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NATURAL PRODUCTS FROM MARINE HETEROBRANCHS: AN OVERVIEW OF RECENT RESULTS

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Abstract. Heterobranchs are a fascinating group of marine mollusks that are recognized as an important source of bioactive natural products. Often, these molecules, which are either selected from the diet or *de novo* biosynthesized by the mollusks, play a fundamental role for their survival being utilized as defensive chemicals against predators. A summary of the studies carried out by our group, in the last decade, on heterobranchs is presented here. A number of new compounds exhibiting different molecular architectures have been chemically characterized. Some of them have also shown an interesting pharmacological potential. Some ecological studies that we conducted on selected species of heterobranchs are also reviewed.

Keywords: marine mollusk, natural product, chemical ecology, bioprospecting.

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Introduction

The subclass Heterobranchia is a large and diverse subclass of the Gastropoda (phylum Mollusca) comprising several ten thousand species ("non-prosobranchs") [1–3], within an enormous variety of forms living in almost all marine, freshwater and terrestrial habitats [2]. Among the heterobranchs, the so-called "sea hares" and "sea slugs" have attracted the interest of naturalists for more than 2,000 years [4]. The human interest in these groups of mollusks also focused on their putative medicinal and toxicological properties. The Greeks used sea hare extracts for medical treatment whereas the Romans considered them to be highly toxic [5,6]. During last four decades several species of heterobranchs including nudibranchs, sacoglossans, anaspideans, and pulmonates have been object of numerous chemical studies [7]. A vast array of chemical substances, sequestered from food or formed *de novo* and used as defensive weapons by the mollusks, have been characterized showing an extraordinary chemical diversity [8–11] as well as interesting pharmacological potential [12,13]. This made heterobranchs an important target for natural products research and bioprospecting for pharmaceutical purposes [14] and, especially, excellent model systems for addressing a variety of questions in chemical ecology [15] and evolution [16].

In the course of our continuing studies on marine heterobranchs from distinct geographical areas throughout the world, a number of different nudibranch, sacoglossan and pulmonate species have been chemically analyzed. In this paper, an overview of the natural products that we isolated and characterized in the last decade from this group of mollusks is presented. The compounds have been grouped by their chemical structures into three main structural classes: a) nitrogen-containing compounds, b) polyketide-derived compounds and c) terpenoids.

Background

Nitrogen-containing compounds

The most interesting nitrogen-containing compounds that have been characterized in recent years in our lab are undoubtedly phidianidines A (**1**) and B (**2**) (Figure 1), two bromoindole alkaloids isolated from a South China Sea collection of the aeolid nudibranch *Phidiana militaris* [17]. Phidianidines contain the first reported 1,2,4-oxadiazole system in a marine natural product. Even though it is so rare in nature, there is a wide interest in 1,2,4-oxadiazole scaffold being a bioisostere of esters and amides and a dipeptide mimetic. Different pharmacological properties have been evidenced for several synthesized 1,2,4-oxadiazole compounds [18-22].

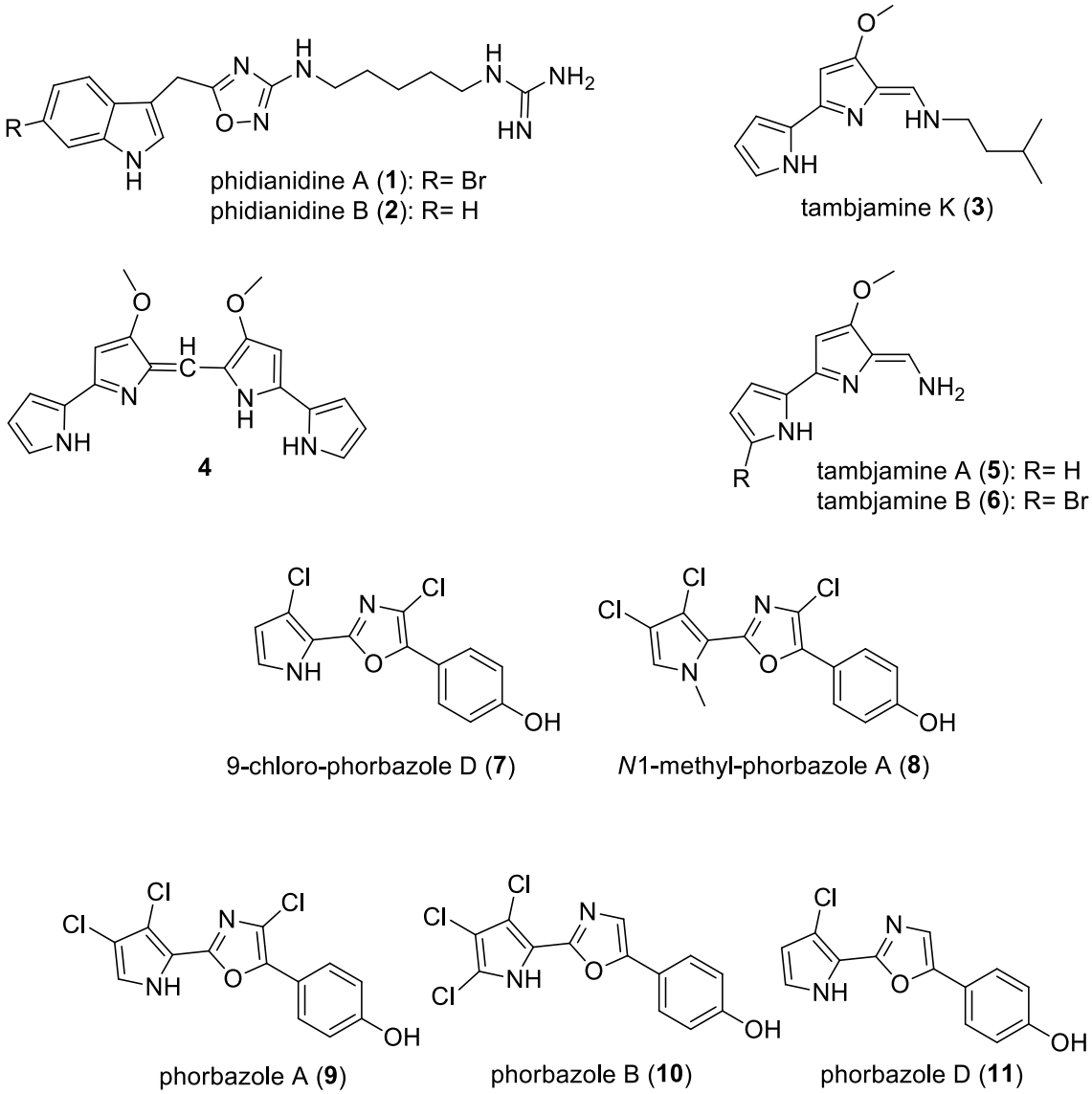
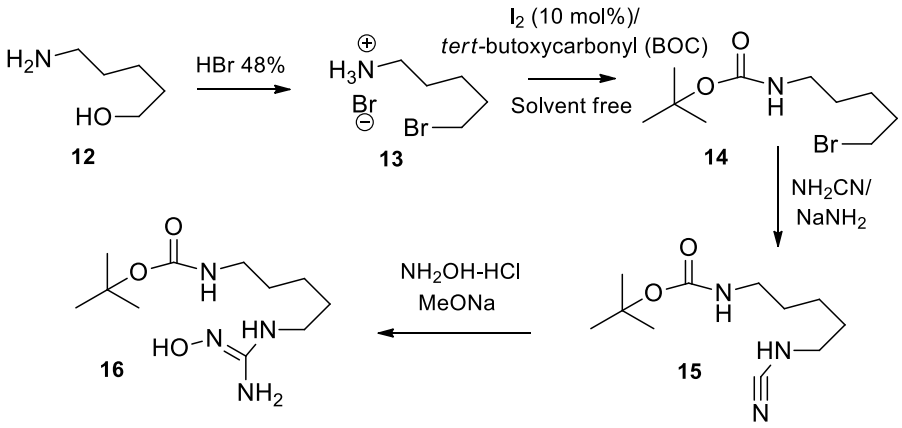


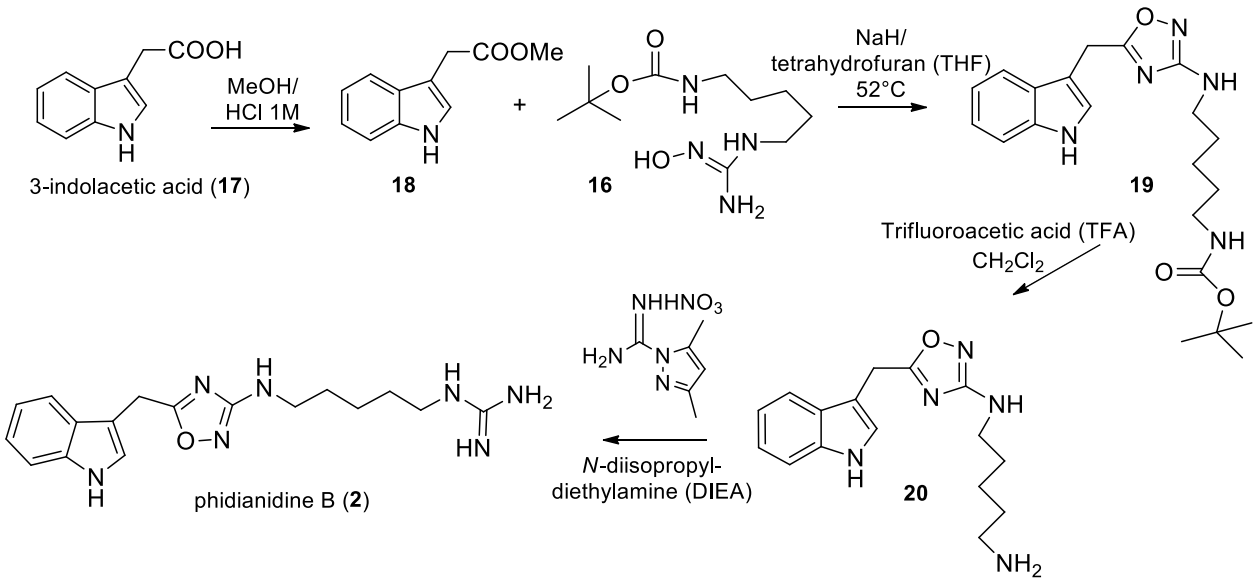
Figure 1. Structures of nitrogen-containing compounds 1-11.

A preliminary biological screening of phidianidines showed promising and selective cells grow inhibition against various tumor and non-tumor mammalian cell lines at nanomolar concentration [17]. Further, phidianidine A was identified by a virtual screening as a possible ligand of CXCR4 [23], that is a chemokine receptor exhibiting a complex pattern of activities and is deeply involved into a wide range of pathologies including several types of cancer and immunodeficiency disorders. Molecular docking analysis on phidianidine A suggested that the molecule significantly interacts with the receptor cavity by competing with natural ligand CXCL12 [23]. Functional assays showed that phidianidine A is really a CXCR4 antagonist [23]. The synthesis of phidianidines was also performed in our laboratory (in Scheme 1, synthesis of phidianidine B) [24,25]. This procedure, which is based on the coupling of a 3-indolacetic acid methyl ester with an opportunely prepared amino-alkyl hydroxy guanidine intermediate, is of general application and allows the synthesis of analogs with either different alkyl chain length or substitution on the indole ring (Scheme 2). A number of further studies on the evaluation of different pharmacological properties of phidianidines and synthetic analogs have been subsequently appeared in the literature [26–29].

Tambjamines belong to the group of 4-methoxypyrrolic natural products and exhibit a 2,2'-bis-pyrrole ring system containing at the C-5 position of the pyrrole ring an enamine moiety with the nitrogen substituted with a two to four carbon saturated alkyl chain. They have been found to occur in bacteria and marine invertebrates including bryozoans, nudibranchs and ascidians [7,11,30].

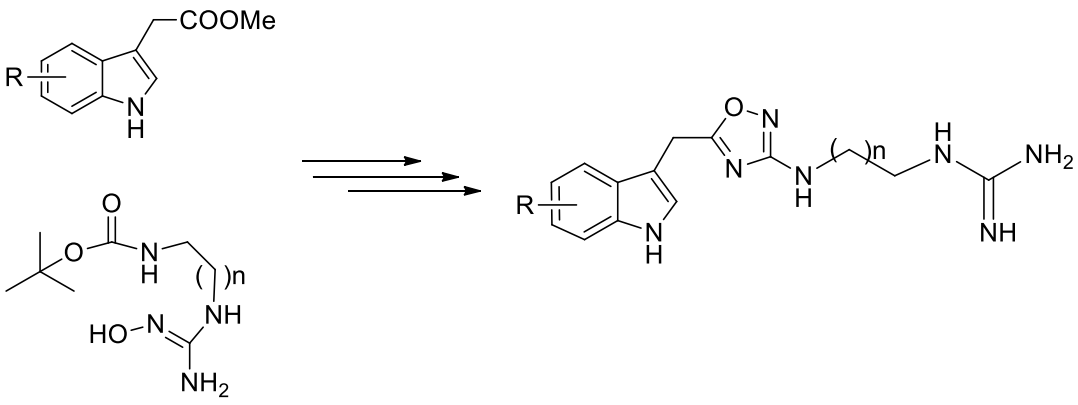


Step 1. Preparation of intermediate 16



Step 2. C**oupling of intermediate 16 and 3-indolacetic acid methyl ester (18)**

Scheme 1. Synthesis of phidianidine B (2) [24].



Scheme 2. General scheme for phidianidine analogs preparation [24].

Different and significant pharmacological properties have been evidenced for this class of compounds [31–33]. An additional member of tambjamine family, tambjamine K (**3**), was isolated from the Azorean nudibranch *Tambja ceutae* [34] along with previously reported related metabolites, tetrapyrrole (**4**) [35] and tambjamines A (**5**) and B (**6**) [36] (Figure 1). The same metabolites were also detected in the bryozoan *Bugula dentata*, prey of the mollusks, strongly indicating the dietary origin of these alkaloids in the mollusks. In agreement with the significant cytotoxic activity showed by several members of tambjamine family, probably related to their DNA-targeting properties [37], compounds **3** and **4** exhibited a remarkable and concentration-dependent cytotoxic activity against both tumor and non-tumor mammalian cells [34,38].

Phorbazoles are peculiar chlorinated phenyl-pyrrolyloxazoles first described from the sponge *Phorbas aff clathrata* [39–41] and later isolated by us from the Indo-Pacific dorid nudibranch *Aldisa andersoni* [42]. So, it is quite probable that in the mollusks they could derive from a diet based on *Phorbas* sponges. *A. andersoni* was found to contain two new phorbazoles, 9-chloro-phorbazole D (**7**) and *N*1-methyl-phorbazole A (**8**), together with previously described phorbazoles A (**9**), B (**10**), and D (**11**) [39,40] (Figure 1). However, phorbazoles were found to be present mainly and selectively in the external part of the mollusk, more exposed to predation, suggesting their involvement in chemical defense. The HPLC profile of the crude mantle extract showed a quite pure phorbazole mixture [42]. Selected phorbazoles were tested for the feeding deterrent properties in the assay on the shrimp *Palaemon elegans* [43], a generalist predator, and resulted to be active at a concentration of 1.0 mg/mL [42]. Feeding-deterrent phorbazoles also display *in vitro* growth inhibitory properties on a panel of five human cancer cell lines. In particular, for *N*1-methyl-phorbazole A (**8**), quantitative videomicroscopy analysis allowed to relate the observed inhibitory activity on human SKMEL-28 melanoma and U373 glioblastoma cells to cytostatic effects [42].

Isoquinolinequinones and their reduced forms represent an important class of alkaloids [44] isolated from a diverse range of marine organisms such as bacteria, sponges, mollusks, and tunicates [7]. This class of compounds comprises ecteinascidins, including the commercial drug Yondelis® [45], renieramycins, and saframycins exhibiting well-known antitumor and antibiotic properties [44–46]. A series of bistetrahydroisoquinolinequinones and isoquinolinequinones were found in the skin of the dorid nudibranch *Jorunna funebris* sampled in the South China Sea together with its possible sponge-prey *Xestospongia* sp. [47]. All compounds were also isolated from the sponge confirming the trophic relationship between the two organisms [47]. Nudibranch metabolites included two new renieramycin-type alkaloids, fennebricins A (**21**) and B (**22**), and eight previously described compounds, including three bistetrahydroisoquinolinequinones, renieramycin J (**23**) [48], jorumycin (**24**) [49], and renieramycin G (**25**) [50], and five isoquinolinequinones, *N*-formyl-1,2-dihydrorenierol acetate (**26**) [51], *N*-formyl-1,2-dihydrorenierone (**27**) [52], renierol (**28**) [53,54], renierol acetate (**29**) [54,55], and mimosamycin (**30**) [52] (Figure 2). Two compounds of ecteinascidin series, ecteinascidin-637 (**31**) [56] and the unreported *N*-deacetyl derivative **32** (Figure 2), were also found to co-occur, in very few amount, with phidianidines in *Phidiana militaris* (unpublished data).

Another interesting group of nitrogen-containing metabolites of heterobranchs is represented by kahalalides, a large family of peptides isolated from both the herbivorous sacoglossans of the genus *Elysia* and their algal prey of the genus *Bryopsis* [57]. The representative member of the class is kahalalide F (KF) (**33**) [58] (Figure 3), the most biologically active cyclic peptide of the group. Treatment of cancer cells with KF resulted in dramatic changes in lysosomal membranes and large vacuoles, leading to cell swelling [59]. Bioassay-guided fractionation of the extract of the mucous secretion collected from an Indian population of sacoglossan *Elysia ornata* led to the finding of KF (**33**), co-occurring with two previously unreported analogues, kahalalide Z_1 (**34**) and kahalalide Z_2 (**35**) [60] (Figure 3). These compounds differing from KF in the nature of *N*-terminal acid moiety and in some of the aminoacid units of the peptide chain interestingly displayed a bioactivity profile comparable with KF [60].

Diacylguanidines are secondary metabolites not frequently encountered in marine mollusks [61]. A very few examples were previously reported including unique symmetrical triophamine (**36**) [62,63] and limaciamine (**37**) [64], both isolated from some *Polyceridae* species, and dotofide (**38**), found in eolidacean *Doto pinnatifida* [65] (Figure 4).

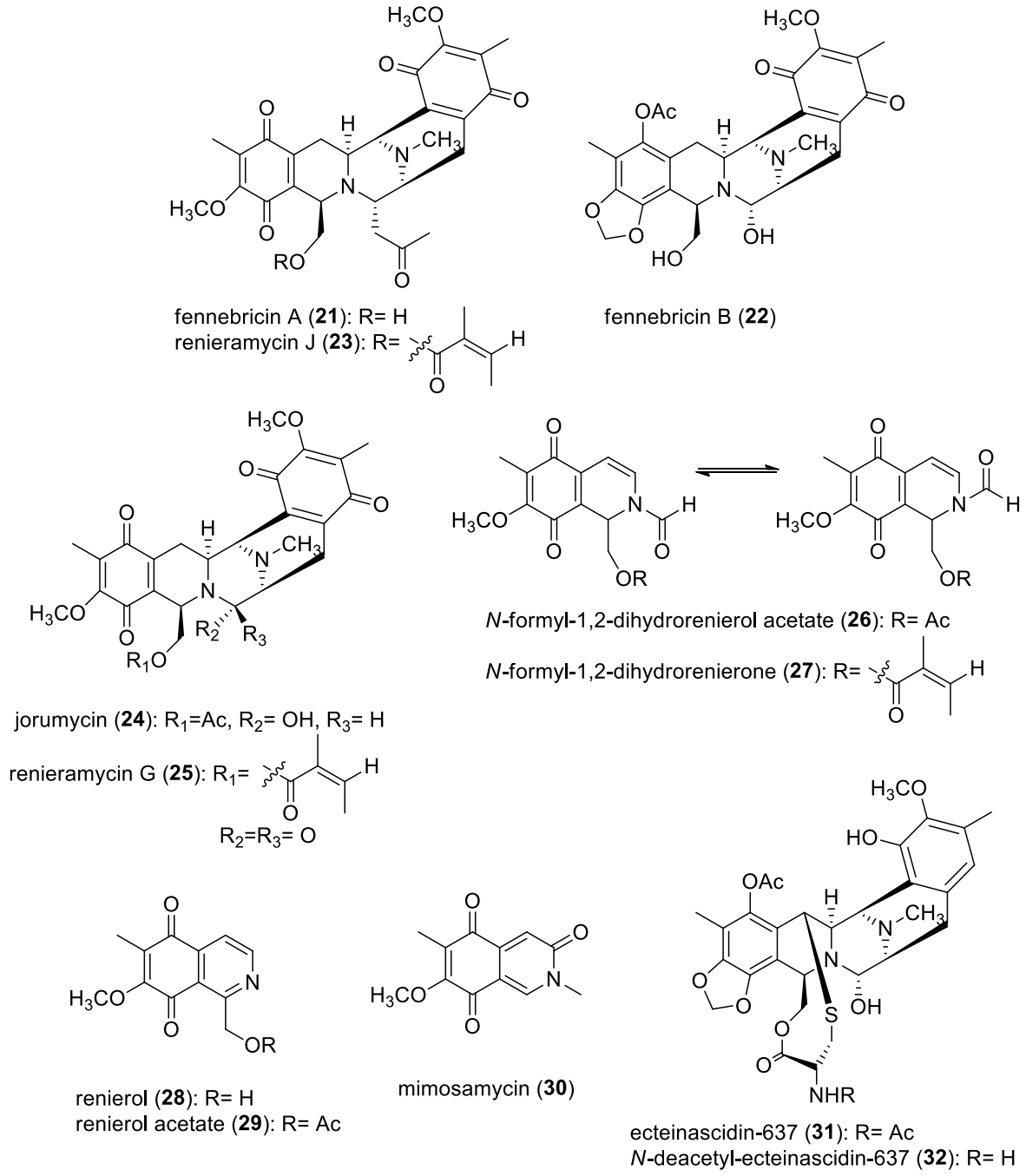


Figure 2. Structures of nitrogen-containing compounds 21-32.

Compounds **36** and **37** exhibit the guanidine moiety bearing polyketide acyl units whereas in compound **38** the guanidine is linked to terpenoid acyl residues. A recent our study on three Polyceridae nudibranchs, *Thecacera pennigera*, *Polycera elegans*, and *Plocamopherus maderae*, from Canary Islands evidenced the peculiar presence of either triophamine (**36**) or limaciamine (**37**) in these mollusks [66] according to the literature data on different species of the same taxonomic group [62–64]. This finding led us to the suggestion that these diacylguanidines are distinctive chemical markers of Polyceridae nudibranchs [66]. Another interesting terpenoid diacylguanidine, actinofide (**39**) (Figure 4), which is structurally related to dotofide (**38**), was recently isolated from the dorid nudibranch *Actinocyclus papillatus* [67]. Both compounds **38** and **39** showed the guanidine core acylated by a senecioyl moiety and a C_{15} isoprenoid residue, which was cyclic (monocyclofarnesoyl) in **38** whereas it was linear (farnesoyl) in **39**.

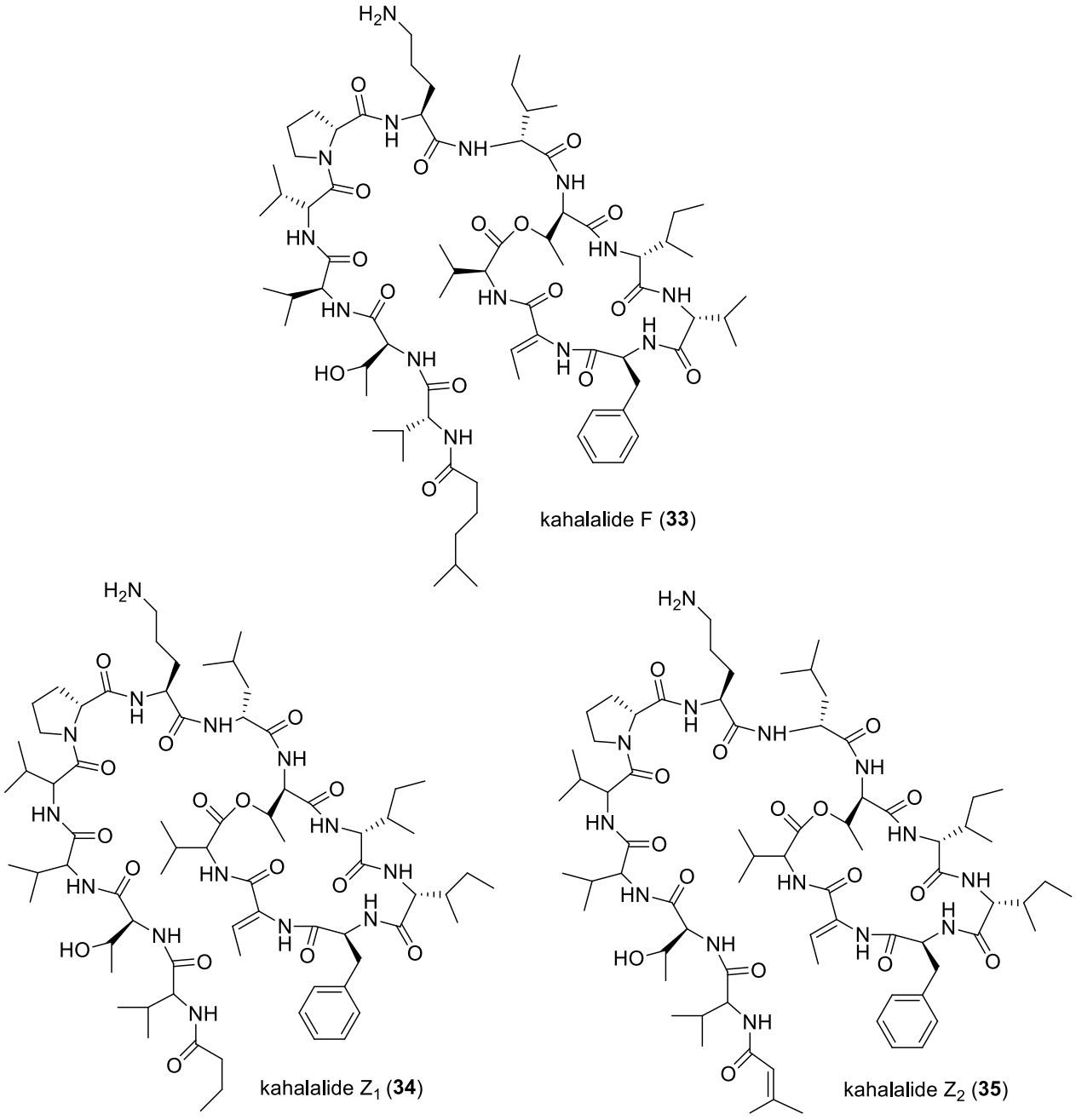


Figure 3. Structures of nitrogen-containing compounds 33-35.

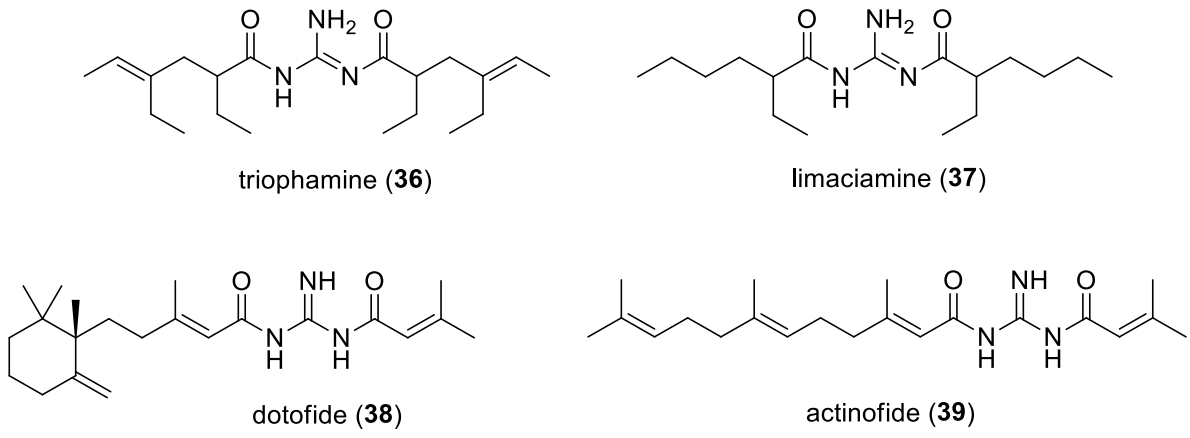
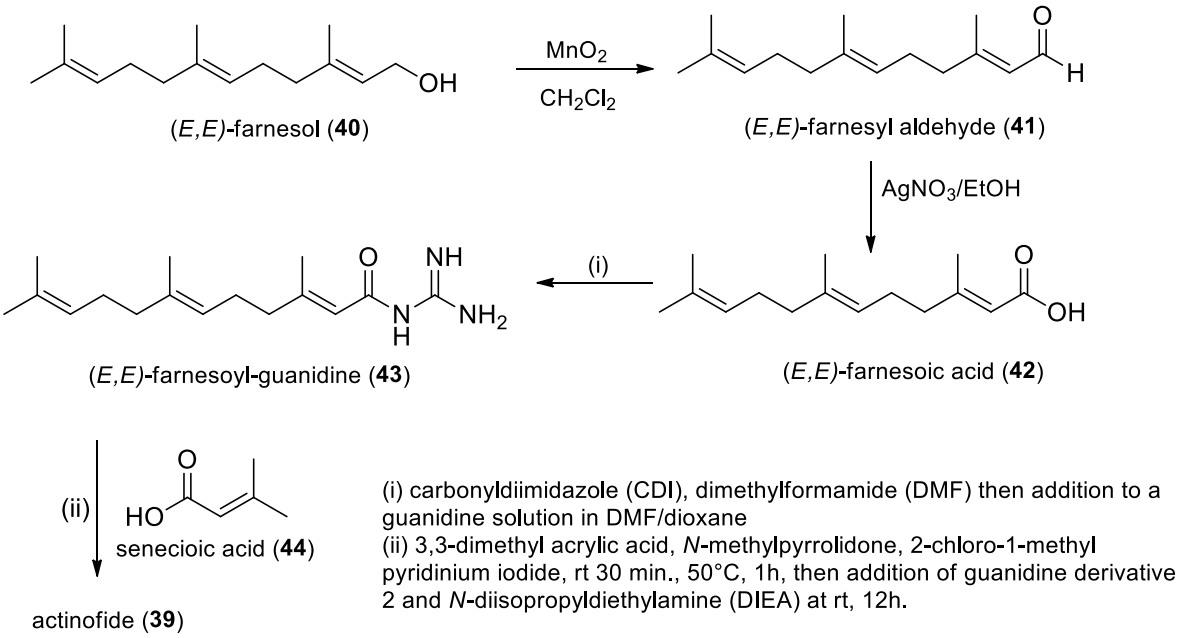


Figure 4. Structures of nitrogen-containing compounds 36-39.

The synthesis of diacylguanidine **39** was also performed, based on the coupling of guanidine with two terpenoid acid units, (*E,E*)-farnesoic acid (**42**) and senecioic acid (**44**), in two sequential steps, to form first monoacylguanidine derivative **43** and then diacylguanidine **39** (Scheme 3) [67]. Subsequently, a series of structural analogues **45**-**51** (Figure 5) were opportunely prepared by using the same synthesis strategy as (*E,E*)-farnesoyl guanidine (**43**) and actinofide (**39**). All of the compounds were evaluated *in vitro* for the growth inhibitory activity against a panel of cancer cell lines. Among them, the synthetic derivative *N,N'*-difarnesoyl guanidine **47** showed the most interesting biological activity profile [67].



Scheme 3. Synthesis of actinofide (39) [67].

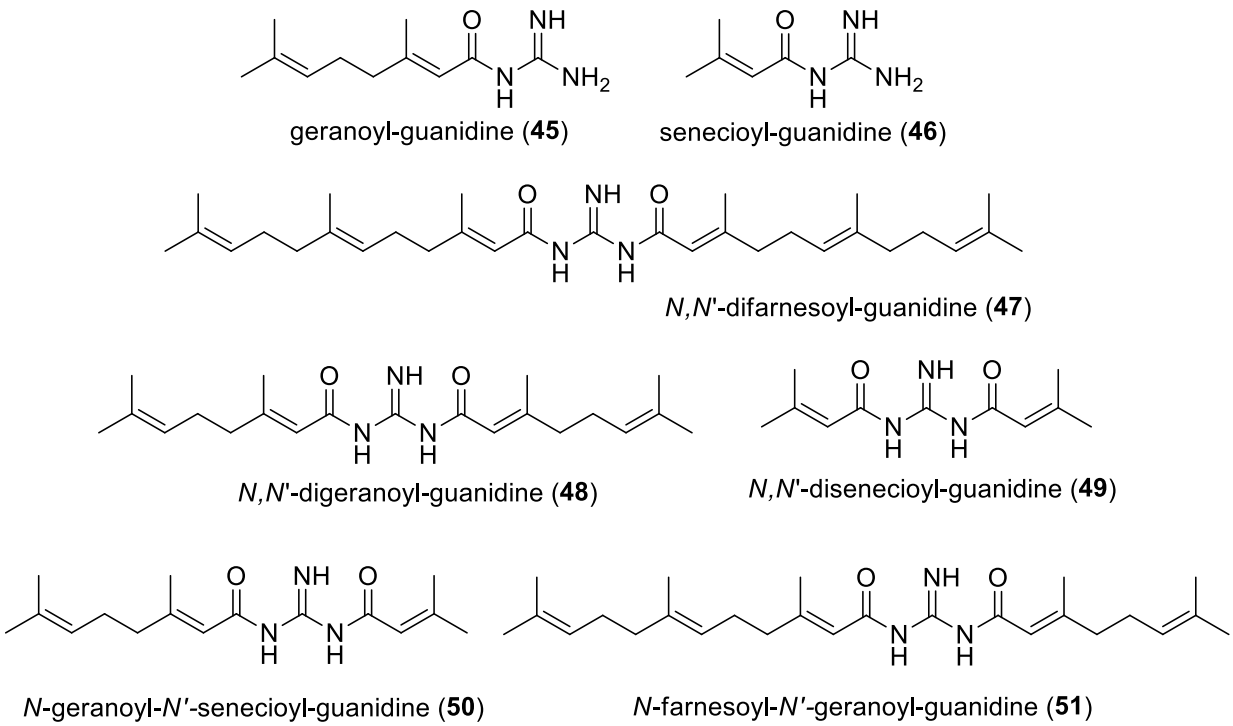


Figure 5. Synthetic diacylguanidine analogues 45-51 [67].

Finally, it should be also mentioned the finding of a unique nitrogen-containing ether lipid, (-)-actisonitrile (**52**), in the lipophilic extract of dorid *Actinocyclus papillatus* [68] and an aromatic alkaloid, (-)-bursatellin (**53**), in two distinct aeolid nudibranchs of the genus *Spurilla*, *Spurilla neapolitana* from Tyrrenian coasts (Bay of Naples, Italy) and *Spurilla* sp. from Atlantic Ocean (Patagonia, Argentina) [69] (Figure 6).

The structure of **52** was characterized by a 1,3-propanediol moiety bearing an isonitrile group at C-2 position [68]. The *R* absolute configuration of the stereogenic center was determined by comparing the optical properties of natural actisonitrile with those of (-)- and (+)-synthetic enantiomers, opportunely prepared. The synthesis of each compound was accomplished in eight steps, as outlined in Scheme 4 for the natural (-)-enantiomer (**52**) [68]. The levorotatory enantiomer was prepared starting from the commercially available *S*-(-)-glycidyl-tritylether whereas the (+)-enantiomer was synthesized starting from *R*-(+)-glycidyl-tritylether. The introduction of the azide group (step 3, Scheme 4) was operated predominantly through a SN_2 mechanism implying the inversion of configuration at C-2. This inversion was verified by applying the modified Mosher method to the amino derivative **58** [68]. Both (-)- and (+)-actisonitrile were tested in preliminary *in vitro* cytotoxicity bioassays on a panel of tumor and non-tumor mammalian cells. Both enantiomers exhibited a parallel concentration-dependent toxic profile, at micromolar concentration [68].

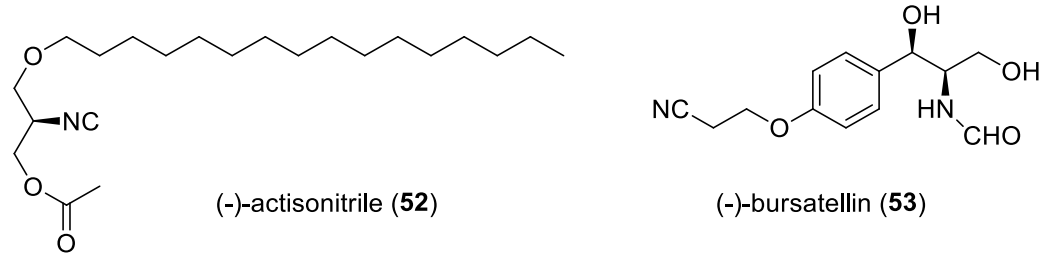
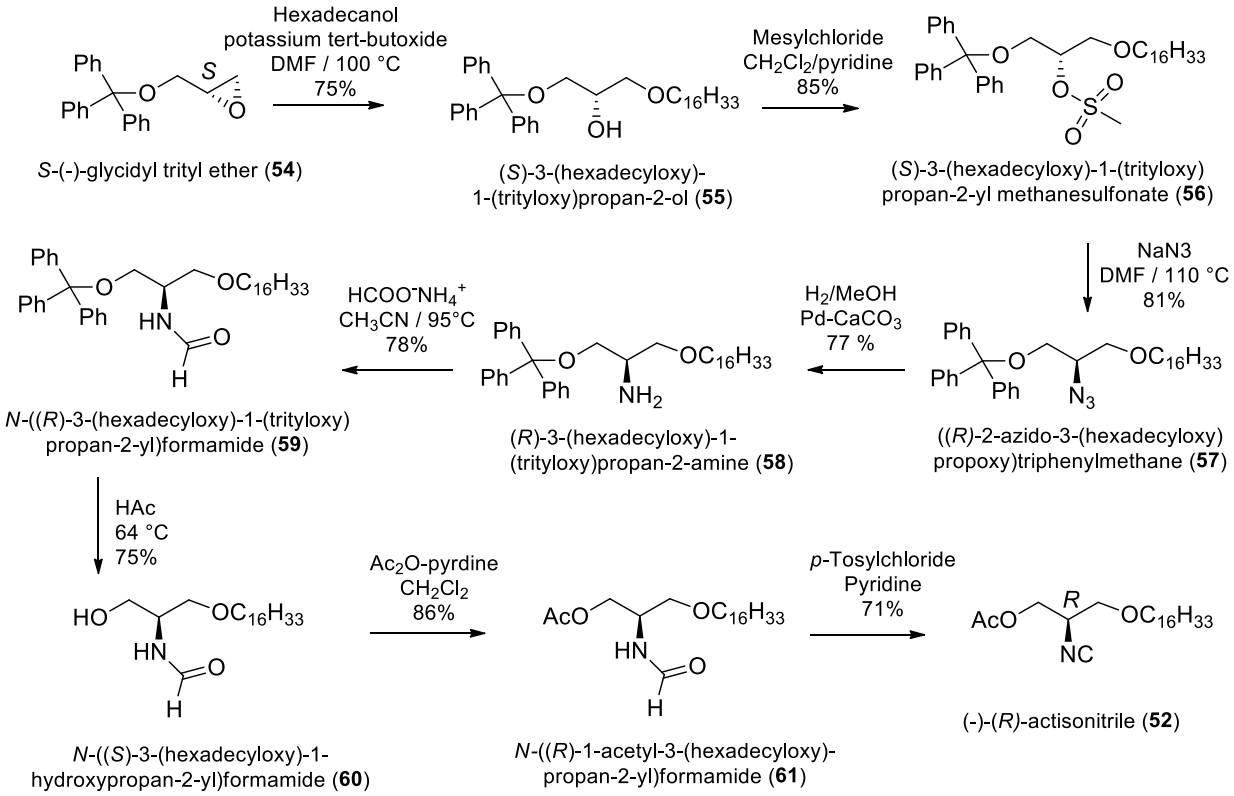


Figure 6. Structures of nitrogen-containing compounds 52 and 53.



Scheme 4. Synthesis of natural enantiomer (-)-(*R*)-actisonitrile (52) [68].

Compound **53**, which is structurally related to chloramphenicol, was not detected in the sea-anemone diet of both nudibranchs being previously reported only from taxonomically unrelated anaspidean *Bursatella* species [70–72]. The finding of bursatellin (**53**) also in nudibranchs of the genus *Spurilla* is ecologically relevant and poses intriguing questions about a possible common origin such as dietary zooxanthellae or a *de novo* biosynthesis pathway working in both unrelated genera *Spurilla* and *Bursatella*.

Polyketide-derived compounds

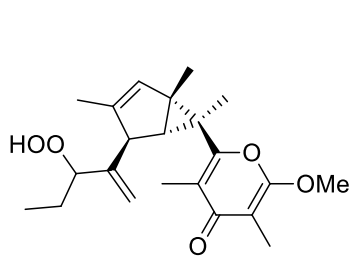
Polypropionates are typical metabolites of some selected groups of marine heterobranchs, in particular sacoglossan, cephalaspidean and pulmonate mollusks, and exhibit different structural architectures depending on taxa [7,16,73,74].

With regards to sacoglossans, it is retained that elysioidean mollusks employ *de novo* biosynthesized polypropionates as sunscreen in heavily photolytic habitat and that the biosynthesis of these molecules is influenced by light irradiation. The strict dependence of the structural polypropionate arrangement on the light conditions has been also proved [75]. Two chemical studies on sacoglossans of the genus *Elysia* resulted in the isolation of new members of the large elysioidean γ-pyrone propionate family (Figure 7). In particular, phototridachiapyrone J (**62**) was found in a population of *Elysia patagonica* from Patagonia (Argentina) [76] whereas phototridachiahydropyrone (**63**) was identified as a minor component of the extract of *Elysia crispata* from Venezuela [77], the main metabolite of which, tridachiahydropyrone (**64**) was described previously [78]. Phototridachiapyrone J (**62**) belonging to the bicyclo[3.1.0]hexane polypropionate group is a hydroperoxyl derivative, the origin of which could be ascribed to a photochemical oxidation *via* singlet oxygenation of a suitable precursor [76]. On the other side, phototridachiahydropyrone (**63**) with a fused pyrone-containing bicyclic ring was suggested to arise by a concerted rearrangement mechanism in the course of the photochemical electrocyclic formation of the main co-occurring **64**, under prolonged irradiation with UV light [77]. Interestingly, the existence of phototridachiahydropyrone (**63**) as a natural product was previously supposed by synthesis studies of tridachiahydropyrone (**64**) [79].

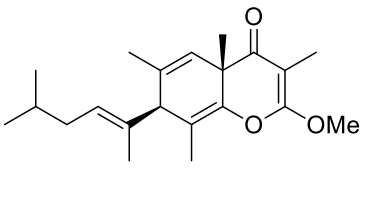
Polypropionates from pulmonates display acyclic structures with three up to eleven propionate units exhibiting contiguous stereogenic centers and often including α- or γ-pyrone moieties [74]. Among marine pulmonates, shell-less species of the family Onchidiidae are characterized by polypropionates whose skeletons contain 32 carbon atoms, two γ-pyrone rings and a number of hydroxyl groups [74]. Our studies led us to isolate in these years a family of bis-γ-pyrone polypropionates from *Onchidium* species sampled during distinct collection campaigns along the coast of Hainan, in the South China Sea. The structure of these compounds was characterized by an additional hemiketal ring in the middle part of the propionate chain between the two γ-pyrones located at terminal moieties. Onchidione (**65**) (Figure 7) was the first member to be characterized [80]. It was isolated as the main component of the mucous secretion collected from a population of *Onchidium* sp. The structure and the relative configuration of all of eight stereogenic centers of **65** were secured by X-ray diffraction analysis [80], whereas the absolute configuration was later determined by solid-state time-dependent density functional theory electronic circular dichroism (TDDFT ECD) [81]. A series of onchidione-related polypropionates, whose structures differed either in the stereochemistry of selected stereogenic centers or in the oxidation degree at oxygenated carbons or in the acylation of hydroxyl groups (Figure 7), have been subsequently isolated along with main co-occurring **65** from different *Onchidium* populations.

In particular, onchidiol (**66**) [81–83], 4-*epi*-onchidiol (**67**) [81,82], 13-propanoyl-onchidiol (**68**) [82], onchidionol (**69**) [82], 3-acetyl-onchidionol (**70**) [82], 3-propanoyl-onchidionol (**71**) [82], 16-*epi*-onchidione (**72**) [83], 4-*epi*-onchidione (**73**) [83], and 4,16-di-*epi*-onchidiol (**74**) (Figure 7) [84], were chemically characterized. Interestingly, bis-γ-pyrone polypropionates of ilikonapyrone family [74,85,86] lacking the hemiketal ring were found in a distinct population of *Onchidium* sp. from the same collection site [82]. They included 11-(3-methylbutanoyl)-ilikonapyrone (**75**), 13-acetyl-11-(3-methylbutanoyl)-ilikonapyrone (**76**), 3,13-diacetyl-11-(3-methylbutanoyl)-ilikonapyrone (**77**), 11-(3-methylbutanoyl)-13-propanoyl-ilikonapyrone (**78**), 3-acetyl-11-(3-methylbutanoyl)-13-propanoyl- ilikonapyrone (**79**), and 11-(3-methylbutanoyl)-3,13-dipropanoyl-ilikonapyrone (**80**) (Figure 7) [82]. The *in vitro* growth inhibitory properties of selected polypropionates of both structural families were investigated on a panel of human cancer cell lines. The most active compound was

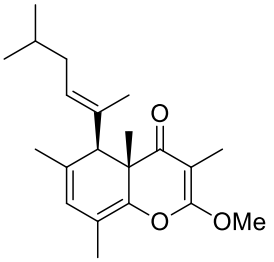
79 with IC_{50} growth inhibitory activity < 10μM in all cell lines analyzed. The activity profile was comparable to those of etoposide and camptothecin used as positive control [82]. Additional biological properties were evidenced for onchidione (**65**) and related polypropionates **70** and **73** [83]. These compounds showed significant effects on the splicing of XBP1 mRNA, that is an important regulator of a subset of genes related to tumor growth [83].



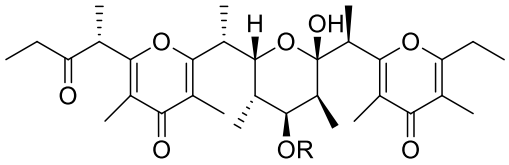
phototridachiapyrone J (**62**)



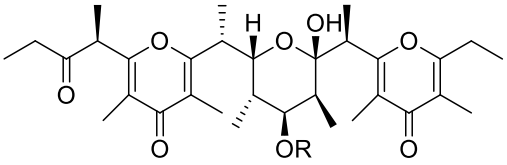
phototridachiahydropyrone (**63**)



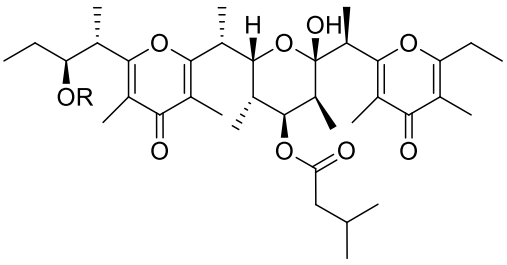
tridachiahydropyrone (**64**)



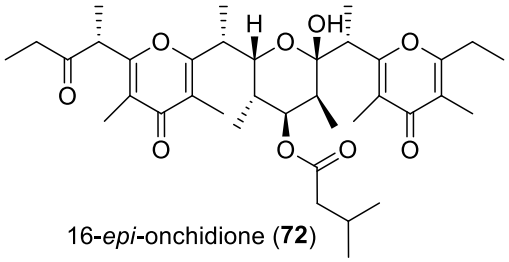
onchidione (**65**): R = $COCH_2CH(CH_3)CH_3$
onchidiol (**66**): R = H
13-propanoyl-onchidiol (**68**): R = $COCH_2CH_3$



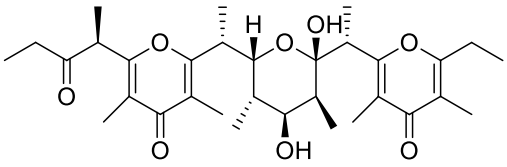
4-*epi*-onchidiol (**67**): R= H
4-*epi*-onchidione (**73**): R = $COCH_2CH(CH_3)CH_3$



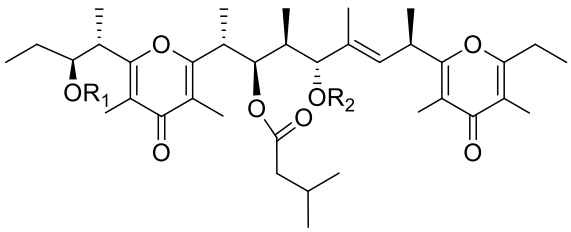
onchidionol (**69**): R = H
3-acetyl-onchidionol (**70**): R = $COCH_3$
3-propanoyl-onchidionol (**71**): R = $COCH_2CH_3$



16-*epi*-onchidione (**72**)



4,16-di-*epi*-onchidiol (**74**)



11-(3-methylbutanoyl)-ilikonapyrone (**75**): R_1=R_2 = H
13-acetyl-11-(3-methylbutanoyl)-ilikonapyrone (**76**): R_1=H; R_2= $COCH_3$
3,13-diacetyl-11-(3-methylbutanoyl)-ilikonapyrone (**77**): R_1=R_2 = $COCH_3$
11-(3-methylbutanoyl)-13-propanoyl-ilikonapyrone (**78**): R_1=H; R_2= $COCH_2CH_3$
3-acetyl-11-(3-methylbutanoyl)-13-propanoyl- ilikonapyrone (**79**): R_1=CH_3CO; R_2= $COCH_2CH_3$
11-(3-methylbutanoyl)-3,13-dipropanoyl-ilikonapyrone (**80**): R_1=R_2= $COCH_2CH_3$

Figure 7. Structures of polyketide-derived compounds 62-80.

Most acetylene compounds isolated from mollusks appear to be from dietary sources, in particular red and brown algae (C_{15} acetylenes) and sponges (long-chain polyacetylenes) [87]. A number of C_{15} acetylenes have been described from heterobranch species mainly of the genus *Aplysia*, typically feeding on algae, whereas the few reports of long-chain polyacetylenes in mollusks refer to dorid nudibranchs associated to haplosclerid sponges [87]. In agreement with these data, the chemical investigation of dorid *Peltodoris atromaculata*, which was collected on the sponge prey *Haliclona fulva* off Procida Island (Gulf of Naples), resulted in the characterization of a series of long-chain polycetylenes [88] structurally related to fulvinol [89], a C_{46} linear symmetric polyacetylene previously reported from a Spanish specimen of the sponge. These polyacetylenes, fulvindione (**81**), fulvinone (**82**) which was an inseparable mixture of two isomers **82a** and **82b**, isofulvinol (**83**), and hydroxydehydroisofulvinol (**84**) (Figure 8), were also found in the sponge confirming the dietary origin in the mollusk [88]. Interestingly, the presence in *P. atromaculata* of structurally different C_{46} polyacetylenes, petroformines, was shown in a previous study [90]. In such a case, the nudibranch was found associated to another polyacetylene-containing sponge, *Petrosia ficiformis*, and petroformines were derived from the sponge [90].

Terpenoids

To the structural group of terpenoids belong the majority of compounds reported from heterobranchs, and in particular from nudibranchs [11]. Almost all of them have a dietary origin being terpenoids widely distributed in sponges, cnidarians, and algae on which heterobranchs mainly feed even though the *de novo* biosynthesis of terpenoids in nudibranchs has been also demonstrated in some cases [91]. The chemical studies we conducted on four nudibranchs belonging to the suborder Cladobranchia and two elysioidean sacoglossans resulted in the characterization of sesquiterpenoids and diterpenoids with different carbon skeletons.

Tritoniopsins A-D (**85**-**88**) (Figure 9) were isolated from the South China Sea nudibranch *Tritoniopsis elegans* and its prey, the soft coral *Cladiella krempfi* [92].

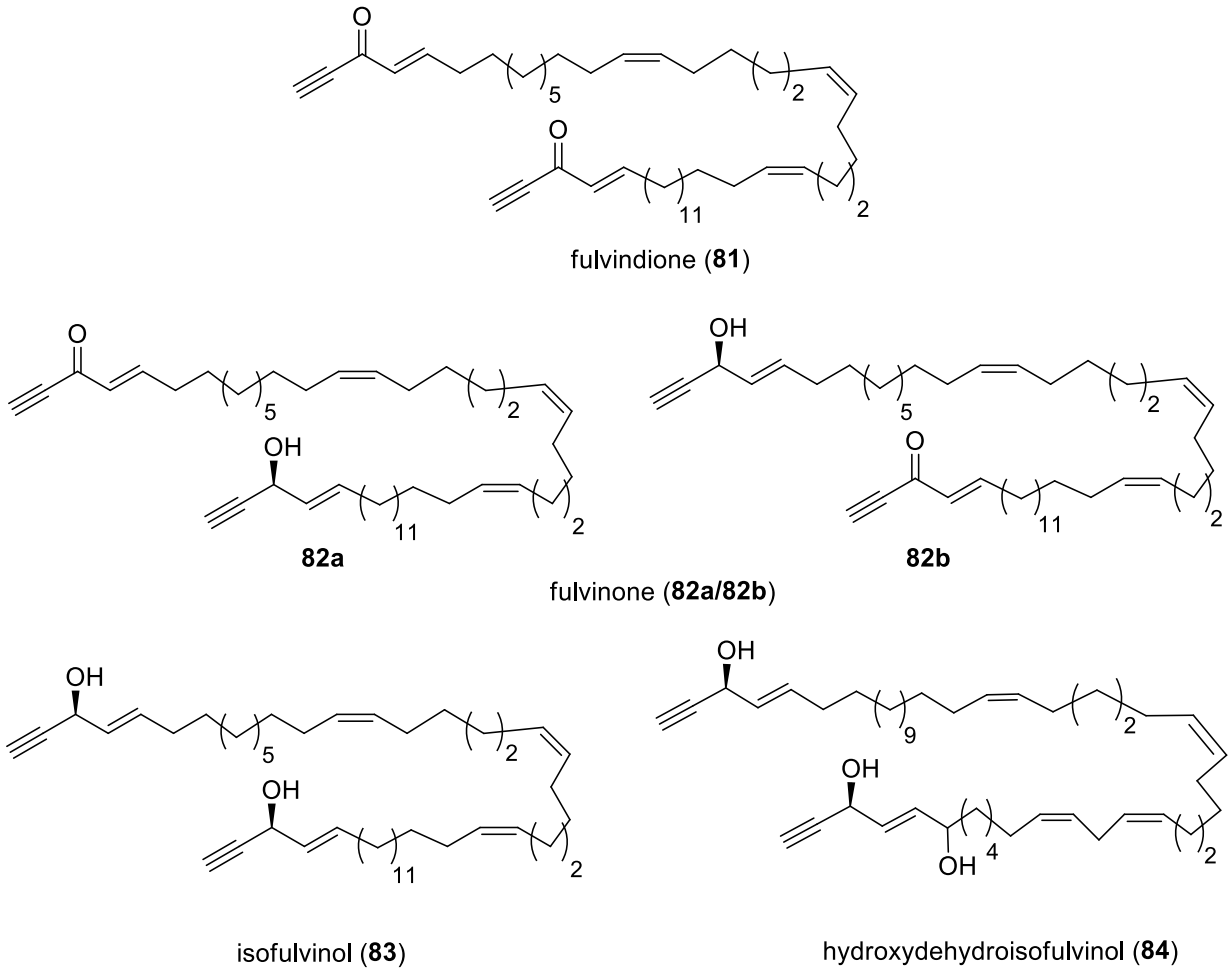


Figure 8. Structures of polyketide-derived compounds 81-84.

Tritoniopsins displayed an unprecedented pyran ring in the cladiellane framework representing a novel cladiellane-based diterpene family. The relative configuration of compound **85** was secured by X-ray analysis whereas the structures of **87** and **88** were confirmed by chemical correlation [92]. The presence of these unique diterpenoids in both the nudibranch and the soft coral clearly indicated the trophic relationship between the two organisms. However, it is interesting to note that tritoniopsin A (**85**) and tritoniopsin B (**86**) were the main metabolites for both animals but they were present in a different relative ratio (**85**> **86** in the nudibranch, **86**> **85** in the soft coral). This finding was explained by the ability of the mollusk to accumulate dietary compounds selectively [92].

The eolid nudibranch *Phyllodesmium magnum*, collected from Hainan Island, South China Sea, contained a series of sesquiterpenoids exhibiting different structural features [93]. They included asterisca-2(9),6-diene (**89**) and the already described 1-africanene (**90**) [94], 9(15)-africanene (**91**) [95], (-)-*β*-elemene (**92**) [96], (+)-*β*-selinene (**93**) [97], (-)-*α*-selinene (**94**) [98], 2-[(2*E*,5*E*)-2,6-dimethylocta-2,5,7-trienyl]-4-methylfuran (**95**) [99], and methyl 5-[(1*E*,5*E*)-2,6-dimethylocta-1,5,7-trienyl] furan-3-carboxylate (**96**) (Figure 9) [99]. All known compounds **90**-**96** were previously reported from soft corals of genus *Sinularia* strongly indicating that these organisms should be included in the diet of *P. magnum*. Interestingly, compound **89** displayed a rare asteriscane skeleton, which was previously reported from terrestrial plants and never encountered in marine organisms [93].

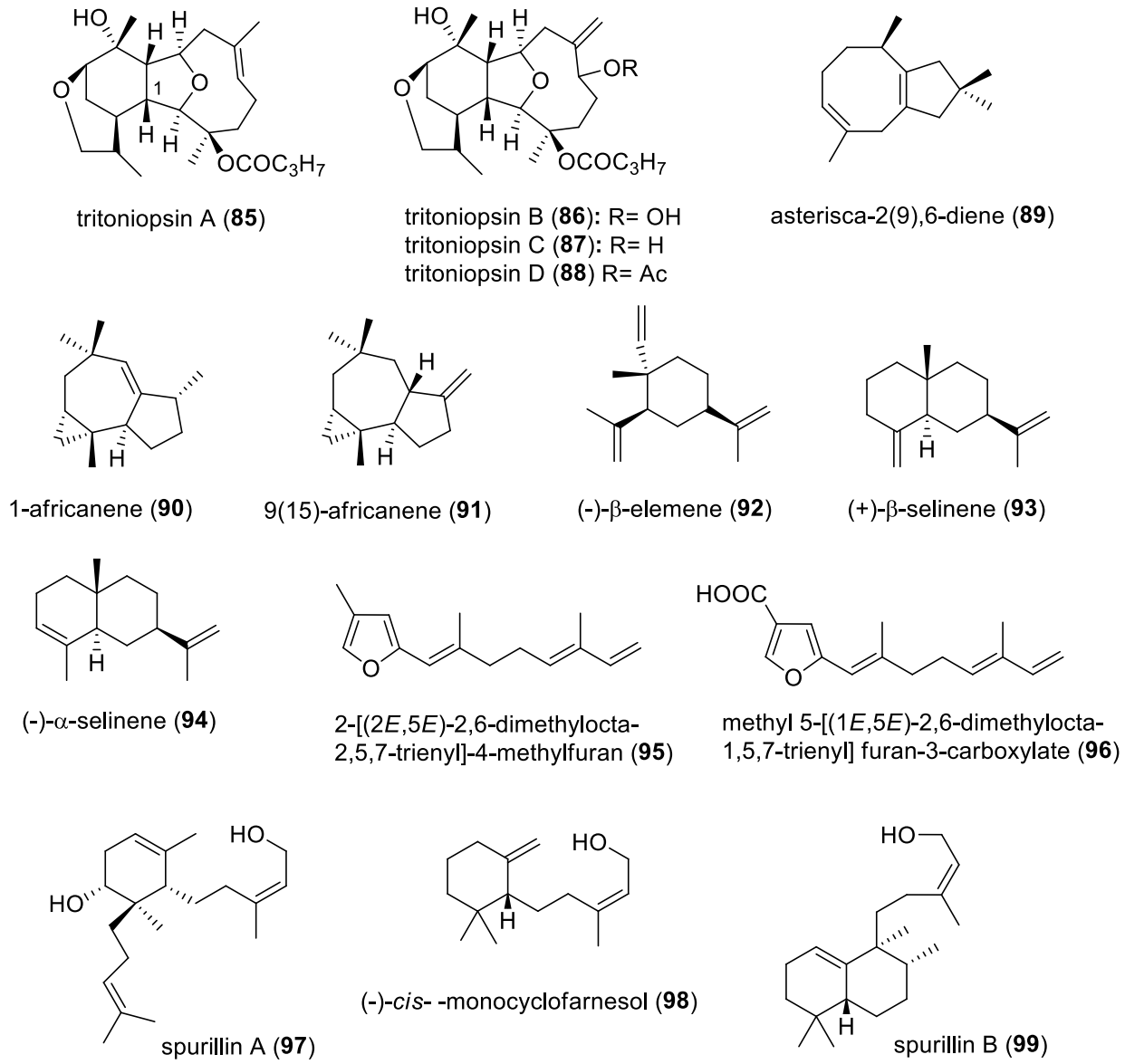


Figure 9. Structures of terpenoids 85-99.

The terpenoid content of two distinct *Spurilla* species, *Spurilla neapolitana* from Tyrrenian coasts and *Spurilla* sp. from Atlantic Ocean (see *Nitrogen-containing compounds* paragraph) was analyzed and chemically characterized [69]. Diterpenoid spurillin A (**97**) was isolated from the Italian nudibranch whereas two sesquiterpenoids, (-)-*cis*-*γ*-monocyclofarnesol (**98**) and spurillin B (**99**) (Figure 9) were found in the Patagonian species. Compound **98** was previously described as synthesis product [100]. Analogous with bursatellin (**53**) (Figure 6**)**, compounds **97**−**99** were not detected in the sea-anemone diet of both nudibranchs. Terpenoids are not common metabolites of sea-anemones suggesting for *Spurilla* metabolites **97**−**99** either a *de novo* biosynthesis origin or a dietary derivation from different sources including symbiotic microorganisms.

The thuridillins are a small group of unique diterpenoids occurring in sacoglossans of the genus *Thuridilla*. First members to be isolated were thuridillin A (**100**), thuridillin B (**101**), and thuridillin C (**102**) (Figure 10) from two Mediterranean *Thuridilla hopei* collections from Ionian [101] and Tyrrhenian Sea [102]. Thuridillins were assumed to be derived from a dietary algal precursor [103] the structure of which was closely related to **100**−**102**.

All these diterpenes feature a central *α*,*β*-epoxy-*δ*-lactone ring substituted by an uncyclized or cyclized isoprenoid chain and a terminal protected form of a 1,4-conjugated dialdehyde, including either a 2,5-diacetoxy-2,5-dihydrofuran ring or a 1,4-diacetoxy-1,3-butadiene moiety. This terminal structural motif could easily generate reactive aldehyde functional groups that are responsible for different biological activities due to the ability to link the free amino groups of putative receptors. Additional members of thuridillin class, thuridillin D (**103**), thuridillin E (**104**), and thuridillin F (**105**) (Figure 10), were isolated along with compound **100** from an Australian collection of *Thuridilla splendens* [104]. The partial relative configuration of thuridillin D (**103**) was also determined by a detailed NMR study including a series of experiments to accurately measure $J_{H\text{-}H}$ and $J_{H\text{-}C}$ coupling constants and NOESY data as well as by conformational analyses [104]. A subsequent re-investigation of Mediterranean *T. hopei* resulted in the isolation of three thuridillin-derived aldehyde metabolites, *nor*-thuridillonal (**106**), dihydro-*nor*-thuridillonal (**107**) and deacetyl-dihydro-*nor*-thuridillonal (**108**) (Figure 10), co-occurring with previously described thuridillins **100**−**102** [105]. The main aldehyde **106** was assayed for the feeding-deterrence in the food palatability test with the shrimp *Palaemon elegans* and resulted to be active at a concentration of 5.0 mg/mL [105].

Recent advances in the chemical ecology of heterobranchs

Terpenoids from terrestrial plants are well known to represent a kind of complex language mediating crucial ecological interactions [106]. A growing body of literature, however, shows that this also applies to aquatic animals [107,108]. In particular, recent chemoecological studies have emphasized the critical roles played by marine natural products, especially terpenoids, in defensive and alimentary behaviors of heterobranch mollusks.

The nudibranch *Felimare* (= *Hypselodoris*) *fontandraui* belongs to a group of conspicuous blue, white, and yellow Mediterranean and northeastern Atlantic species of heterobranchs, for which the existence of a Müllerian mimetic circle has been hypothesized implying that similarly colored nudibranch species reduce risk of predations by sharing a common visual warning signal, which is associated to the presence of toxic and/or distasteful chemicals [109,110]. However, *F. fontandraui* lacks the so called “mantle dermal formations” (MDFs) acting as reservoirs of feeding deterrent compounds in many other nudibranchs. Consequently, it seemed possible that this animal lacks chemical defense, acting like a Batesian mimic that gains protection from predation through its visual similarity to species that possesses defensive chemical weapons. Instead, the chemical investigation of *F. fontandraui* collected along Portuguese coasts led to the isolation of the feeding deterrent furanosesquiterpenoid tavacpallescensin (**109**) (Figure 11), which is most likely derived from sponges of the genus *Dysidea* upon which the nudibranch feeds [111]. Even in the absence of MDFs, compound **109** (Figure 11) turned out to be accumulated at very high concentrations in the mantle rim of *F. fontandraui*, considerably exceeding the threshold value of concentration showing a significant feeding deterrent against the generalist shrimp *P. elegans*. This finding demonstrated that *H. fontandraui* is chemically defended, much as other aposematic blue-colored species within a Müllerian mimetic circle, and does not represent a Batesian mimic.

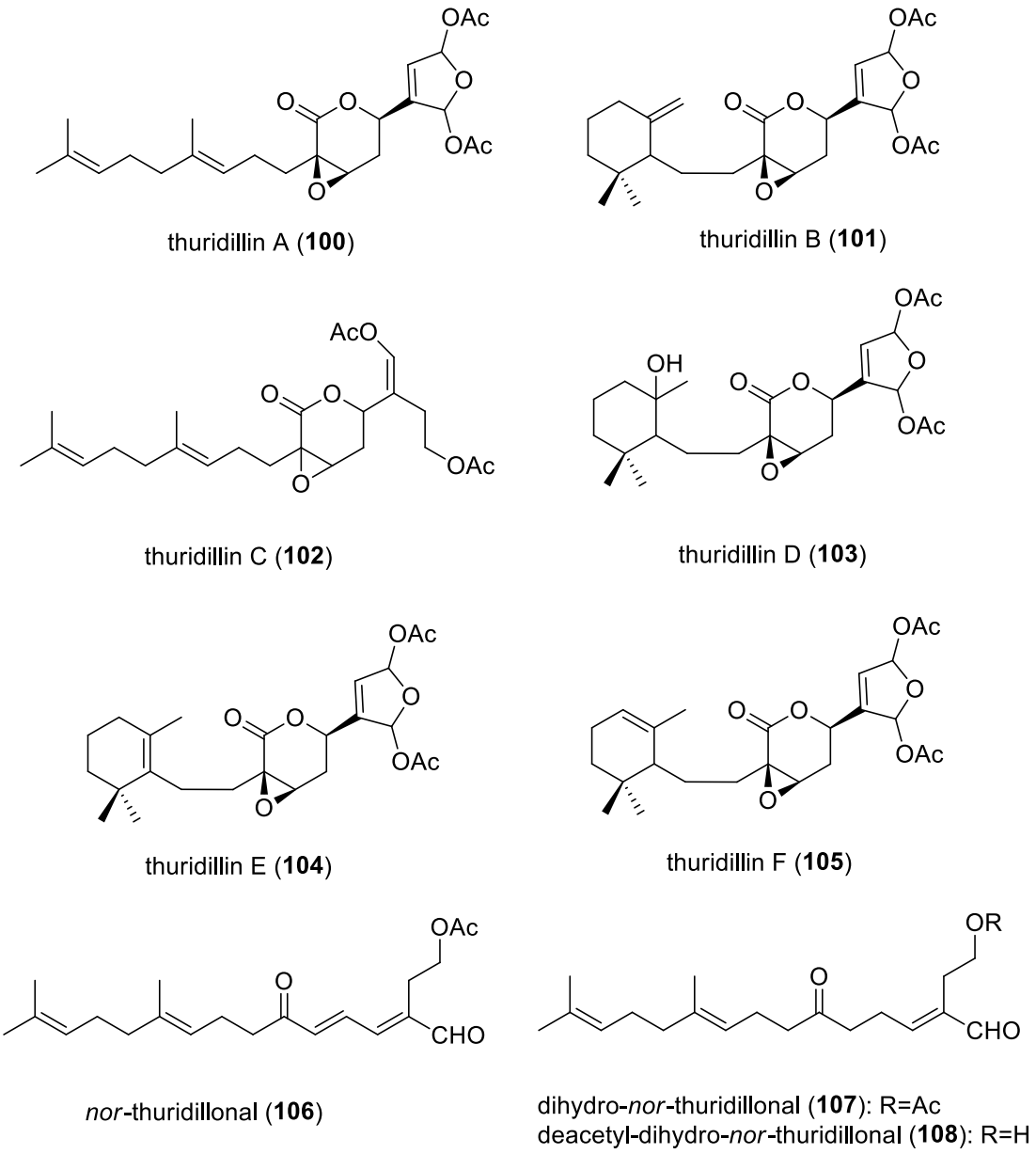


Figure 10. Structures of terpenoids 100-108.

Supporting that Müllerian mimicry does not involve visual mimicry only, but may also employ aposematic chemosensory signals, the toxic and feeding deterrent 16-membered macrolide latrunculin A (**110**) (Figure 11) was found in the mantle rim of five different nudibranch species from Australian coasts [112]. In this view, compound **110** can be detected also by potential predators devoid of well-developed visual systems.

The study of the anatomical distribution of defensive metabolites in six chromodorid species from Chinese coasts, combined with feeding deterrence assays on shrimp, led us to demonstrate that unpalatable compounds reach high concentrations in the MDFs, which are located in the more exposed parts of the body, also confirming that nudibranchs belonging to the family Chromodorididae are trophic specialists that derive terpenoids from the sponges they eat [113]. In particular, *Dorisprismatica* (= *Glossodoris*) *atromarginata* was found to contain the furanospongianes spongiatrioltriacetate (**111**) and spongiatrioldiacetate (**112**) especially accumulated in the MDFs, while spongiatriol (**113**) was distributed in the mantle and viscera of the nudibranch. Instead, the border of the mantle (which includes the MDFs) of *Goniobranchus* (= *Chromodoris*) *sinensis*, which includes the MDFs, contained a 1:3 mixture of compounds aplyroseol-2 (**114**), and its corresponding dialdehyde (**115**) (Figure 11). From the MDFs of an unidentified *Hypselodoris* species of the genus

Hypselodoris was isolated compound **116**, (+)-tetradehydrofurospongin-1 (Figure 11). In the MDFs of *Hypselodoris infucata* and *Hypselodoris* (= *Risbecia*) *tryoni* (Garrett, 1873) was only found compound **117**, (-)-furodysinin. Along with **117**, nakafuran-9 (**118**) (Figure 11) was also found in the MDFs of *Ceratosoma gracillimum*. Overall, only distasteful compounds were found to be accumulated in the MDFs at extremely high concentrations. Given that MDFs usually lack a duct system, the mechanism for exudation of their contents remains unclear, as does their adaptive significance. Given that MDFs usually lack a duct system allowing the exudation of their contents, the above results supported that their breakage occurring during harmful attacks on chromodorid nudibranchs, allows the release of a huge quantity of highly repellent lipophilic metabolites in the predator's mouths.

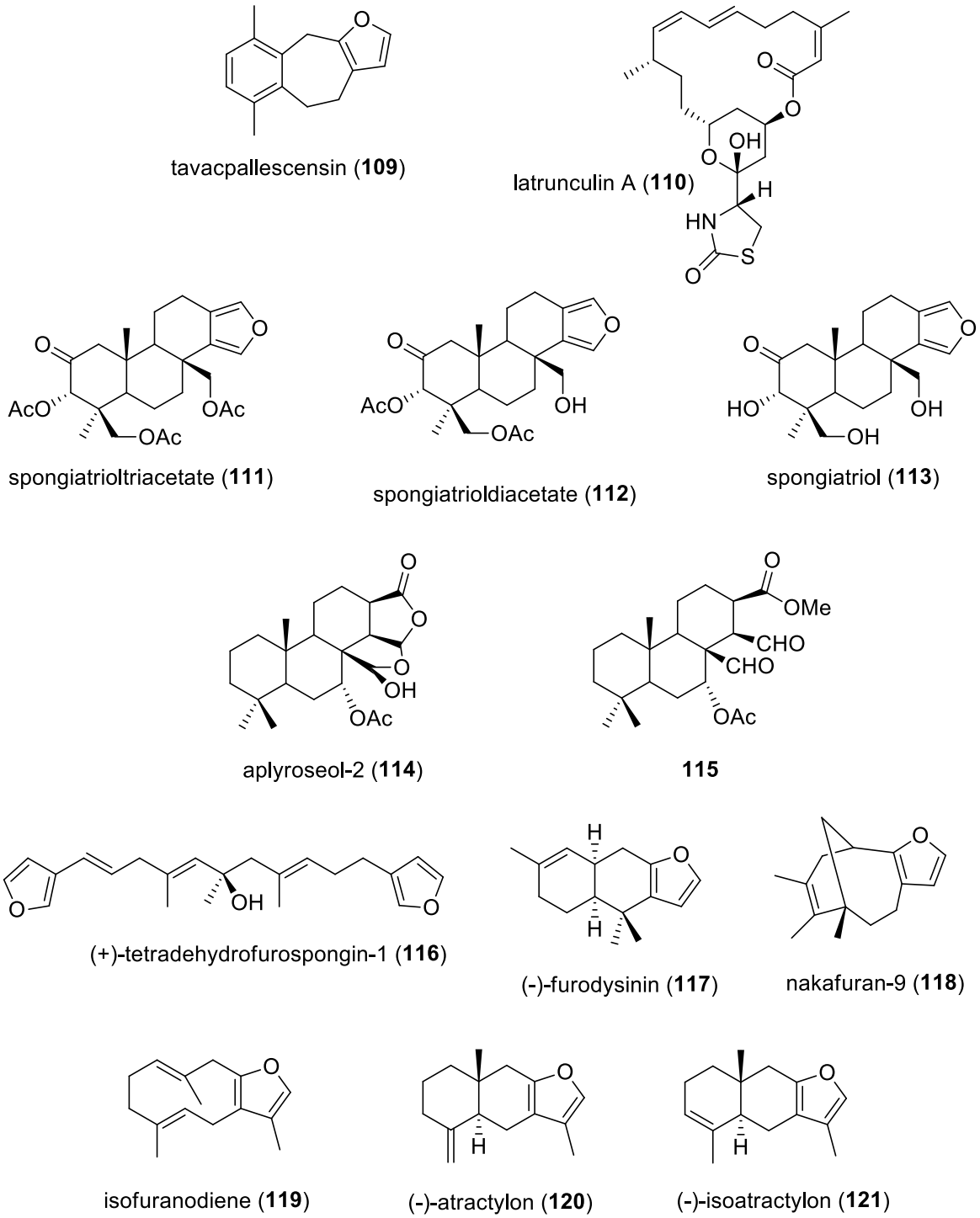


Figure 11. Structures of terpenoids 109-121.

In this view, chromodorid nudibranchs offer the most exposed parts of their bodies to the predators as a defensive variant of the strategic theme of the *Trojan horse* [113].

Furanosesquiterpenes isofuranodiene (**119**), (-)-atractylon (**120**), and (-)-isoatractylon (**121**) (Figure 11) have been isolated both in the tritonid nudibranch *Tritonia striata* and in its prey, the octocoral *Maasella edwardsi* (Cnidaria: Anthozoa: Alcyonacea) [114]. Food treated with the terpenes elicited avoidance responses in shrimp, but rejection was also induced by the memory recall of postingestive aversive effects (vomiting), evoked by repeatedly touching the food with chemosensory mouthparts. The shrimp's mouthparts have been thus shown to act as "aquatic noses," supporting a contact form of olfaction in aquatic environments, which takes place when the olfactory signals are biomolecules that combine volatility in air and insolubility in water. Consistent with their multiple ecological roles as toxins, avoidance-learning inducers, and aposematic odorant cues, compounds **119**–**121** were also highly toxic to brine shrimp [114]. This was suggestive of their involvement in the alimentary strategies of *M. edwardsi* in nature, helping in the capture of zooplanktonic crustaceans. In spite of their toxicity, however, compounds **119**–**121** evidently do not deter *T. striata* from feeding on *M. edwardsi*. Conversely, those compounds seem to help the monophagous nudibranch to find its only possible food source. Apparently, *T. striata* evolved the ability to handle and reuse dietary terpenes **119**–**121** in self-defense.

Conclusions

This overview summarizes our recent studies on heterobranch mollusks and show an amazing chemical diversity in these marine organisms. Natural products play fundamental ecological roles in heterobranchs acting as chemical mediators in numerous intra- and inter-specific communication mechanisms such as the protection from predators, the regulation of the feeding behavior, the regulation of the life-cycle. Heterobranchs are able to detect in the habitat where they live these bioactive compounds and to sequester them from diet. Often, such ecologically relevant molecules display also a biotechnological potential for pharmacological applications. Due to this, heterobranchs can be considered as a very promising source to select new drugs.

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Short biography of the corresponding author

Margherita Gavagnin received her doctoral degree in organic chemistry in 1983 at the University of Naples. After spending a postdoctoral year at the Institute of Organic Chemistry of Naples, in 1985 she moved, as researcher of the Italian National Council of Research, to the Institute of Chemistry of Molecules of Biological Interest (ICMIB), now ICB, where she has been First Researcher (2001-2006) and subsequently Research Director (from 2006 up to now).

The scientific activity has been mainly oriented to the structure elucidation of new natural products from marine invertebrates, in particular from heterobranch molluscs, which are extraordinary

models to select hit-compounds for drug development. These studies have produced about 180 papers on international peer-reviewed journals and more than 130 scientific communications in international symposia. She has received numerous invitations to prepare reviews on marine chemistry and invited lectures to international symposia.

In recent years, the research interest has been mainly focused to the discovery of new antitumor molecules from molluscs, sponges and marine plants. Some studies have been also undertaken on terrestrial plants from desert regions of North Africa.

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