. V. Lamouroux and *Dilophus spiralis* (Montagne) G. Hamel (Ioannou et al., 2009). New brominated selinane (**32**) and cadinane (**33**) sesquiterpenes were reported from the genus *Dictyopteris* Lamouroux (Ji et al., 2009; Qiao et al., 2009; Wen et al., 2009). The cytotoxic activity of new bisprenylated quinols (**34**), accumulated in Sporochnus comosus C Agradh, were reported by Oveden et al. (2011). In addition, two dolastane diterpenes isolated from the Brazilian brown alga *Canistrocarpus cervicornis* (Kützing) De-Paula & De Clerck were described as promising antiviral compounds (Vallim et al., 2010), besides phlorotannins from *Ecklonia stolonifera* Okamura and *Eisenia bicyclis* (Kiellman) Stchell, which were responsible for preventing diabetes complications (Moon et al., 2011).





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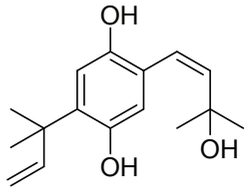

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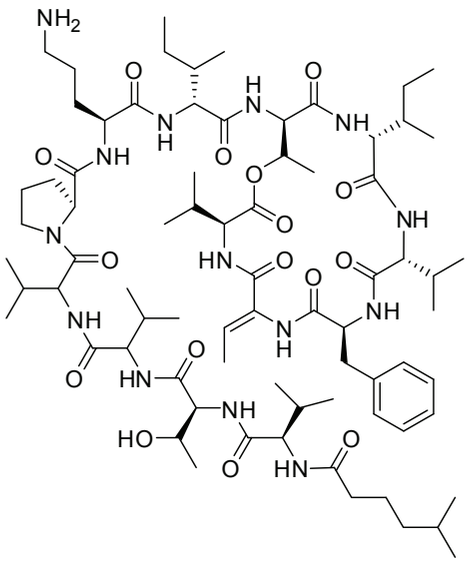

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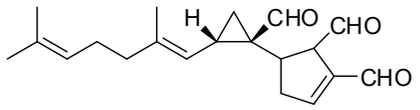

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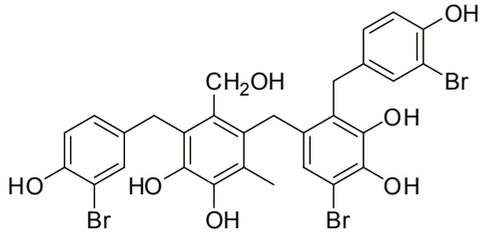

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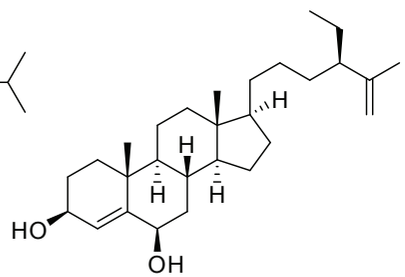

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Green algae

The main representative substances of the phylum Chlorophyta are isoprenoid derivatives. Acetogenins, amino acid derivatives, carbohydrates and shikimate derivatives have also been isolated from these algae (McClintock & Baker, 2001). Only a small percentage of this phylum belongs to the marine environment (13%) and, consequently, they are the least representative macroalgae division in marine natural products chemistry.

The most remarkable in terms of bioactive metabolites isolated from marine green algae is the cyclic depsipeptide kahalide F (**35**). Kahalide F was initially obtained from the herbivorous sea slug *Elysia rufescens*; however, it is assumed that the genuine source of this compound is the chlorophyta *Bryopsis* sp., which is the main element of the sea slug's diet (Folmer et al., 2010). Kahalide F (**35**), developed by the Spanish biopharmaceutical company PharmaMar, is a novel antitumor drug candidate currently in phase II clinical trials and causes oncosis in cancer cells by lysosomal induction and cell membrane permeabilization (Folmer et al., 2010). Other metabolites isolated from green algae, like the diterpene halimedatrial (**36**) from *Udotea flabellum* (J.Ellis & Solander) M. A. Howe and *Halimeda* sp. Lamouroux, besides the bromophenolic compound isorawsonol (**37**) from *Avrainvillea rawsonii* (Dickie) M. A. Howe, have demonstrated interesting anticancer potential (Folmer et al., 2010). Recently, a new sterol, 24-*R*-stigmasta-4,25-diene-3β,6β-diol (**38**), among another known compounds, was isolated from *Codium divaricatum* Holmes, a traditional Chinese medicine used as an anticancer agent since the remote past (He et al., 2010).

Endophytic marine microorganisms

Microbial natural products are a large and promising area for obtaining new and potent therapeutic agents (Demain, 2009; Lam, 2007). Combining the particularities of the marine environment and microbial versatility, marine microorganisms have been considered to be the most hopeful natural source for drug discovery (Glaser & Mayer, 2009; Lam, 2007). Marine microorganisms have shown an excellent biosynthetic ability to generate bioactive metabolites (Jensen et al., 2005; Simmons et al., 2008).

Marine fungi comprise a small group of ecologically well-known filamentous ascomycetes, yeasts and their anamorphs (Pang & Mitchell, 2005). The assumption regarding the strong symbiotic relationship between microorganisms and their invertebrate hosts has been increasingly solidified, since several studies indicate that the active substances isolated from sponges, sea squirts, and corals, among others, may actually have originated from their associated microorganisms (Glaser & Mayer, 2009; Simmons et al., 2008). Moreover, of twenty substances derived from (or inspired by) marine organisms that are in final trial for approval as new cancer treatment drugs, sixteen are directly related to microbial biosynthesis and five are, in fact, isolated from microorganisms (Simmons et al., 2008).

Considering the fundamental role of microorganisms in the invertebrate's bioactive metabolite production, it is important to point out the relevance of the endophytism regarding macro- and microorganisms. Endophytic microorganisms consist of fungi and bacteria living at least part of their life cycle within the healthy tissue of their host (generally plants, algae or invertebrates), in a relationship that can diverge between latent phytopathogenesis and mutual symbiosis (Strobel et al., 2004; Tan & Zou, 2001).

The complexity and importance of this ecological relationship are reflected in the chemical and biological potential of endophytes in natural products research. In general, the study of endophytic microorganisms represents a relatively new branch and, therefore, an unexplored field (Guo et al., 2009; Strobel et al., 2004). The association between algae and fungi has been well established; however, there are only a few studies with reference to metabolites isolated from fungi associated with marine algae inner tissues (Jones et al., 2008).

Table 1 summarizes unknown compounds isolated from fungi derived from marine algae inner tissues. To obtain endophytic fungi cultures, authors usually make use of superficial sterilization methods to avoid the isolation of epiphytic microorganism. Analyzing the data presented, we can infer that the search for new metabolites from marine red algae endophytic fungi is quite recent, the first report being from the beginning of the last decade. An evident growth in interest in this field is justified by 33 papers dealing with chemical investigations of endophytic fungi from marine algae, more than 50% of which appeared in the literature after 2008.

Related to the endophytic fungal source, it is clear that the fungi were isolated from the most representative species belonging to different macroalgae phylum. These algal species had already been studied, such as the green ones from the genera *Codium* Stackhouse and *Ulva* L. (including *Enteromorpha* Link in Nees), the brown algae from the genera *Sargassum* C. Agardh and Fucus, and *Laurencia* as the red algae example. In addition, there is no problem with the marine algae, since its role is just to serve a host for the endophytic microorganisms, as noted in Table 1. Moreover, these marine seaweed species are responsible for the great chemical structure diversity, besides the expressive biological potential.

The metabolites derived from endophytes collected from marine green algae presented, in general, bicyclical structures with some oxygenations or even aromatic moieties, demonstrating cytotoxicity, antiprotozoa and antimicrobial activities (Elsebai et al., 2010; Zhu et al., 2009; El-Beih et al., 2007; Osterhage et al., 2000), besides fat-accumulation inhibitory activity (Almeida et al., 2010), modulation of carcinogen metabolizing enzymes and protection from DNA damage (Gamal-Elden et al., 2009).

Related to substances obtained from endophytes associated with brown algae, we can highlight a greater structural and bioactivity assortment: naphto- and pyrone derivatives presenting antifungal and antioxidant activity (Zhang et al., 2010; Zhang et al., 2007a, b), macrolides showing antibacterial potential (Holler et al., 2000; Yang et al., 2006), isobenzofuranone derivative and bicyclic lactones (Abdel-Lattef et al., 2003; Osterhage et al., 2002a), antioxidant benzodiazepine derivatives (Cui et al., 2009) and cytotoxic ergosterolide derivates with an unusual pentalactone B-ring (Cui et al., 2010).

Considering red algae as the source of endophytes, the metabolites also presented some interesting chemical structure variations and biological potential. Some examples are the new oxylipin and steroidal acetylcholinesterase inhibitors (Qiao et al., 2011); curvularin-type macrolides presenting antibacterial, antifungal and algicide properties (Dai et al., 2011), several classes of terpenes like the antimicrobial indoloterpenes (Qiao et al., 2010), sesquiterpenoids with antiplasmodial activity (Osterhage et al., 2002b), tetracyclic diterpenes (Gao et al., 2011a) and one antimicrobial monoterpene (Gao et al., 2011b). Moreover, other interesting properties are exemplified by polyoxygenated compounds with antifungal potential,

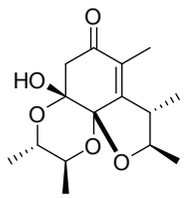
cytotoxic steroids with tetrahydroxy and C-16-acetoxy groups (Gao et al., 2011c), antimicrobial and cytotoxic polyketides (Gao et al., 2011b), aromatic pentaketides of the dihydroisocoumarins class (Pontius et al., 2008a) and cytotoxic benzaldehyde derivatives (Wang et al., 2006).

Finally, we point out some characteristics of metabolites from unidentified marine algae endophytes: antioxidant hydroquinone derivates (Abdel-Lattef et al., 2002), prenylated polyketide benzophenone derivatives (Kralj et al., 2006), monomeric xanthones showing cancer chemopreventive action by inhibition of cytochrome P450 and other correlated enzymes (Krick et al., 2007). Exploring carbonylated structures, some motivating compounds include the dihydroisocoumarins derived from aromatic pentaketides (Pontius et al., 2008a), dimeric chromanones and some other polyketides containing two uniquely modified xanthone derived units, besides enzyme inhibitor properties (Pontius et al., 2008a,c) and a rubralactone derivative showing enzymatic inhibition of DNA polymerase (Naganuma et al., 2008).

Table 1. Unknown substances isolated from marine algae endophytic fungi.

	Algae(host)	Fungi(endophyte)	Structures* number	Reference
Chlorophyta (green algae)	*Blidingia minima* (Nägeli ex Kützing) Kylin	*Penicillium* sp.	**39**	Zhu et al., 2009
	Codium fragile (Suringar) Hariot	*Valsa ceratosperma* (Tode ex Fries) Maire	**40**	El-Beih et al., 2007
	Enteromorpha sp.	*Cadophora malorum* (Kidd & Beaumont) W. Gams	**41-44**	Almeida et al., 2010
	Enteromorpha sp.	*Coniothyrium cereale* E. Müll	**45-51**	Elsebai et al., 2010
	Ulva sp.	*Ascochyta salicorniae* Magnus apud Jaap	**52-54**	Osterhage et al., 2000
	Ulva sp.	*Penicillium* sp.	**55**	Gamal-Elden et al., 2009
	Valonia utricularis (Roth) C.Agardh	*Chaetomium* sp.	**56**	Abdel-Lateff, 2008
Phaeophyta (brown algae)	*Colpomenia sinuosa* (Mertens ex Roth) Derbès & Solier	*Aspergillus niger* Van Tieghem	**57-62**	Zhang et al., 2007a,b; Zhang et al., 2010
	Cytoseira sp.	*Varicosporina ramulosa* Meyers et Kohlm	**63, 64**	Holler et al., 2000
	Fucus spiralis L.	*Phoma tropica* R. Schneid. & Boerema	**65**	Osterhage et al., 2002a
	Fucus vesiculosus L.	*Epicoccum* sp.	**66**	Abdel-Lateff et al., 2003
	Sargassum sp.	Not identified	**67, 68**	Yang et al., 2006
	Sargassum kjellmanianum Yendo	*Aspergillus ochraceus* Wilhelm	**69-72**	Cui et al., 2009 Cui et al., 2010
Rhodophyta (red algae)	*Corallina officinalis* L.	*Aspergillus flavus* Johann Heinrich. Friedrich Link	**73,74**	Qiao et al., 2011
	Gracilaria folifera (Forsskål) Borgesen	*Curvularia* sp.	**75, 76**	Dai et al., 2011
	Heterosiphonia japonica Yendo	*Aspergillus oryzae* (Ahlburg) E. Cohn	**77-79**	Qiao et al., 2010
	Kappaphycus alvarezii (Doty) Doty ex P.C.Silva	*Mycelium sterillium* (KT 29)	**80**	Tarman et al., 2011
	Liagora viscida (Forsskål) C.Agardh	*Drechslera dematioidea* (Bubak & Wroblewski) Subram, & Jain	**81-90**	Osterhage et al., 2002b
	Laurencia sp.	*Penicillium chrysogenum* Thom	**91-98**	Gao et al., 2011a,b,c
	Laurencia similis Nam & Saito	*Exophialia oligosperma* Calendron ex de Hoog & Tintelnot	**99****	Li et al., 2011a
	Plocamium sp.	*Acremonium* sp.	**100**	Pontius et al., 2008a
	Polysiphonia urceolata (Lightfoot ex Dillwyn) Greville	*Chaetomium globosum* Kunze	**101**	Wang et al., 2006
Undefined		*Acremonium* sp.	**102, 103**	Abdel-Lateff et al., 2002
		Emericella nidulans var. *acristata* (Fennell & Raper) Subram	**104, 105**	Kralj et al., 2006
		Monodictys putredinis (Wallr.) Hughes	**106-111**	Krick et al., 2007; Pontius et al., 2008b
		Nodulisporium sp.	**112, 113**	Pontius et al., 2008a,c
		Not identified	**114**	Naganuma et al., 2008

*Unknown structures and unknown as natural products; **Unknown structure as fungi natural product.



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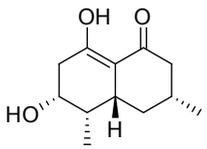

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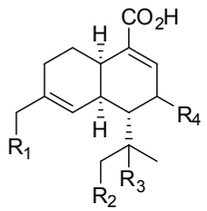
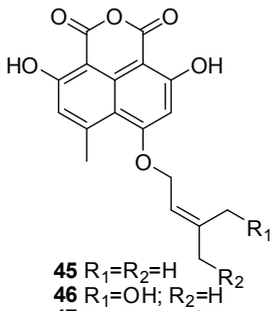
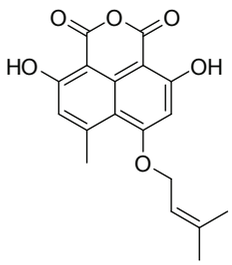


41 R_1=OH; R_2=R_3=R_4=H
42 R_2=OH; R_1=R_3=R_4=H
43 R_3=OH; R_1=R_2=R_4=H
44 R_4=OH; R_1=R_2=R_3=H



45 R_1=R_2=H
46 R_1=OH; R_2=H
47 R_1=H; R_2=OH



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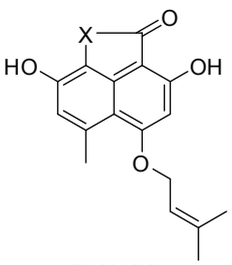
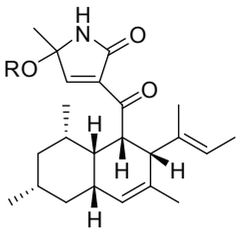
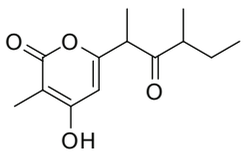


50 X=CO
51 X=O



52 R=$CH_2CH_2CH_2CH_3$
53 R=CH_3



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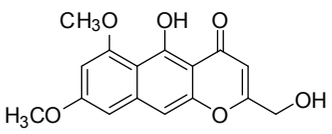

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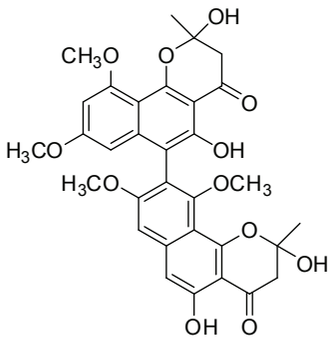

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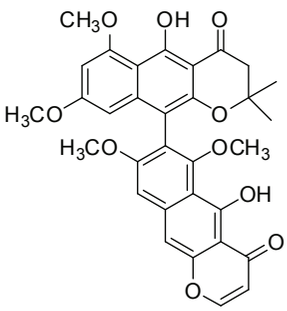

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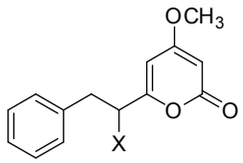
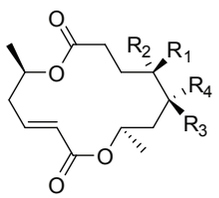
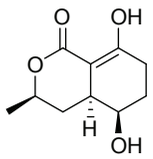


61 X=$HCOCH_3$
62 x=OH



63 R_1=R_4=H; R_2=R_3=OH
64 R_1=R_4=OH; R_2=R_3=H



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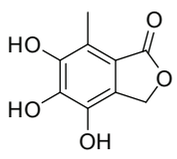

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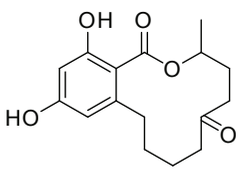

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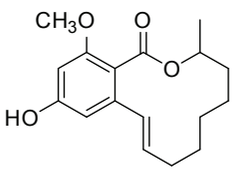

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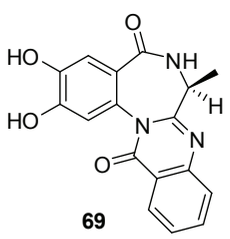

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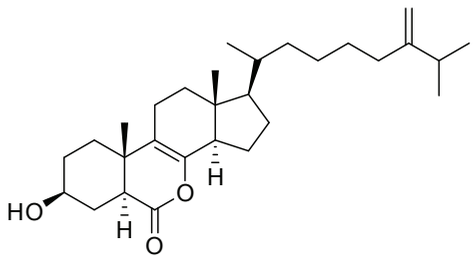

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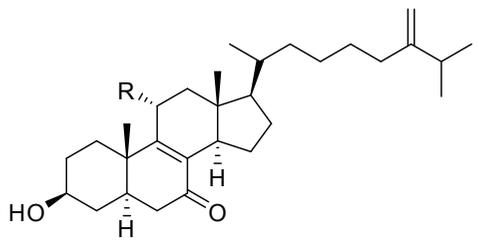
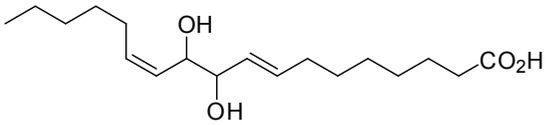


71 R=OH
72 R=H



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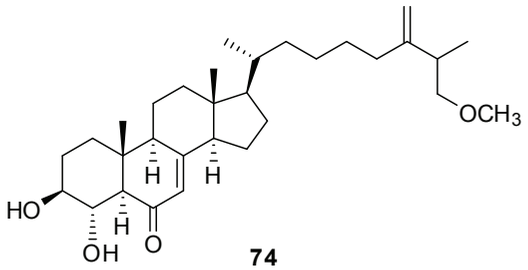

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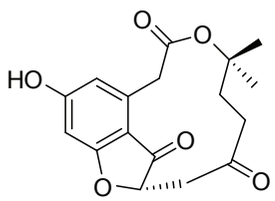

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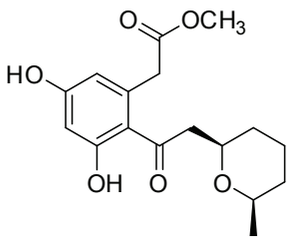

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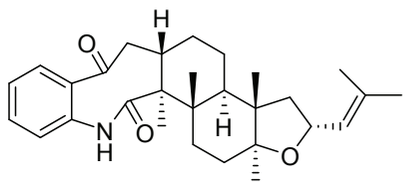

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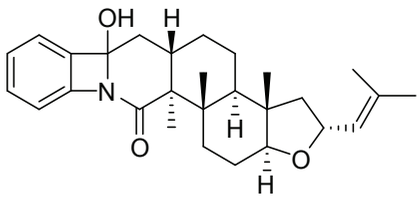

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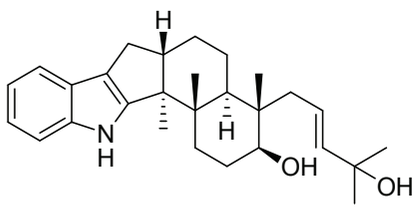

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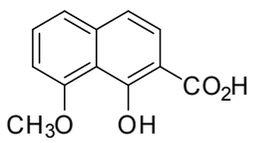

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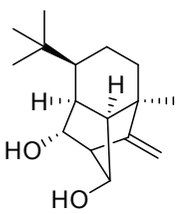

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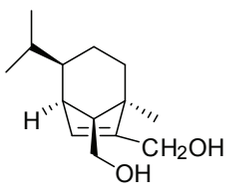

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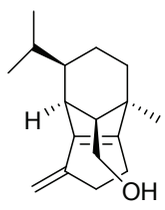

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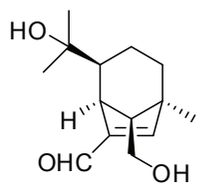

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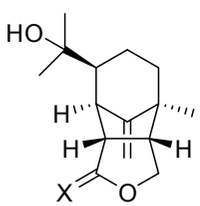
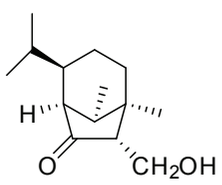


85 X=O
86 X=α-H, β-OCH_3



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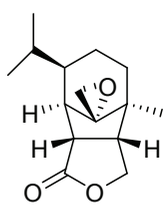

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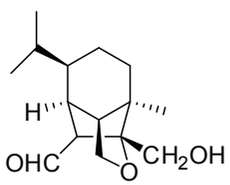

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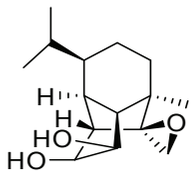

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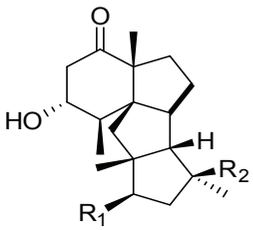
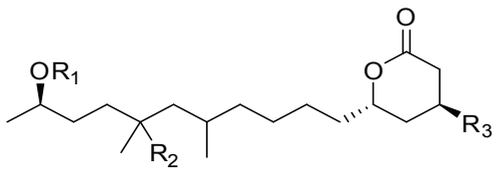
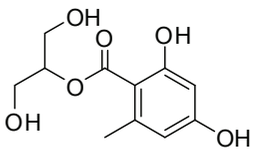


91 R_1=OH; R_2=OCH_3
92 R_1=H; R_2=CH_2OH



93 R_1=R_2=H; R_3=OH
94 R_1=H; R_2=R_3=OH



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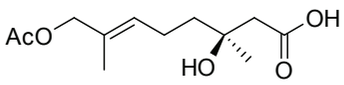

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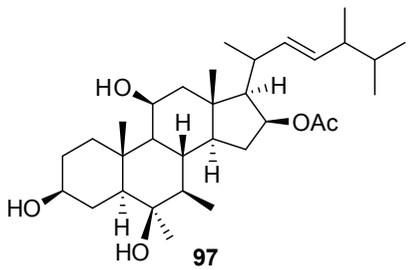

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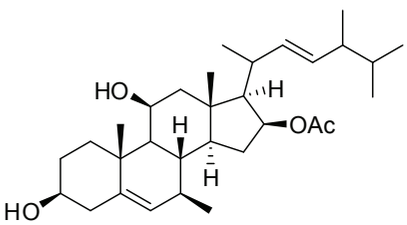

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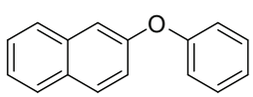

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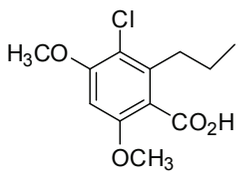

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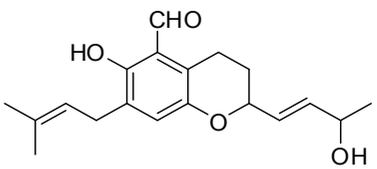
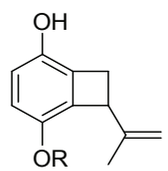
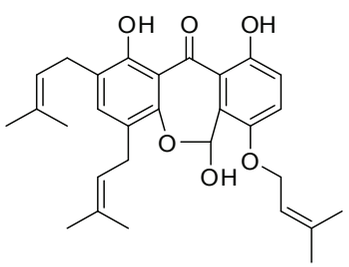


101



102 R=H
103 β-D-glucopyranose



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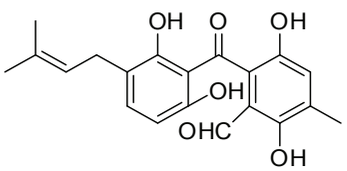

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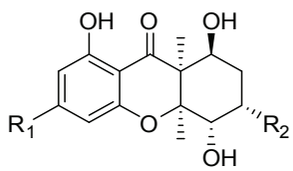
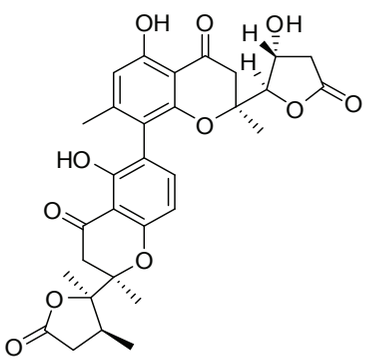


106 R_1=CH_3; R_2=OH
107 R_1=H; R_2=CH_3
108 R_1=OCH_3; R_2=CH_3



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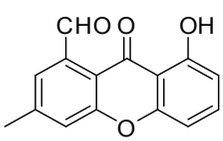

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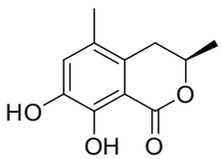

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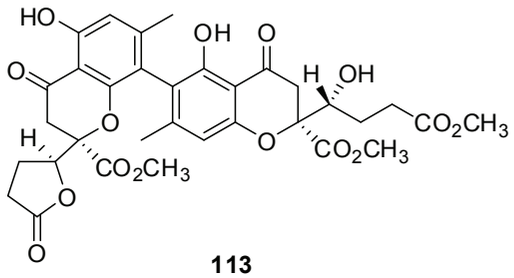

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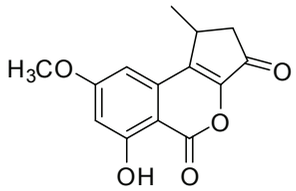

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Conclusion

Marine organisms have been the focus of interesting discoveries, which have led to important drugs actually available from the pharmaceutical industry, such as Ara-A, Ara-C, Yondelis and Prialt. Since the early studies concerning the marine environment, seaweeds have emerged as a vast source of unique structures and bioactive metabolites. Currently, an innovative approach that has been taken is the isolation of endophytic microorganisms from macroalgae, exploring an interesting ecological relationship. This new research frontier, which represents a new natural products source to be explored, implies that, in the future, the intriguing chemical structures already isolated from these microorganisms may provide high-quality drug candidates to improve human health.

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