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Recent Sino-Italian collaborative studies on marine organisms from the South China Sea*

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Abstract: In this communication, selected results obtained in the course of a 10-year Sino-Italian collaborative project are presented. During this collaboration, several studies on marine organisms collected in the South China Sea have been conducted, resulting in the characterization of a large number of novel natural products. The main interest has been focused on sponges, cnidarians, and molluscs. Here, the recent research, including some not yet published studies, on cnidarians and molluscs, in particular, opisthobranchs and pulmonates, will be briefly described. The study of cnidarians and pulmonates led to isolate molecules, in particular, biscembranoids and polypropionates, displaying carbon skeletons already described in previous papers. Our studies resulted in their complete structural characterization including the absolute stereochemistry that was clarified by coupling X-ray diffraction to circular dichroism (CD) spectra analysis. Some unique nitrogenous molecules containing either an isonitrile function or an 1,2,4-oxadiazole moiety, this latter found for the first time in a marine organism, as well as known sesterterpenoids and diterpenoids were isolated from opisthobranchs. Owing to their anatomical location, these metabolites should play a relevant role in the protection of the molluscs. Finally, a series of alkaloids structurally related to known anticancer agents were also characterized.

Keywords: bioactive molecules; cnidarians; marine chemistry; molluscs; natural products; NMR; organic chemistry; polypropionates; structures; terpenoids.

INTRODUCTION

Interest in marine natural products (MNPs) from Chinese organisms has increased significantly during the last 10 years. Recently, the average number of MNPs per year isolated from geographically distinct areas between 1965 and 2007 was reported [1]. This number is almost 50 for the China Sea, but it increases to more than 200 in the period from 2001 to 2007. Japanese waters follow with almost 125 MNPs. Probably the number of new compounds reported could be drastically reduced if all artifacts were eliminated. In fact, it is likely that the naturally occurring products can be modified during extraction and purification work-up. However, the correct structural characterization of many new molecules, even if artifacts, belonging to different classes of compounds provides the researchers with basic

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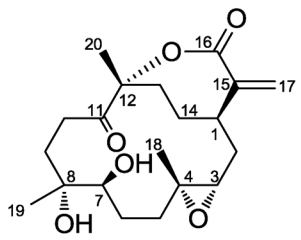
tools to rapidly identify new molecules. This will allow the researchers to undertake more in-depth studies on these compounds in the future. Thus, the scientific work that the Chinese scientists are performing could provide a solid basis to rapidly develop in an impressive manner innovative research on marine organisms. A significant contribution to these studies has been offered by a Sino-Italian project "Study on Bioactive Metabolites of Marine Organisms from Chinese Coasts" between the Institute of Biomolecular Chemistry (ICB, Naples) and the Shanghai Institute of Materia Medica (SIMM, Shanghai). The project started in 2002, and two of us (E.M. and Y.G.) organized many sampling campaigns, all in the South China Sea and, in particular, in three different locations around Hainan (Sanya, 2002; Lingshui, 2003, 2004, 2010; Yalong Bay, 2006), and in the small Wei Zhou Island (2007) close to the Vietnamese coasts. Some microorganisms such as dinoflagellates [2] and fungi [3] were investigated, but the majority of the studies were directed to sponges [4], cnidarians, opisthobranchs, and pulmonates. In this communication, significant results obtained from studying cnidarians, opisthobranchs, and pulmonates will be discussed.

RESULTS AND DISCUSSION

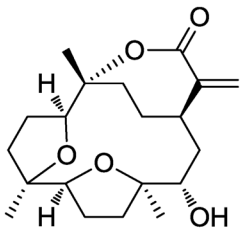
Studies on cnidarians

Cnidarians are extremely abundant in the South China Sea; many gorgonians and alcyonaceans were collected and studied. New polyhydroxylated steroids [5] and terpenes [6] were characterized from gorgonians, whereas the metabolism from alcyonaceans was dominated by cembrane diterpenes. This topic will be treated with more details reporting some selected recent studies.

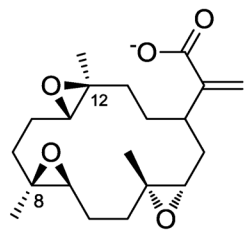
Two new cembranes, sinulaparvalide A (**1**) and B (**2**), were isolated from the soft coral *Sinularia parva* [7]. Their structures were characterized by a seven-membered *exo*-conjugated lactone ring. The structures were supported by X-ray diffraction analysis. A common biogenetic precursor could be triepoxide **3**, which undergoes a cyclization by nucleophilic attack of the carboxy anion at C-12 with opening of the epoxide ring. Compound **1** could be formed by a further opening of the epoxide at C-8, whereas compound **2** could be obtained by a cascade of nucleophilic reactions involving the opening of both epoxides at C-8 and C-4.



sinulaparvalide A (**1**)



sinulaparvalide B (**2**)



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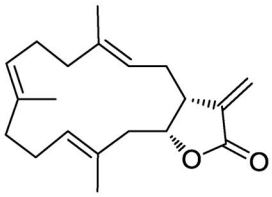
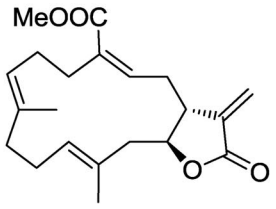
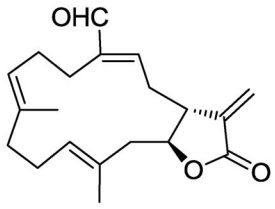
Other new *exo*-conjugated γ-lactones (lobophytolides A–F, **4–9**) were isolated from a soft coral belonging to the genus *Lobophytum* [8], together with six already described cembranes (e.g., compound **10** [9]). The absolute stereochemistry of lobophytolide A (**4**) was assigned by comparison of its optical rotation ($[\alpha]^{25}_D = -65$) with that ($[\alpha]^{25}_D = +31.4$) of its synthetic enantiomer (**11**) [10] even though the absolute values of the specific rotations are quite different.



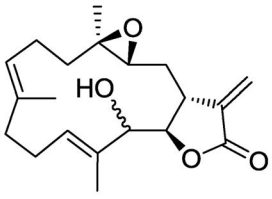
lobophytolide A (**4**)



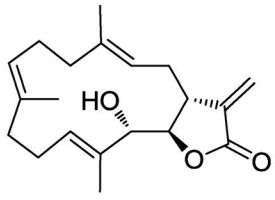
lobophytolide B (**5**)



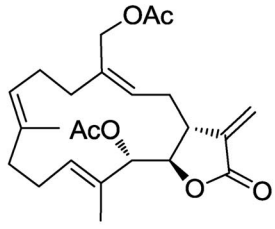
lobophytolide C (**6**)



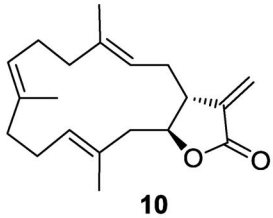
lobophytolide D (**7**)



lobophytolide E (**8**)



lobophytolide F (**9**)



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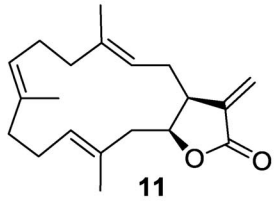

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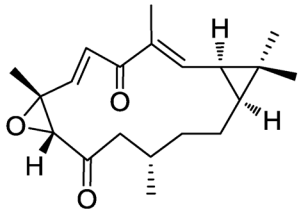
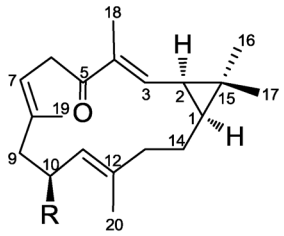
The α orientation of the substituent at C-1 of lobophytolide A (**4**) is according to the empirical rule suggested by Tursch and co-workers [11] that the isopropyl groups at C-1 in all cembrane diterpenes isolated from gorgonians and alcyonaceans are β- and α-oriented, respectively.

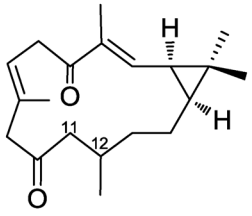
An apparent exception to this rule was found studying the casbane diterpenoids from the soft coral *Sinularia depressa* [12]. Casbane diterpenoids are characterized by the presence of a dimethylcyclopropyl moiety fused to the 14-membered ring. These terpenes are extremely rare in nature and in marine organisms were found only in *Sinularia microclavata* [13] (microclavatin **12**). Two epimers at C-1, depressin (**13**) and 1-*epi*-depressin (**14**), isolated from *S. depressa*, were easily characterized on the basis of both the diagnostic ^{13}C NMR chemical shifts of the geminal methyls, very close in the *trans*- and well distinct in the *cis*-isomer, and the almost identical circular dichroism (CD) profiles. The soft coral contained other seven related diterpenoids. Two of them, 10-hydroxydepressin (**15**) and 1-*epi*-10-hydroxydepressin (**16**), played a key role in the assignment of the absolute stereochemistry to this group of metabolites. In fact, the *S* configuration at C-10 of both compounds was easily assigned by Mosher's method. Subsequent conformational studies [12] on the four possible diastereoisomers led us to assign 1*S*,2*S*,10*S* and 1*R*,2*S*,10*S* absolute configurations in compounds **15** and **16**, respectively. Other casbanes (**17–19**) displayed identical structures with the exception of the stereochemistry at the ring junction, *cis* in **17** and *trans* in both **18** and **19**. The CD profiles for **17** and **18** were almost identical to those of compounds **13** and **14** but opposite to that of **19** leading to assign the *R* absolute configuration at C-2 of this latter compound. The substituents at C-1 of the casbane diterpenoids from *S. depressa* can be α- or β-oriented. Apparently, this conflicts with the empirical rule suggested by Tursch and co-workers [11],



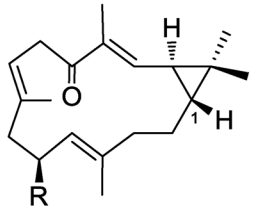
microclavatin (**12**)



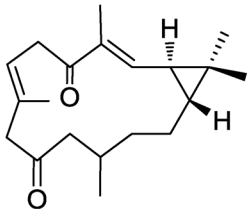
depressin (**13**): R = H
10-hydroxydepressin (**15**): R = OH



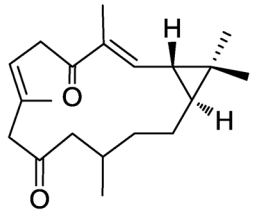
10-oxo-11,12-dihydrodepressin (**17**)



1-*epi*-depressin (**14**): R = H
1-*epi*-10-hydroxydepressin (**16**): R = OH



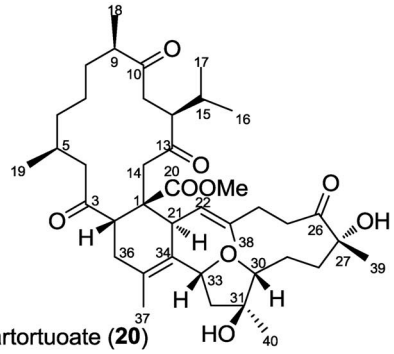
1-*epi*-10-oxo-11,12-dihydrodepressin (**18**)



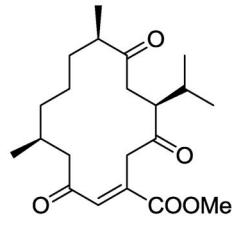
2-*epi*-10-oxo-11,12-dihydrodepressin (**19**)

but before drawing conclusive statements it should be necessary to know exactly the biosynthetic mechanism leading to the cyclopropyl moiety.

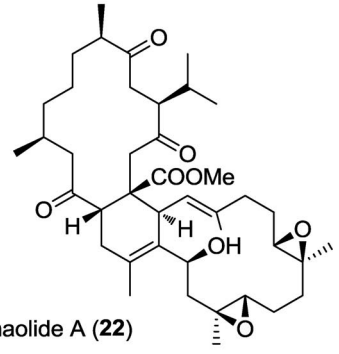
Soft corals belonging to the genus *Sarcophyton* contain unusual tetraterpenoids constructed by coupling two cembranoid units through a Diels–Alder reaction. The first biscembranoid, methyl isosartortuoate (**20**), was isolated from *Sarcophyton tortuosum* [14]. A recent reinvestigation of this soft coral [15,16] has resulted in the isolation of seven new biscembranoids, ximaolides A–G along with a new cembranoid, methyl tortuosate (**21**), which should be the monomeric dienophilic unit leading to all ximaolides and also to compound **20**. The structures of ximaolides A (**22**) and E (**23**) were supported by X-ray diffraction analysis. Coupling these data with CD spectra in solution (CH_3CN) and solid state (NaCl) and applying the time differential density functional theory (TDDFT) CD methodology [17], in collaboration with Prof. Kurtan (University of Debrecen, Hungary), the absolute stereochemistry was assigned to both compounds [18]. Surprisingly, this revealed that the isopropyl group in this family of compounds is β-oriented in apparent conflict with Tursch's rule. Ximaolide-A (**22**) could be the precursor of all ximaolides.



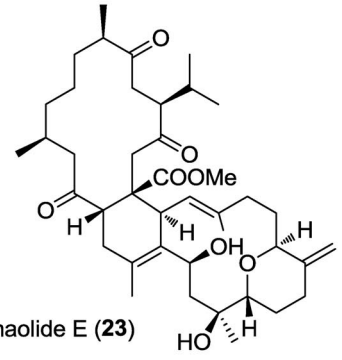
methyl isosartortuoate (**20**)



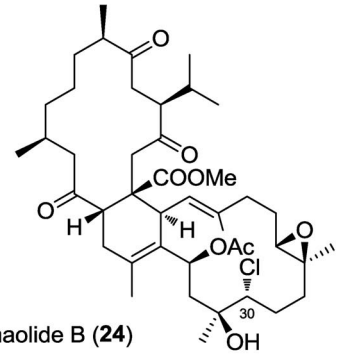
methyl tortuosoate (**21**)



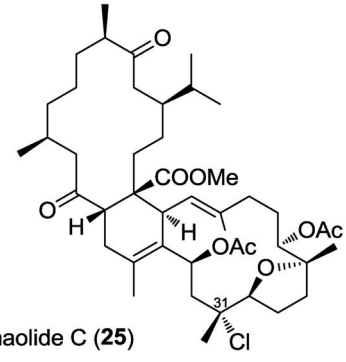
ximaolide A (**22**)



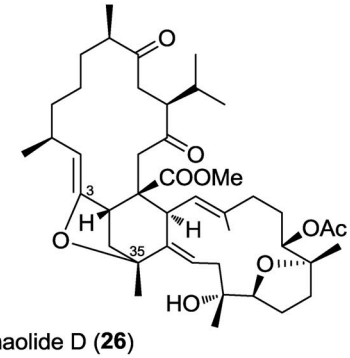
ximaolide E (**23**)



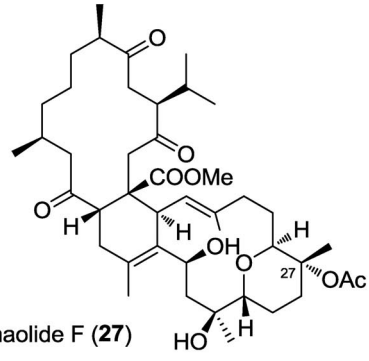
ximaolide B (**24**)



ximaolide C (**25**)



ximaolide D (**26**)



ximaolide F (**27**)

Nucleophilic attack of a chlorine ion at C-30 and C-31 should lead to ximaolide B (**24**) and C (**25**), respectively. Ximaolide D (**26**) exhibits an unprecedented oxygen bridge between C-3 and C-35, the loss of the hydroxyl at C-33 and a substitution pattern similar to that of ximaolide C (**25**) owing to a nucleophilic attack at C-31 of a hydroxy group. Ximaolide F (**27**) can be obtained directly from compound **22** by acetate attack at C-27. Figure 1 summarizes a biogenetic hypothesis for all ximaolides starting from two monomers, methyl tortuosate (**21**) and a diterpenoid unit possessing a conjugated diene system, e.g., compound **28**. Following Diels–Alder coupling to ximaolide A (**22**), nucleophilic attacks at C-27, C-30, and C-31 produce the chemical diversity exhibited by ximaolides B–F.

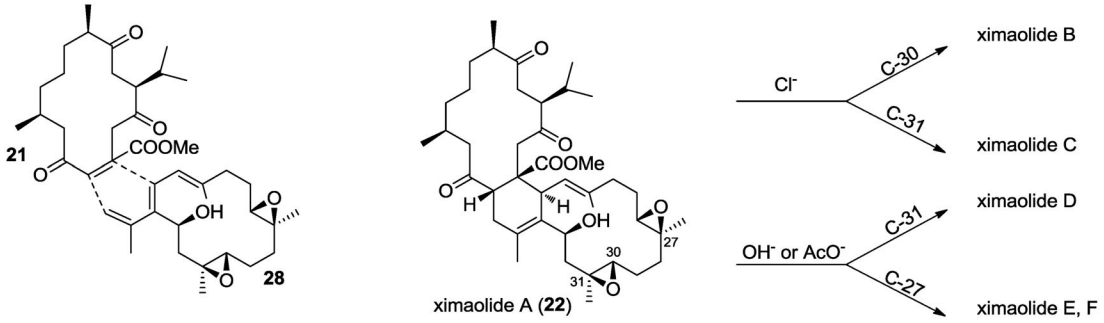
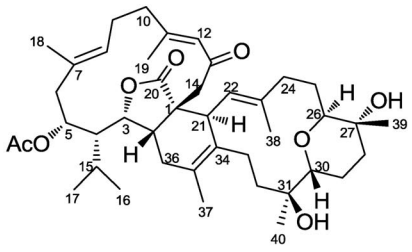
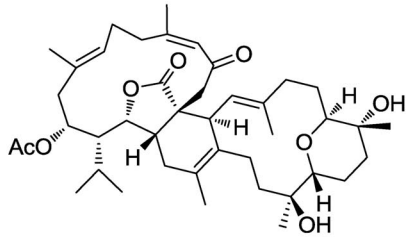


Fig. 1 A biogenetic hypothesis for all ximaolides.

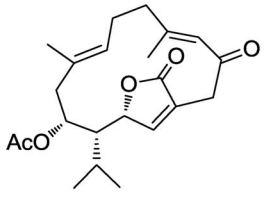
The study of *Sarcophyton latum* led to the discovery of [19] two unprecedented biscembranoids, bislatumlide A (**29**) and B (**30**), where the dienophilic double bond belongs to an α,β-conjugated-γ-lactone. The two compounds differ in the configuration of the double bond at C-11, *E* for **29** and *Z* for **30**. However, it has been proven that easy isomerization of the double bond in **29** occurs in the presence of trace amounts of acid. One of the two monomers of compound **29** isolated from the same soft coral, isosarcophytonolide D (**31**), was the isomer of a metabolite previously isolated from *S. tortuosum* [20], sarcophytonolide D (**32**).



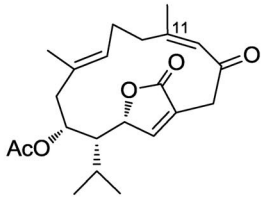
bislatumlide A (**29**)



bislatumlide B (**30**)



isosarcophytonolide D (**31**)



sarcophytonolide D (**32**)

This molecule could be considered the dienophilic monomer that leads to the dimer **30** by coupling to a hypothetical cembrane with a conjugated diene (e.g., **33**). A biogenetic hypothesis for the origin of bislatumlide A (**29**) is reported in Fig. 2.

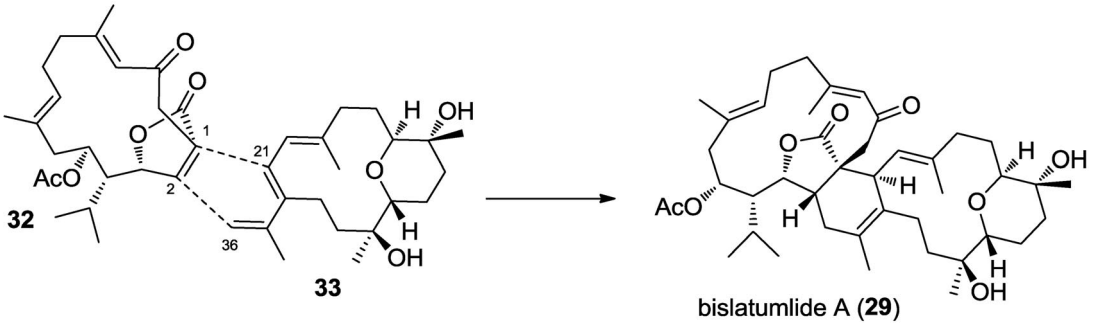
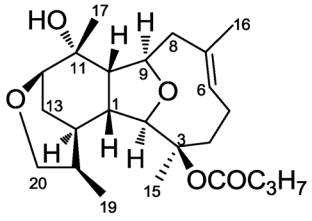
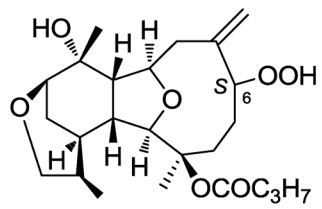


Fig. 2 A biogenetic hypothesis for the origin of bislatumlide A (**29**).

The study of *Cladiella krempfi* led to some diterpenoids [21] displaying a cladiellane skeleton characterized by an unprecedented ether bridge between one of the two geminal methyls and C-12. The structure of one of the two main components, tritoniopsin A (**34**), was supported by X-ray diffraction analysis. The second, tritoniopsin B (**35**), contained at C-6 a hydroperoxy substituent with the *S* absolute configuration assigned by applying the Mosher's method on the corresponding alcohol. Compound **35** was the most abundant metabolite isolated from *C. krempfi*. The stability of the hydroperoxy group could be justified by the presence of an intramolecular hydrogen bond. The two molecules were detected also in an opisthobranch feeding on the soft coral *Tritoniopsis elegans* but, surprisingly, the major compound in the mollusc was tritoniopsin A (**34**). The different metabolite distribution could be due to the ability of the mollusc either to modify dietary tritoniopsin B (**35**) or to selectively accumulate **35** among dietary tritoniopsins [21].



tritoniopsin A (**34**)

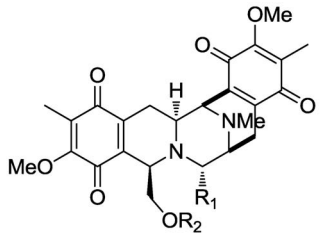


tritoniopsin B (**35**)

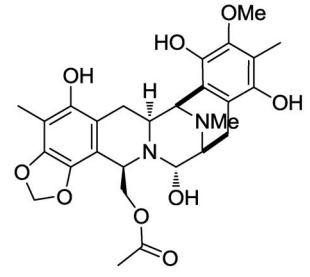
Studies on opisthobranchs

T. elegans introduces the second topic of this communication: the opisthobranchs. These molluscs are apparently unprotected being the mechanical protection of the shell either reduced or completely absent. On the contrary, they are rarely victims of predators having elaborated some defensive strategies that include the use of chemicals [22]. The protective molecules are sometimes produced de novo but generally are sequestered from dietary organisms: sponges, cnidarians, algae, tunicates, bryozoans. It is extremely rare in nature to detect other organisms able like opisthobranchs to select bioactive molecules from their natural habitat.

At the end of May 2009, two of the five PharmaMar's drugs tested in clinical trials, Irvalec® and Zalypsis®, were formulated on molecules isolated from opisthobranchs, *Elysia rufescens* and *Jorunna funebris*, respectively [23]. Zalypsis (PM00104/50) is under phase II clinical trials for the treatment of endometrial and cervical tumors. Its chemical component is a derivative of jorumicin (**36**), an alkaloid that was isolated from the nudibranch *J. funebris* collected off the Indian coasts [24]. The same mollusc from the South China Sea possesses related metabolites, **37–40** [25]. Compounds **39** and **40**, closely related to the already described renieramycin J (**41**) [26], should be artifacts produced in the presence of acetone. The methylene bridge and the aromatization of the *p*-benzoquinone ring exhibited by compound **38** is a structural peculiarity also present in Yondelis® (trabectedin) (**42**) a drug developed and marketed by PharmaMar which, recently (2009), has received marketing authorization from the European Commission for the treatment of patients with advanced soft tissue sarcoma.



jorumycin (**36**): R_1= OH; R_2= $COCH_3$
37: R_1= OCH_3; R_2= $COCH_3$
39: R_1= CH_2COCH_3; R_2= H
40: R_1= CH_2COCH_3; R_2= $COCH_3$



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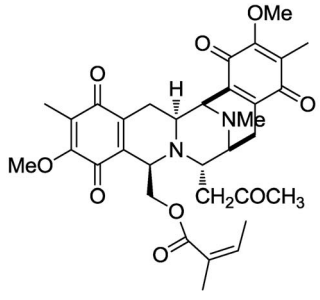
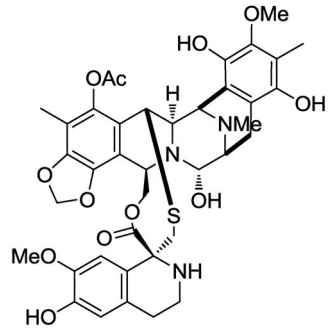
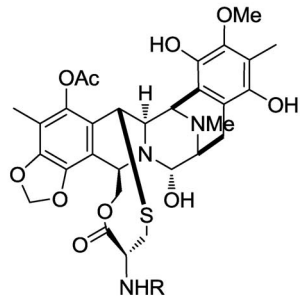


renieramycin J (**41**)



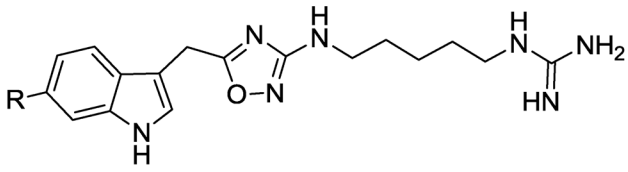
42



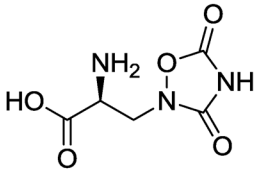
43: R= H
ecteinascidin-637 (**44**): R= $COCH_3$

Compound **42** is also characterized by a sulfur bridge. A closely related metabolite (**43**), the deacetyl derivative of ecteinascidin-637 (**44**) [27], was isolated from the nudibranch *Phidiana militaris* from the South China Sea [25]. These studies confirm the ability of opisthobranch molluscs to provide excellent drug leads.

P. militaris belongs to the family Glaucidae, which has never been chemically studied to date. It possesses other interesting metabolites, phidianidines A (**45**) and B (**46**) [28]. These two unprecedented 3-substituted alkaloids are characterized by a 1,2,4-oxadiazole ring linked to indole through a methylene bridge and substituted with a 3-aminoalkylguanidine group. The 1,2,4-oxadiazole ring is extremely rare in nature. In fact, it is present only in quisqualic acid (**47**), a metabolite of *Quisqualis indica* [29]. However, 1,2,4-oxadiazole scaffold is found in several drugs and drug leads [30–33].



phidianidines A (**45**): R= Br
phidianidines B (**46**): R= H



quisqualic acid (**47**)

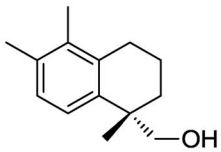
Phidianidines were tested in a panel of tumor cell lines (C6 rat glioma cells, HeLa human epithelial cervical cancer cells, and CaCo-2 human epithelial colorectal adenocarcinoma cells) and nontumor cell lines (H9c2 rat embryonic cardiac myoblasts and 3T3-L1 murine embryonic fibroblasts), showing a strong and selective activity against C6 and 3T3-L1 cells, as reported in Table 1 [28].

Table 1 Cytotoxicity profile of compounds **45** and **46** against tumor and nontumor cell lines, IC_{50} (μM).[a]

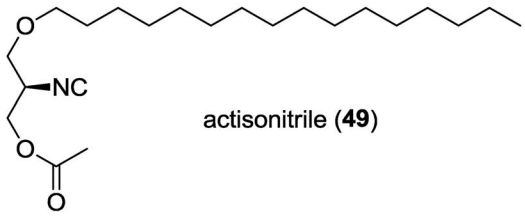
Cell line	Phidianidine A (**45**)	Phidianidine B (**46**)
C6	**0.642 ± 0.2**	**0.98 ± 0.3**
HeLa	1.52 ± 0.3	**0.417 ± 0.4**
CaCo-2	35.5 ± 4	100.2 ± 8.5
3T3-L1	**0.14 ± 0.2**	**0.786 ± 0.3**
H9c2	2.26 ± 0.6	5.42 ± 0.8

[a]IC_{50} values are expressed as mean ± SEM (n = 24) of three independent experiments. Bold values show IC_{50} of less than 1 μM.

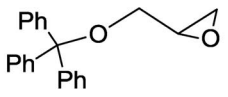
Actinocyclidae is another family of opisthobranchs ignored by chemists to date. *Actinocyclus papillatus* was collected off Wei Zhou Island. It contains in both mantle and mucus a norsesquiterpenoid, ionenol (**48**), previously reported from Baltic amber [34] and, selectively in the mantle, a very unusual molecule, actisonitrile (**49**) [35]. In spite of the apparently simple structure, the determination of the absolute stereochemistry of **49** was solved only by a synthetic approach. Both *S* and *R* enantiomers were synthesized starting from *R*(+) and *S*(–)-glycidyl-tritylether (**50**), respectively. Comparison of optical rotation and CD profile of the natural compounds with those of the pair of synthetic enantiomers led to the assignment of the *R* configuration to compound **49** [35]. It has been recently reported that "the Actinocyclidae have not been chemically studied whereas the Chromodorididae have been extensively studied and with very interesting results" [22].



ionenol (**48**)



actisonitrile (**49**)



glycidyl-tritylether (**50**)

This is true also for Chinese chromodoridids. Almost all chromodoridids are very selective in their alimentary preferences. They eat sponges containing sesquiterpenoids (*Hypselodoris* spp., *Ceratosoma* spp.), diterpenoids (*Chromodoris* spp.), and sesterterpenoids (*Glossodoris* spp.). Less selective are *Cadlina* nudibranchs and, surprisingly, similar for dietary habits to *Cadlina* seems to be *Hexabranchus sanguineus*, which contains both sequiterpenoids and diterpenoids [36]. The study of different *Chromodoris* species (*reticulata*, *geometrica*, *sinensis*) from the South China Sea confirms this general pattern [25]. All contain already described spongiane diterpenoids. For one of these, aplyroseol-2 (**51**), there has been reported antiproliferative activity against murine lymphoma LI210 and human epidermoid carcinoma KB cell lines [37]. Aplyroseol-2 (**51**) was isolated from *C. geometrica* and tested in an antifeedant bioassay with the shrimp *Palaemon elegans* [38], and this resulted in **51** showing significant feeding deterrence. It was also found in *C. sinensis*, but the border of the mantle contains mainly a related compound **52**, already described from an Australian *Chromodoris* [39]. The crude extract of the mantle of *C. sinensis* was dissolved in $CDCl_3$ and submitted to ^{1}H NMR analysis. The spectrum revealed the presence of great amounts of compound **52** but, after filtration on silica gel, it was completely transformed in aplyroseol-2 (**51**) (Fig. 3). In the *P. elegans* bioassay, compound **52** resulted to be four-fold more feeding deterrent than aplyroseol-2 (**51**). Along the border of the mantle of chromodoridids are concentrated some glands named mantle dermal formations (MDFs) where the

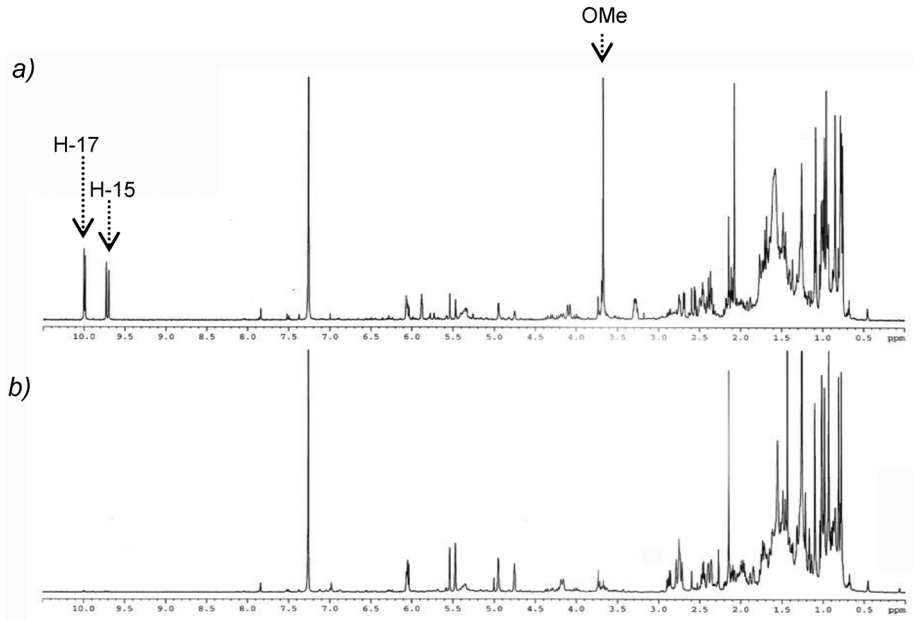
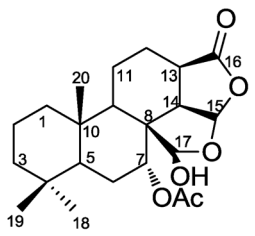
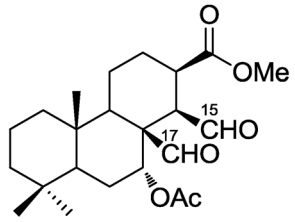


Fig. 3 (a) ^{1}H NMR spectrum of the crude extract of the mantle of *C. sinensis*. (b) ^{1}H NMR spectrum of the crude extract of the mantle of *C. sinensis* after filtration on silica gel.



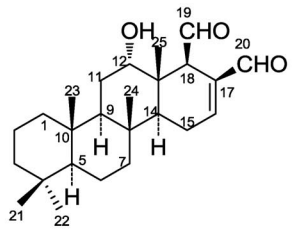
aplyroseol 2 (**51**)



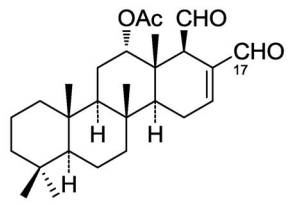
52

protective molecules sequestered from the dietary organisms are transferred. They play a clear defensive role. The presence of compound **52** only in the border of the mantle is of great interest. Probably the mollusc accumulates compound **51** from sponges, then transforms it into the more feeding deterrent **52**.

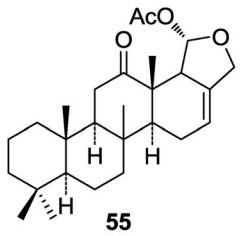
Generally, chromodoridids belonging to *Glossodoris* genus possess sponge-derived sesterterpenoids [40]. Studying *Glossodoris rufomarginata* from the South China Sea and its unidentified dietary sponge [41], it was observed that the main sponge metabolites 12-deacetyl-scalaradial (**53**) and scalaradial (**54**) were completely absent in the mollusc. The analysis of the chemical components of *G. rufomarginata* proved its ability to modify dietary molecules. A series of metabolites (**55–59**), which could derive by both oxidation at C-12 and reduction of the aldehyde group at C-17, was detected in the mollusc. Some of these molecules (**55**, **58**, **59**) contain a carbonyl at C-12, function never found in either sponges or in other molluscs.



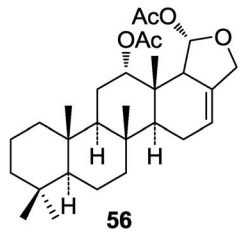
12-deacetylscalaradial (**53**)



scalaradial (**54**)



55



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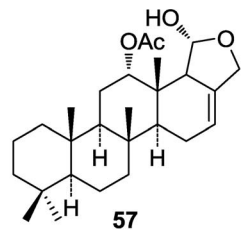

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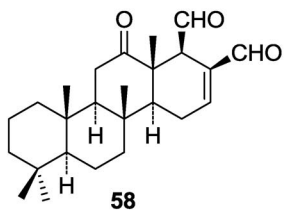

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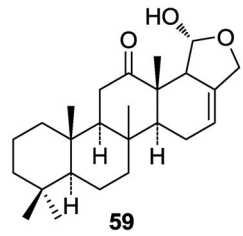
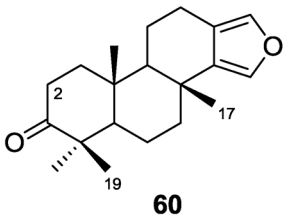


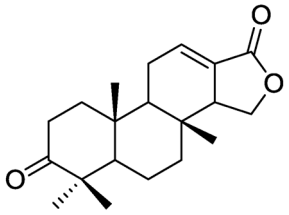
59

Bearing in mind that also a collection from India of *Glossodoris atromarginata* was found to contain 12-keto-scalarane **59** [42], it was suspected that this structural peculiarity could be a chemical marker possessed by many *Glossodoris* molluscs. This hypothesis was confirmed by studying *G. pallida* from China and from Guam, *G. vespa* and *G. averni* from Australia [43]. In fact, all nudibranchs contained 12-ketoscalaranes with the exception of *G. pallida* from Guam, which confirmed the metabolism previously described [44].

The diets of *Glossodoris* molluscs also include sponges possessing spongiane diterpenoids [45,46]. These molecules are characterized by an unusual pattern of oxidation at carbons C-2, C-17, and C-19 of the hypothetical precursor **60**, closely related to isoagatholactone (**61**), the first spongiane diterpenoid isolated from a marine sponge [47].

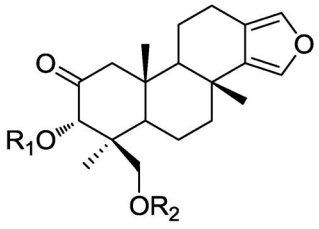


60

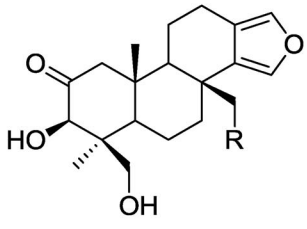


isoagatholactone (**61**)

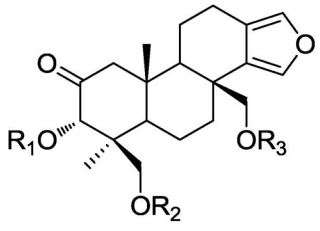
The study of *Glossodoris atromarginata* from Australia confirmed this observation [48]. In fact, the nudibranch contains compound **60** along with a series of related metabolites selectively distributed in the different organs of the mollusc. In particular, the less polar compound **62** was detected only in the MDFs, whereas its deacetylated corresponding alcohol (**63**) was present in the internal organs. Surprisingly, some alcohols displaying a β-oriented hydroxyl group at C-3 (**64**, **65**), opposite to that of compound **62**, were extracted from the mantle. The results of this study could be justified either by a selective accumulation of acetylated diterpenoids in the MDFs or by the presence of two distinct reductive enzymatic systems leading to two series of 3-hydroxy derivatives. The interest in this topic prompted the study of *G. atromarginata* collected from the South China Sea [25].



62: R_1= R_2= Ac
63: R_1= R_2= H



64: R= H
65: R= OH

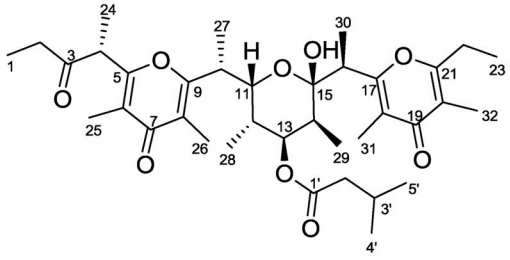


66: R_1= R_2= R_3= Ac
67: R_1= R_2= R_3= H

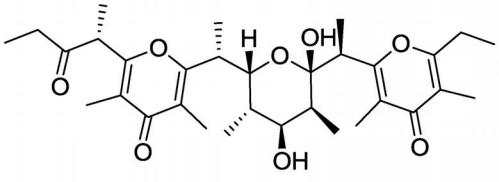
This research confirmed the presence of spongiane diterpenoids in the nudibranch. The selective compartmentalization in the MDFs of the fully acetylated compound **66** was also confirmed. The corresponding alcohol **67** was completely absent in the MDFs but significantly present in both internal organs and mantle where compound **66** was present only in trace amounts. Probably, compound **66** plays a protective role for the mollusc. This suggestion was confirmed by its strong feeding deterrence against *Palaemon elegans*, whereas the alcohol **67** was completely inactive in the same bioassay [25].

Studies on pulmonates

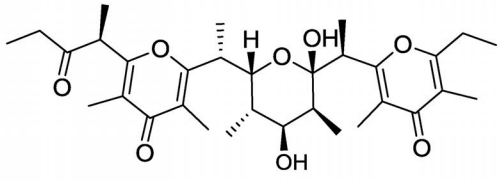
The last part of this paper reports the recent studies on the pulmonate *Onchidium* sp. collected off Hainan Island in 2004 and 2010. The chemical investigation conducted on the first collection led to the characterization of the main metabolite, onchidione **68**, which was present in the mucus and in the mantle of the mollusc [49]. The polypropionate structure was suggested by the analysis of spectral data. In particular, the relative stereochemistry of the central ring was supported by a series of nuclear Overhauser enhancement (NOE) experiments. The full structure was confirmed by X-ray diffraction analysis. This structure is closely related to those of onchitriols and peronatriols previously found in pulmonates from the South Pacific [50]. The main structural difference is in the presence of an oxygen bridge between C-11 and C-15 in compound **68**. The recent study of a second collection of the mollusc resulted in the isolation of two minor metabolites, onchidiol (**69**) and 4-*epi*-onchidiol (**70**) [51]. Their structures, including the relative stereochemistry, were confirmed by X-ray diffraction analysis. The absolute configuration was also established by combining crystallographic data with ECD data—spectra were recorded in solution (CH_3CN) and solid state (NaCl)—and applying the TDDFT CD methodology [51].



onchidione (**68**)



onchidiol (**69**)



4-*epi*-onchidiol (**70**)

CONCLUSIONS

This partial presentation of the main results obtained through a very productive collaboration between the Italian ICB and the Chinese SIMM proves that the marine organisms from the South China Sea are an inexhaustible mine of new molecules that often display unique structural peculiarities and sometimes very interesting pharmacological properties. These results strongly encourage further research directed to clarify the ecological role and the biosynthesis of many of the new molecules.

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the establishment of the absolute stereochemistry by CD methodology. The authors are deeply grateful to Profs. K.-X. Chen and J. Ding, past and present directors, respectively, of State Key Laboratory for Drug Discovery of SIMM, for having supported and strongly encouraged this collaboration. Finally, the authors thank Prof. M. Ghiselin (California Academy of Sciences) for a critical reading of the manuscript. Financial support was mainly from bilateral CNR/CAS projects (2001–2010), and, with regards to the most recent research here presented, also from PRIN-MIUR 2007 (Italian Minister of Education, University and Research), the Natural Science Foundation of China (Nos. 30730108, 21072204) and the STCSM Project (No. 10540702900).

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