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# The chemistry and chemical ecology of nudibranchs

Lewis J. Dean and Michèle R. Prinsep \*

Covering: up to the end of February 2017

Nudibranchs have attracted the attention of natural product researchers due to the potential for discovery of bioactive metabolites, in conjunction with the interesting predator-prey chemical ecological interactions that are present. This review covers the literature published on natural products isolated from nudibranchs up to February 2017 with species arranged taxonomically. Selected examples of metabolites obtained from nudibranchs across the full range of taxa are discussed, including their origins (dietary or biosynthetic) if known and biological activity.

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## 1 Introduction

Nudibranchs, often called sea slugs or more poetically, “butterflies of the sea”,<sup>1</sup> are a diverse group of marine gastropod molluscs, representing over 4700 known species.<sup>2</sup> After shedding their shells as larvae, nudibranchs thereafter remain shell-less; indeed the name nudibranch literally translates to “naked gill”, a reference to the exposed cerata on the backs of many species.<sup>3</sup> Whilst essentially blind, nudibranchs perceive their environment through chemosensory interactions with two specialised rhinophores on their heads.<sup>3,4</sup> These carnivores are important consumers in benthic communities, feeding mostly upon sessile organisms, (sponges, cnidarians, tunicates and bryozoans), although some species hunt other nudibranchs. Both specialist and generalist feeders are known and can be found in practically all oceans.<sup>3</sup>

Having lost the physical protection of a shell, nudibranchs often utilise chemical defences to deter predators.<sup>3</sup> Given that their typical prey species are some of the most prolific producers of natural products,<sup>5</sup> it is perhaps unsurprising to

School of Science, University of Waikato, Hamilton 3240, New Zealand. E-mail: Michele@waikato.ac.nz



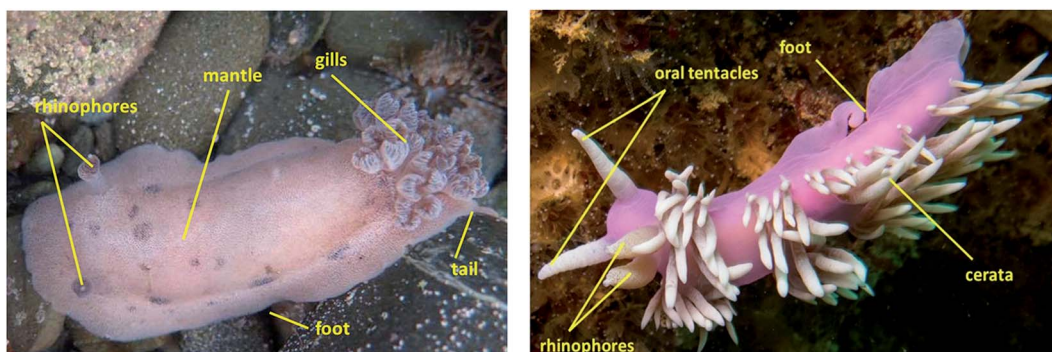


Fig. 1 General morphology of a dorid nudibranch (*Alloiodoris lanuginata*) (left), highlighting the dorsal gill plumage and an aeolid nudibranch (*Jason mirabilis*) with characteristic cerata (right). Note the presence of rhinophores on both. Photographs courtesy of Tracey Bates. (After Picton and Morrow, 2006).<sup>3</sup>

find that many nudibranchs are known to sequester these defences.<sup>6</sup> The vibrant colours associated with many nudibranch species are often correlated with those of their prey,<sup>6</sup> however, *de novo* production of defences is also known.<sup>7</sup> Nudibranchs have thus attracted many natural product researchers due to the potential for discovery of bioactive metabolites, in conjunction with the chemical ecological interactions between predator and prey that exist for many species.

## 2 Taxonomy

Broadly speaking, nudibranchs can be separated into two distinct groups based on their general morphology (Fig. 1)<sup>3</sup> and digestive glands; dorids and aeolids.<sup>7</sup> Dorid nudibranchs (clade: Euctenidiacea) have an intact digestive gland<sup>7</sup> and are distinguished by a feather-like plume of gills on their dorsal side, circling the anus.<sup>3</sup> They also commonly feature discrete pockets, bumps and other distortions, on their skin known as mantle dermal formations (MDFs), in which bioactive defence chemicals are typically stored.<sup>3,8</sup> Aeolid nudibranchs (clade: Cladobranchia) have a branched digestive gland<sup>7</sup> and lack gills.<sup>3</sup> They are characterised by the presence of dorsal projections known

as cerata, which function in place of gills by facilitating gas exchange through the epidermis.<sup>3</sup> In many aeolid species, the digestive tract also extends into the cerata and the tips often contain cnidosacs; stinging cells absorbed from prey species that are used for the nudibranch's own defence.<sup>3</sup>

Strictly speaking, a branched digestive gland is indicative of a non-dorid nudibranch, known as a cladobranch<sup>7</sup> and true aeolids are only those belonging to the parvorder Aeolidida (Fig. 2), the only nudibranchs to possess cnidosacs.<sup>7,9</sup> However, many of the non-dorid nudibranchs are said to be aeolid-like as they possess cerata, or cerata-like projections, instead of gills.<sup>3</sup> Others do possess gills, often tucked between the mantle and foot, but they bear little resemblance to the dorsal plumes of dorids.<sup>3</sup>

The classification of nudibranchs is far from settled. There have been a number of taxonomic revisions in the past,<sup>10–12</sup> the one presented here being that currently used as in WoRMs.<sup>13</sup> A clear distinction between dorid and non-dorid nudibranchs is well established, although a number of cladobranch families have yet to be assigned to an appropriate superfamily.<sup>13</sup>

Molecular studies are offering new insights into phylogenetic relationships. A relatively recent report analysing RNA



Lewis Dean obtained his BSc(Hons) at the University of Waikato in 2016, completing his research dissertation on the natural products of New Zealand nudibranchs. A past winner of a prestigious University of Waikato Sir Edmund Hillary Scholarship, he was recently awarded a University of Waikato Doctoral Scholarship and is currently undertaking a PhD under the chief supervision of Michèle Prinsep, focusing on the isolation and characterisation of bioactive metabolites from New Zealand marine algae.



Michèle Prinsep received her BSc(Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral research on cyanobacteria with Richard Moore at the University of

Hawaii before returning to New Zealand to take up a lectureship at the University of Waikato, where she is currently an Associate Professor.



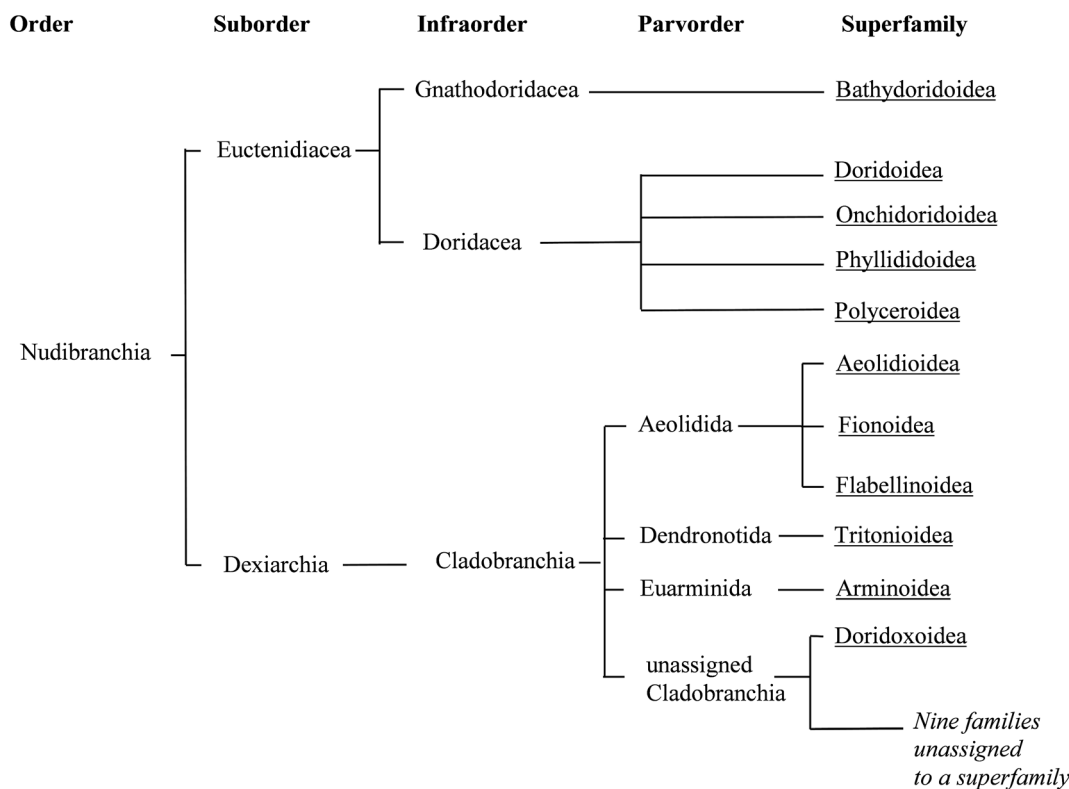


Fig. 2 Phylogenetic relationships between the taxonomic divisions currently recognised for Nudibranchia, and that are used in this review. Branches are terminated with superfamilies (underlined), whilst the roots represent taxonomic divisions (as used in WoRMS<sup>13</sup>).

sequence data, attempted to reconcile the groupings within Cladobranchia.<sup>14</sup> Whilst many of the relationships highlighted in past classifications<sup>12</sup> are retained, some new clades have been suggested (although unnamed), incorporating some of the previously unassigned families. However, this analysis is by no means conclusive since only 10 of the 32 families currently recognised were investigated.<sup>14</sup> A similar study analysed the mitochondrial and nuclear genes of the *Doridoxa* genus (the only genus in the current superfamily Doridoxoidea).<sup>15</sup>

The changes proposed by the above studies serve to highlight the ever evolving nature of taxonomy. This can lead to confusion for anyone attempting to navigate the literature covering nudibranch natural products, as invariably one will come across outdated phylogenetic relationships as well as old or repurposed taxonomic names. As an example, Doridacea is now recognised as an Infraorder within Euctenidiacea representing a subdivision of dorid nudibranchs,<sup>13</sup> whereas historically it was used as a suborder covering all dorids.<sup>3,7</sup> Some species may also have been renamed and others folded into one another. This confusion has in some, thankfully rare, cases extended to a non-nudibranch sea slug (*Pleurobranchaea meckeli*) being reported as such.<sup>16</sup>

### 3 The origin of nudibranch natural products

Given that both sequestration and *de novo* synthesis of natural products are known in nudibranchs, it is rarely immediately clear if an isolated metabolite is of dietary origin. Feeding

experiments with isotopically labelled precursors, are the only accepted procedures to prove biosynthesis of a metabolite.<sup>17</sup> Unfortunately, the low uptake of feedstock by many marine organisms often forces the use of radioactive isotopes.<sup>17</sup> Advances in nuclear magnetic resonance (NMR) spectroscopy have improved sensitivity and thus stable isotope experiments are increasingly becoming viable options, yet the cost of precursors, radioactive or stable, combined with the costs of very sensitive NMR instruments has inevitably restricted the use of feeding experiments in nudibranch studies.

There are many cases in the literature where *de novo* synthesis has been assumed, despite no feeding experiments being conducted. As the digestive glands of all nudibranchs are the source of nutrient distribution throughout the organism, it stands to reason that if a natural product is found therein, it is likely of dietary origin.<sup>7</sup> Conversely if a metabolite is only present in the skin or mantle, and not in the viscera of a nudibranch, then it is probable that the compound is either biosynthesised in full or secondarily modified.<sup>7</sup> Likewise, the absence or presence of the same, or structurally related, metabolite(s) in possible food species are also used to argue for biosynthesis or sequestration respectively.<sup>18</sup> It has been further reasoned that any species of nudibranch that synthesises its own metabolites should consistently possess all metabolites, across all geographic collections.<sup>18</sup> Species known to show variation in their natural products, especially from differing locations, may be indicative of metabolite sequestration.<sup>18</sup> In addition, as one of the evolutionary advantages of *de novo*



synthesis is to liberate a nudibranch from a singular food source, specialist feeders may be more likely to sequester metabolites.<sup>7,18</sup>

## 4 Scope of review

There have been a number of excellent reviews of nudibranch chemistry over the years, including reviews on chemical ecology,<sup>19–21</sup> chemical defence<sup>7,22,23</sup> and bioactive metabolites.<sup>24,25</sup> Many focus on specific groups of metabolites such as diterpenes,<sup>26</sup> terpenoids,<sup>27</sup> cyanide and isothiocyanates<sup>28</sup> and isocyanides<sup>29</sup> (but all also include other marine invertebrates). A number of these reviews are regional in their focus, dealing with nudibranchs and other molluscs found in New Zealand,<sup>30,31</sup> Australia,<sup>31,32</sup> North America,<sup>33</sup> Japan,<sup>34</sup> Africa,<sup>35</sup> South America<sup>35</sup> and Antarctica.<sup>35</sup>

The annual review of marine natural products that appears in Natural Product Reports has a section on molluscs<sup>36a-f</sup> but given the wide scope of this review, there is no capacity to discuss nudibranchs in any detail or in a comprehensive manner over a considerable time period. There have only been three relatively recent reviews that deal with nudibranch chemistry, but two of these are not specific to nudibranchs (focus respectively on the terpene chemistry of marine molluscs<sup>37</sup> and marine molluscs as a source of antiviral drugs<sup>38</sup>) and the third is limited in scope (deals with lipids and fatty acids of nudibranchs but only eight species were examined).<sup>39</sup>

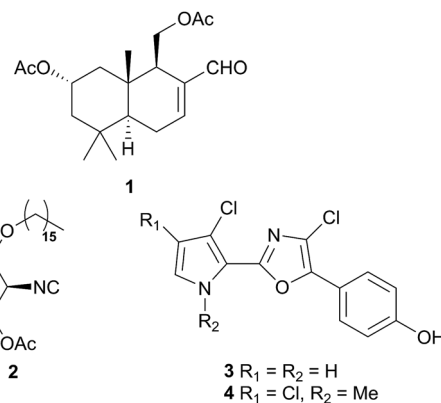
This current review focusses on the chemistry and chemical ecology of nudibranchs. It is arranged taxonomically and species are ordered as per their superfamily in the World Register of Marine Species (WoRMS)<sup>13</sup> to highlight both the different and similar defensive strategies adopted by the various clades. Species are referred to and ordered by the name used in the original publication but where a taxonomic revision has taken place, the correct name is given in Table 1 and noted in brackets in the text. In each section, a selection of representative, significant or otherwise interesting, nudibranch natural products are discussed, including their origins (dietary or biosynthetic) if known and biological activity.

## 5 Dorid nudibranchs

### 5.1 Bathydoridoidea

**5.1.1 Bathydorididae.** Bathydoridoidea is a small superfamily of deep water nudibranchs containing only the family Bathydorididae, comprised of one genus, *Bathydoris*. It has received little attention from natural product chemists, presumably due to difficulties in collecting specimens. A single investigation of one species has been reported to date. Hodgsonal (1), a novel, drimane sesquiterpene was isolated from the mantle of *Bathydoris hodgsoni*<sup>40</sup> and was the first known 2-substituted drimane sesquiterpene of marine origin.<sup>40,41</sup> The distribution of 1 among individual *B. hodgsoni* specimens collected from various sites was found to be reasonably consistent and it was only detected on the extremities of the nudibranch and not in the viscera. Given that the stomach contents of *B. hodgsoni* indicated that this species is a generalist

and opportunistic feeder, it was suspected that 1 is *de novo* synthesised.<sup>41</sup> In experiments, 1 deterred feeding in a potential starfish predator (*Odontaster validus*) at natural concentrations, highlighting its probable use as a defence allomone.<sup>41</sup>



### 5.2 Doridoidea

Comprising five families, Doridoidea is by far the most studied nudibranch superfamily in terms of species, genera and metabolites reported. Searching within the MarinLit database<sup>42</sup> for natural products investigations into nudibranchs (Taxonomy filter: Phylum-Mollusca; Article free text filter: nudibranch) reveals 152 records (as of 28 February 2017). Of these, 80 concern species of Doridoidea (56%).

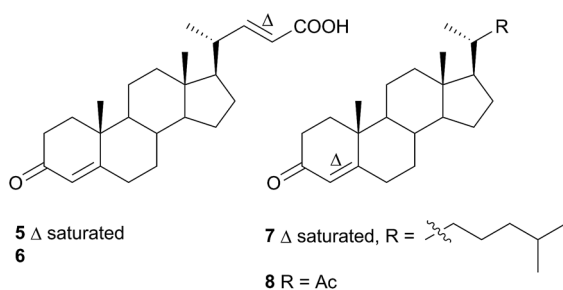
**5.2.1 Actinocyclusidae.** Actinocyclusidae is a small family comprising two genera (*Actinocyclus* and *Haliaxa*) and only one study has been conducted on a species in this family. An isonitrile lipid, actisonitrile (2) was obtained from the mantle of a South China Sea specimen of *Actinocyclus papillatus* as the major component. Total synthesis was achieved and both enantiomers exhibited moderate cytotoxicity to a mammalian cell line, which, along with the selective distribution of 2, implies a likely defensive function for the metabolite.<sup>43</sup>

**5.2.2 Cadlinidae.** The Cadlinidae family comprises two genera (*Aldisa* and *Cadlina*) and the chemistry of representatives of both has been studied. An Indian collection of *Aldisa andersoni* was the source of some members of the phorbazole family of metabolites,<sup>44</sup> including the new 9-chloro-phorbazole D (3) and N1-methyl-phorbazole A (4), which co-occurred with known phorbazoles A, B and D, previously obtained from the sponge *Phorbasp aff. clathrata*.<sup>45</sup> Although found mainly on the exterior of *A. andersoni*, the compounds were also present in the digestive organs of the mollusc, reinforcing the high probability that these compounds were sequestered from a *Phorbasp* sponge, although none were observed near the collection site.<sup>44</sup> Phorbazole A, 3 and 4 deterred feeding by the shrimp *Palaemon elegans* and both 3 and 4 exhibited cytostatic effects against several human tumour cell lines (HTCLs).<sup>44</sup>

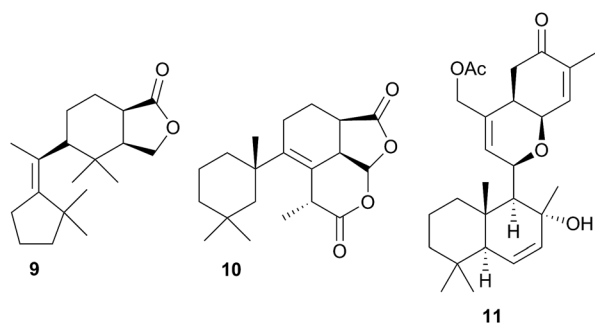
Two steroidal acids, 3-oxo-chol-4-ene-24-oic acid (5) and its unsaturated analogue (6), were isolated from *Aldisa sanguinea cooperi*<sup>46</sup> (*Aldisa cooperi*<sup>359</sup>). Cholestenone (7), an alkyl derivative of 5 and 6 was also present in the extract. *A. cooperi* was consistently found feeding upon the sponge *Anthoarcuata*



*graceae*, which, whilst lacking 5 and 6, was found to contain 7 as one of its major metabolites. Cholestenone, 7, proved to be inactive in feeding experiments whereas 5 was an effective inhibitor of feeding behaviour (common goldfish). This indicated that *A. cooperi* was obtaining an inactive metabolite from its diet and modifying it to provide a defence against predators.<sup>46</sup> It has been suggested that another steroidal metabolite, 24-norchole-4-ene-3,22-dione (8), isolated from the related nudibranch *A. smaragdina* may also be secondarily modified from 7 (ref. 47) or alternatively, result from the  $\beta$ -oxidation and subsequent decarboxylation of 5. However, these suggestions were tentative since no steroidal precursors were noted in the observed prey species *Phorbas fictitius*.<sup>47</sup>



A nudibranch that has attracted significant interest is *Cadlina luteomarginata*, as it is one of only two species of nudibranchs known to both sequester prey metabolites and biosynthesise its own natural products<sup>48</sup> (the other, *Dendrodoris grandiflora*, will be discussed below). To date, 38 terpenoid metabolites, with 22 carbon skeletons, representing mono-terpenes,<sup>49</sup> sesquiterpenes,<sup>49–51</sup> diterpenes,<sup>52,53</sup> sesterterpenes<sup>54</sup> and degraded sesterterpenoids<sup>51,55</sup> and diterpenoids<sup>53,56</sup> have been isolated from *C. luteomarginata*.<sup>57</sup> Examples of the sequestered metabolites are glaciolide (9)<sup>56</sup> and caddinolide A (10)<sup>53</sup> from the sponge *Aplysilla glacialis*, and ansellone A (11)<sup>54</sup> from a prey sponge of the *Phorbas* genus. Their ecological roles are not well defined,<sup>57</sup> but 11 has been shown to be moderately activating towards cellular processes that use the cyclic adenosine monophosphate (cAMP) signal pathway.<sup>54</sup>

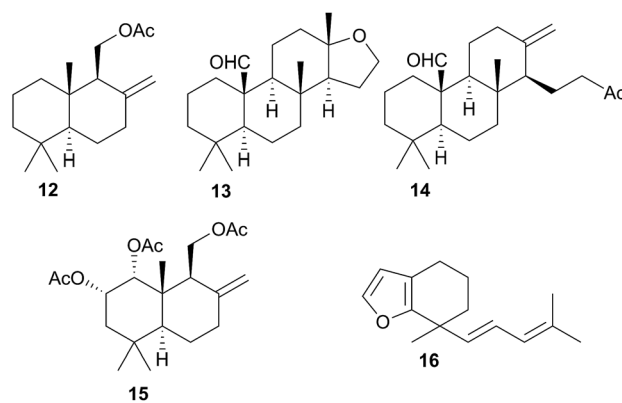


Terpenoid biosynthesis in *C. luteomarginata* was suspected when all previously analysed individuals from a British Columbian (Canadian) study consistently possessed the same three terpenoids.<sup>58</sup> The *de novo* production of these terpenes; albicanyl acetate (12), caddinaldehyde (13) and luteone (14) was subsequently proven by stable isotope labelling experiments.<sup>58</sup>

Antifeeding activity of 12 was detected, and it was found at high concentration in the mantle and mucus, indicating its role as a deterrent.<sup>51</sup> A derivative of 12, 1 $\alpha$ ,2 $\alpha$ -diacetoxyalbicanyl acetate (15), was isolated from the egg masses of *C. luteomarginata* but not detected in the nudibranch itself.<sup>57</sup> Whilst no feeding assays of 15 were conducted, its similarity to 12 indicated that it may act to protect the egg masses.<sup>58</sup> Likewise *de novo* synthesis may be expected for 15, despite it not being detected to date in *C. luteomarginata* nudibranchs.

Initially, there was speculation that *C. luteomarginata* may be divided into subspecies based on geographic distribution, as a Californian population was originally thought not to contain any of the biosynthesised compounds 12–14.<sup>48,58</sup> However, reexamination of this population utilising gas chromatography (GC) indicated that 12–14 were present but at low concentrations.<sup>48</sup> It was found that broadly speaking, individuals of *C. luteomarginata*, from British Columbia, could be separated into two groups. The first group possessed 12–14 at high concentration, with other terpenoids that could be detected by GC at much lower concentration, whilst the second group contained 12–14 at concentrations below those of other GC detectable terpenoids. This variance both between and within geographic populations suggested that *C. luteomarginata* was able to downregulate biosynthesis if sufficient dietary terpenoids could be sequestered.<sup>48</sup>

A number of terpenoids were obtained from *C. pellucida* and *C. laevis*, including the furanosesquiterpene laevidiene (16) from the latter. The structures indicated a dietary origin from sponge prey, although only *C. pellucida* was observed feeding upon a sponge (*Spongia agaricina*).<sup>59</sup>



**5.2.3 Chromodorididae.** Chromodorididae is a large family with 17 accepted genera, 11 of which have been investigated chemically. The majority of natural product studies of nudibranchs have been conducted on this family, especially on the genus *Chromodoris*. There has been one reported study of a nudibranch from the genus *Ardeadoris*. An Australian collection of *A. egretta* yielded a new diterpene (17) but its bioactivity was not tested.<sup>60</sup>

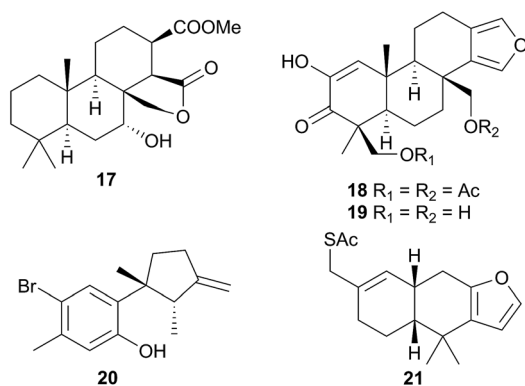
Six furanoditerpenoids were obtained from *Casella atromarginata* (*Doriprismatica atromarginata*)<sup>360</sup> from Sri Lanka.<sup>61</sup> Of these, two were known metabolites of an Australian *Spongia* sp.<sup>62</sup> and two more were minor structural variants but two (18



and 19) were novel metabolites, with a more highly oxidised A-ring, containing a mono-enolised  $\alpha$ -diketone function.<sup>61</sup> It seems likely that *C. atromarginata* obtained these metabolites from its sponge prey.<sup>61</sup>

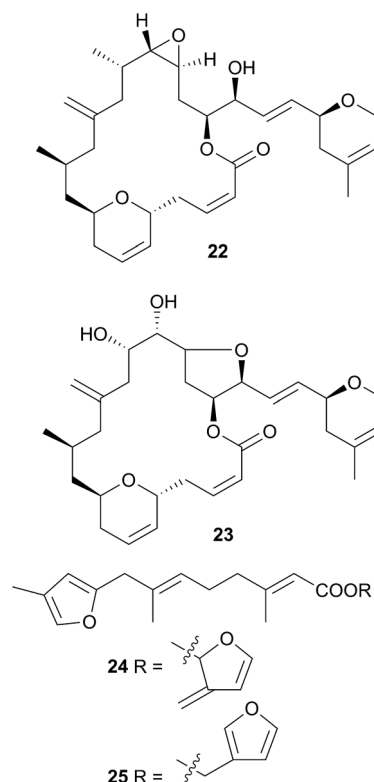
*Ceratosoma amoena* (*Ceratosoma amoenum*<sup>361</sup>) from New Zealand was observed on the red alga *Hymenaea variolosa*.<sup>63</sup> The red algal metabolite allolaurinterol<sup>64</sup> (20) was isolated from both the nudibranch and alga, a surprising result since, as noted by the researchers, the nudibranch dietary system is not capable of breaking down algal tissue. As an alternative explanation for this result, it was suggested that *C. amoenum* could be preying on an organism (or more likely its egg masses) that does sequester this compound from the alga.<sup>63</sup>

Nine new spongiane diterpenes were isolated from a South Australian nudibranch tentatively identified as *Ceratosoma brevicaudatum*<sup>65</sup> but later identified as *Chromodoris epicura*<sup>66</sup> so perhaps it is unsurprising that these do not seem to be typical of the *Cerastoma* genus. A thiosesquiterpene (21) was isolated from the Australian nudibranch *C. brevicaudatum* but believed to be sequestered from a *Dysidea* sponge.<sup>67</sup> The ecological role of 21 has not been studied, but it represents a relatively rare example of a sulphur containing sesquiterpene from the marine environment.<sup>67</sup> Four "typical" sponge furanosesquiterpenoids, pallescensin-B,<sup>68</sup> (-)-furodysin,<sup>69</sup> dehydroherbadysidolide<sup>70</sup> and herbadysidolide<sup>71</sup> were isolated from two species of *Ceratosoma*; *C. trilobatum* and *C. gracillimum*.<sup>66</sup> As previously reported,<sup>72</sup> (-)-furodysin, exhibited feeding deterrent and ichthyotoxic properties, and additionally, concentration of the compound in the dorsal horn glands of the animals, supports the proposed defensive role of the dorsal horns.<sup>66</sup>



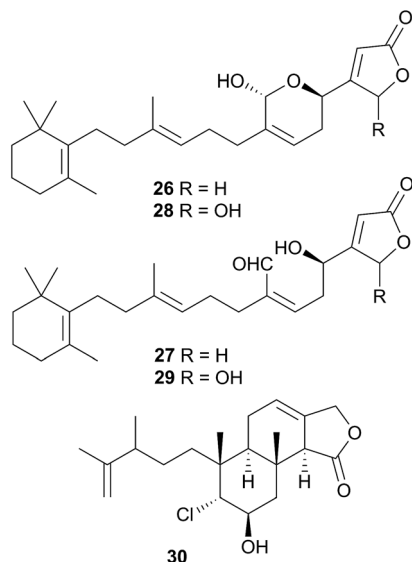
*Chromodoris* is the most examined of all nudibranch genera, with many reported studies,<sup>8,39,73–106</sup> although many of the species in these studies originally classified as *Chromodoris* have been reclassified as *Doriprismatica*,<sup>75</sup> *Felimida*,<sup>73,76,79,80,85,87,90,93</sup> *Glossodoris*,<sup>79,101</sup> *Goniobranchus*,<sup>39,86,88,89,95,98,102–104</sup> or *Hypselodoris*.<sup>74,106</sup> *Chromodoris* species feed exclusively on sponges and sequester a large number of terpenoid metabolites from their prey including sesquiterpenes,<sup>73,74,78,82,106</sup> norditerpenes,<sup>80</sup> diterpenes<sup>8,76,81,85–90,93,95,96,98,99,102–104</sup> and sesterterpenes,<sup>79,84,91,92,92,97,100</sup> although macrolides<sup>77,82,83,105</sup> and bromophenols<sup>78</sup> have also been reported. In some instances, metabolites have been

simultaneously isolated from sponge and nudibranch, highlighting that they are of dietary origin. For example, the macrolides laulimalide (22)<sup>107,108</sup> and isolaulimalide (23)<sup>109</sup> were isolated from sponges of the *Hyattella* genus and from their nudibranch predator *C. lochi*.<sup>83</sup>



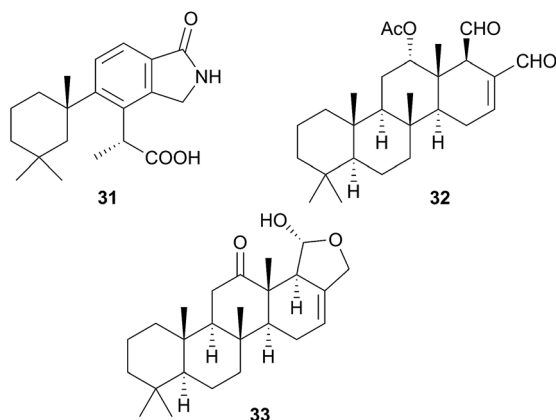
Latrunculin A, a sponge metabolite originally obtained from *Latrunculia magnifica*<sup>110</sup> has been isolated from several *Chromodoris* species,<sup>77,82,94,105</sup> and has been shown to be selectively stored in the mantle rim for protective purposes.<sup>105</sup> In other cases, structural analogues of nudibranch metabolites have been detected in or isolated from, the sponge prey, indicating the likelihood of secondary modification of sponge metabolites. For example, the sesquiterpene marislin (24), obtained from *C. marislae* (*Felimida marislae*<sup>374</sup>), is related to the spongian metabolite pleraplysillin-2 (25), from *Pleraplysilla spinifera*, by a [3,3] sigmatropic rearrangement.<sup>73</sup> Similarly, deoxymanoalide (26) and deoxysecmanoalide (27), isolated from *C. willani*, are modified from manoalide (28) and secmanoalide (29) respectively by loss of an hydroxyl group. Both 28 and 29 were identified in the sponge prey of *C. willani*.<sup>100</sup> Some chlorinated homoditerpenes including hamiltonin A (30)<sup>94</sup> were isolated from *C. hamiltoni* along with latrunculins and a sesterterpene but in this case, the origin of the chlorinated compounds was not clear.<sup>94</sup> Where they have been assessed, virtually all of the metabolites obtained from *Chromodoris* species have displayed a moderate degree of bioactivity, indicating their role in limiting predation. Despite evidence suggesting secondary modification occurs, there have been no reports of *de novo* synthesis within *Chromodoris* to date.



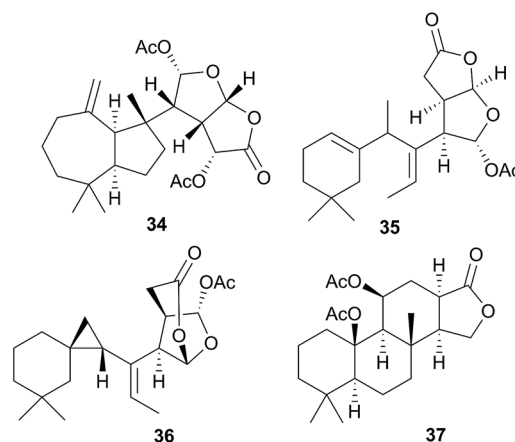


A species, denoted by researchers as *Felimida grahami* (*Felimare grahami*,<sup>383</sup>) sequestered rearranged terpenoids from its sponge prey *Darwinella cf. oxeata*.<sup>111</sup> These included oxeatamide I (31), one of three new oxeatamides H–J<sup>111</sup> found in the sponge to add to those already known<sup>112</sup> and membranolide,<sup>113</sup> previously isolated from the sponge *Dendrilla membranosa*<sup>113</sup> and from nudibranchs *Goniobranchus reticulatus*<sup>102</sup> and *G. splendidus*.<sup>114</sup>

As for *Chromodoris*, many of the species originally reported as *Glossodoris* have been reclassified, in this case as *Ardeadoris*,<sup>115</sup> *Chromodoris*,<sup>116</sup> *Doriprismatica*,<sup>39,117–120</sup> *Felimare*<sup>121</sup> and *Felimida*.<sup>120</sup> Although latrunculin B has been isolated from *G. tricolor*, this is now classified as *Felimare*<sup>387</sup> and all other metabolites isolated from this genus are terpenoids and predominantly sponge derived.<sup>115,117–126</sup> Spongian diterpenes have been obtained,<sup>117,119</sup> but most of the metabolites isolated are based on the sponge-derived scalarane sesterterpene, scalaradial (32),<sup>115,119,121–125</sup> including norscalaranes<sup>119</sup> and homoscalaranes.<sup>120</sup> A number of the scalarane metabolites obtained were 12-keto derivatives such as 33<sup>124</sup> and since in every case, they were only obtained from the nudibranch and not from the sponge prey, it is considered highly likely that biotransformation of the sponge scalarane occurs in the nudibranch,<sup>124</sup> most likely through enzymatic oxidation.<sup>115</sup>



As noted above, taxonomic revisions have led many species that were formerly *Chromodoris* to be reclassified as *Goniobranchus*. From species originally reported as *Goniobranchus*, a range of diterpenes and norditerpenes have been obtained and all studies thus far have been of Australian specimens.<sup>60,114,126–128</sup> In most cases, known sponge metabolites were co-isolated with the novel metabolites reported and compounds were sometimes isolated from both the nudibranch and its prey sponge. 12-Acetoxy dendrillolide (34) for example was obtained from both *G. albonares* and the crimson sponge on which it was feeding.<sup>126</sup> The activity of isolated metabolites has been quite varied. For example, of the six new oxygenated norditerpene/bisnorditerpene metabolites isolated from *G. splendidus*, gracilins M–Q displayed significant potency against the HeLa S3 cell line, aplytandiene-3 was essentially inactive and the rearranged diterpene daphnelactone (35) reported from *G. daphne* in the same study was not tested.<sup>114</sup> Another study of *G. splendidus* yielded some oxygenated diterpenes but these were not tested for activity.<sup>60</sup> *G. verrieri* yielded seven new norditerpenes and diterpenes, all with highly rearranged carbon skeletons, such as the cyclopropyl-containing verriellactone (36) and a biosynthetic pathway to these metabolites from spongialactone was proposed.<sup>127</sup> All six new spongian-16-one diterpenes found localised in the mantle of *G. collingwoodi* (an example being 37) were inactive to a range of HTCLs but preliminary testing of whole body extracts indicated some antifeedant activity against *Palaemon serenus* (rock pool shrimp).<sup>128</sup>



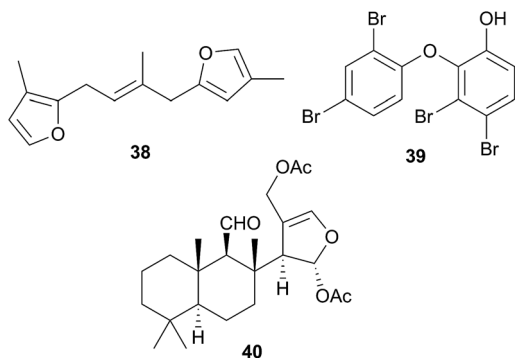
The majority of species originally reported as *Hypselodoris* have been reclassified as *Felimare*<sup>8,72,129–138</sup> or in one case, *Risbecia*<sup>106</sup> but the genus sequesters terpenes,<sup>8,72,98,106,129–139</sup> predominantly furanosesquiterpenes,<sup>8,72,98,106,134–139</sup> from various species of sponge, of which longifolin<sup>138</sup> (38) is typical. Longifolin (38) is sequestered from *Dysidea* sponges<sup>106,130,136,137</sup> and it and other antifeedant compounds are present in the MDFs of many *Hypselodoris* species<sup>8,72,131</sup> and released when the nudibranch is molested. There is one reported isolation of a sesterterpene from this genus.<sup>133</sup> *H. orsini(i)* (*Felimare orsini(i)*)<sup>397</sup> feeds on the sponge *Cacospongia mollior* but contains different metabolites to its prey. It is thought that the nudibranch converts the sponge sesterterpenoid scalaradial, into deoxoscalarin, then, a second chemical transformation produces the



sesterterpenoid, 6-keto-deoxoscalarin which is also stored in MDFs.<sup>133</sup>

A number of oxy-polybrominated diphenyl ethers (O-PBDEs) have been isolated from the nudibranchs *Miamira magnifica* and *M. miamirana* from Australia, of which **39** from *M. magnifica* is a typical example.<sup>140</sup> These compounds are sequestered from sponges and although such compounds have been isolated from nudibranchs previously,<sup>78,141</sup> they were found in the gut tissue, whereas in the *Miamira* specimens, they were additionally located in the mantle and dorsal horn tissues, so likely play a role in chemical defence.<sup>140</sup>

As part of a study of Chromodorid species,<sup>8</sup> *Risbecia tryoni* (*Hypselodoris tryoni*<sup>402</sup>) yielded the sponge metabolite (–)-furodysin<sup>142</sup> and the lipid and fatty acid content has also been examined.<sup>39</sup> There has only been one chemical study of the *Tyrinna* genus. Tyrinnal (**40**), a seco-11,12-spongiane was obtained from the mantle and MDFs of Patagonian *Tyrinna nobilis* (*Tyrinna delicata*<sup>403</sup>) along with three known furanosesquiterpenes.<sup>143</sup>



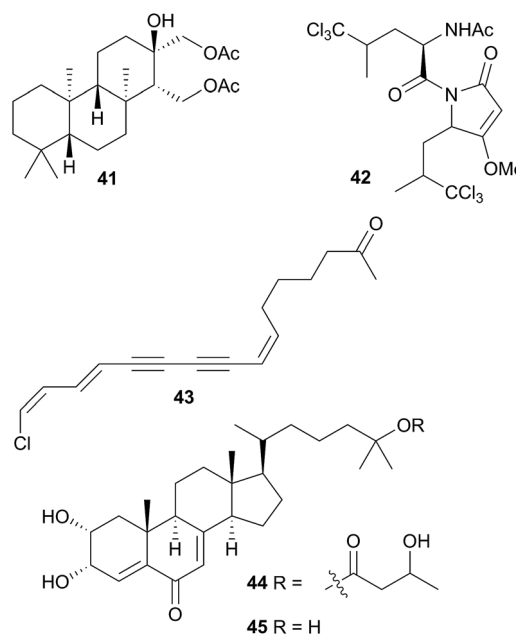
**5.2.4 Discodorididae.** The Discodorididae are a large family of nudibranchs consisting of 30 genera. Only eight of these have been chemically examined (and some of these examples have been reclassified to other genera within the family,<sup>144,145</sup> or in one case, to a genus in the Dorididae family<sup>146</sup>) but they have yielded metabolites from a range of classes.

A number of diterpenoid diacylglycerols have been isolated from this family, including the anisodorins 1–5, which were obtained from the skin of the Patagonian species *Anisodoris fontainei* (*Doris fontainii*<sup>405</sup>) along with two further analogues.<sup>146</sup> These last two compounds were previously reported from the same species<sup>147</sup> (but erroneously classified as *Archidors carvi*<sup>146</sup>) and are diastereoisomers of two further diacylglycerols obtained from *Archidoris tuberculata* (*Doris pseudoargus*<sup>409</sup>), collected along the northern Spanish coast.<sup>147</sup> Surprisingly, the isomers from each source display opposite absolute stereochemistry in their terpenoid moiety. The absolute stereochemistry of anisodorin 5, **41** was established through synthesis of its enantiomer<sup>148</sup> and **41** itself has also been synthesised.<sup>149</sup> *Anisodoris nobilis* (*Peltodoris nobilis*<sup>404</sup>) was the source of doridosine,<sup>144</sup> (1-methylguanosine), a hypotensive compound<sup>150</sup> that was also obtained from the Australian sponge *Tedania digitata*.<sup>151</sup> A degraded sesquiterpenoid was obtained from *A. nobilis* as the odoriferous principle.<sup>152</sup>

*Asteronotus cespitosus* specimens collected from Australia and the Philippines contained a range of halogenated

metabolites and two sesquiterpenes.<sup>141</sup> One of these was a novel chlorinated pyrrolidone (**42**), while all of the other metabolites had been previously isolated from *Dysidea herbacea*.<sup>141</sup> Pyrrolidone (**42**) has a similar structure to dysideapyrrolidone,<sup>153</sup> a sponge metabolite.

Isoguanosine, a compound previously isolated as a constituent of the croton bean<sup>154</sup> was obtained from *Diaulula sandiegensis*.<sup>155</sup> A Californian population of *D. sandiegensis* contained a series of nine chlorinated acetylenes, of which **43** is a typical example.<sup>156</sup> Over twenty years later, six of the metabolites were isolated from the sponge *Haliclona lunisimilis* which was collected in the same area as the nudibranchs were originally.<sup>157</sup> The two major metabolites found in *D. sandiegensis* (both ketones) were not present in the sponge, although the corresponding alcohols were, suggesting modification of the alcohols by the nudibranch.<sup>157</sup> Steroidal metabolites, dialusterols A (**44**) and B (**45**), have been isolated from a British Columbian collection of *D. sandiegensis*.<sup>158</sup> Stable isotope experiments indicated that the polyketide chain of **44** was biosynthesised by the nudibranch itself, whereas there was no evidence of uptake in the steroidal nucleus.<sup>159</sup> Radiolabelled incorporation also failed to prove biosynthesis of the steroid nucleus.<sup>159</sup> This suggested that as for *Aldisa cooperi*,<sup>46</sup> a precursor steroid was sequestered and subsequently modified, although a prey species has yet to be identified.<sup>158,159</sup>



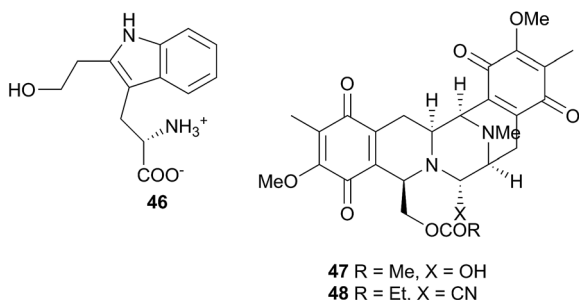
Five species of the *Halgerda* genus collected from various locations around Australia and from Okinawa, Japan were examined. Of these, *H. aurantiomaculata* yielded the new tryptophan derivative halgerdamine (**46**), in addition to four known nitrogenous compounds, while *H. gunnessi* yielded mixtures of acylated tetrasaccharides.<sup>145</sup> No secondary metabolites were detected in *H. theobroma*, *H. rubicunda* (*Sclerodoris rubicunda*<sup>406</sup>) or *H. willeyi*, leading the authors to suggest that these nudibranchs may have evolved to exploit a wider range of food including nontoxic sponges rather than sequestering or synthesising protective compounds.<sup>145</sup> Organic extracts of an Indian specimen





of *H. stricklandi* displayed modest activity to *Staphylococcus aureus* and no activity against a range of other bacterial and fungal species.<sup>160</sup>

*Jorunna funebris* is another nudibranch to yield non terpenoid natural products. Studies of the nudibranch and its prey, sponges of the genus *Xestospongia*, indicate that *J. funebris* sequesters a range of isoquinolinequinones<sup>160–163</sup> and bistetrahydroisoquinolines<sup>162,164,165</sup> from the sponge. Some of the isoquinolinequinones have been synthesised<sup>166</sup> and the metabolites possess a range of biological activities, including antibacterial activity,<sup>161,164</sup> cytotoxicity to HTCLs,<sup>162,164,165</sup> and NF- $\kappa$ B inhibitory activity.<sup>162</sup> Jorumycin (47) was not found in the sponge but was isolated from the mucus and mantle of an Indian collection of *J. funebris*. It exhibited very potent cytotoxicity towards various tumour types but was only available in small quantities due to instability of the carbinolamine moiety.<sup>164</sup> Pretreatment of the nudibranch tissues with potassium cyanide, resulted in isolation of jorunnamycins A–C (C pictured as 48), more stable compounds which retained high cytotoxicity to human tumour cell lines.<sup>165</sup> Zalypsis®, a synthetic compound derived from jorumycin,<sup>167</sup> is currently in Phase II clinical trials for treatment of endometrial and cervical cancer.<sup>168</sup>



Several studies have chemically linked the nudibranch *Peltochordia atromaculata* to its prey sponges *Petrosia ficiformis*<sup>169,170</sup> and *Haliclona fulva*,<sup>171</sup> indicating sequestration of sponge metabolites by *P. atromaculata*, including sterols,<sup>169</sup> the polyacetylene alcohols, petroformynes<sup>170</sup> and fulvinol-related polyacetylenes.<sup>170</sup> One of these last compounds was moderately cytotoxic to the SKMEL-28 melanoma cell line.<sup>171</sup> The lipid and fatty acid content of the related *Platydoris* sp. were examined as part of a study of eight nudibranch species.<sup>39</sup>

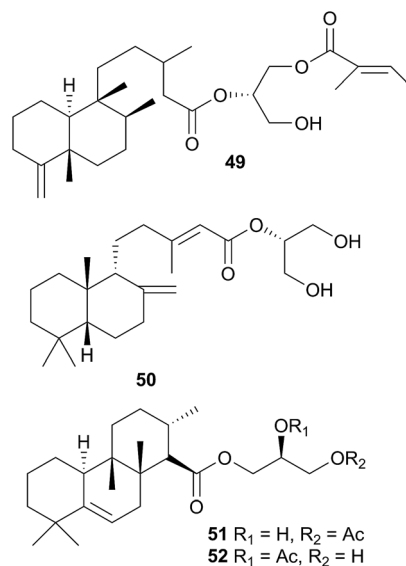
The sesquiterpene glyceride esters, tanyolides A and B were isolated from *Sclerodoris tanya* from Southern California. Located mainly in the mantle of the nudibranch, both deterred feeding by fish predators and were also synthesised.<sup>172</sup> Feeding experiments utilising [2-<sup>13</sup>C]mevalonolactone indicated that *Sclerodoris tanya* is capable of *de novo* biosynthesis of the terpenoid fragment of tanyolide B.<sup>173</sup>

**5.2.5 Dorididae.** The Dorididae family consists of six genera. All Dorididae species originally classified as *Archidoris* and *Austrodoris* have been reclassified as *Doris*<sup>405,407–410</sup> so technically only this genus has been chemically examined, but there have been quite a number of reports published under the original genera names.<sup>147,152,173–180</sup> Given the reclassification, it is unsurprising that terpenoid glyceryl esters have been reported from all three genera and seem to serve as “chemical markers” of the family.<sup>174</sup>

Species originally classified as *Archidoris* have yielded sesquiterpenoid<sup>152,175,176</sup> and diterpenoid acid<sup>147,152,176–178,180</sup> glycerides, in addition to a glyceryl ether.<sup>152</sup> Archidorin (49)<sup>178</sup> is a typical example. Many of these compounds were isolated from the skin or mantle of the nudibranchs and were ichthyotoxic,<sup>147,152,177,178,180</sup> and in one study, were additionally shown to be passed from the adults into the egg masses for protection.<sup>180</sup> Diastereoisomeric variants of some of the diterpenoid acid glycerides were obtained from geographically distinct populations of *Archidoris* nudibranchs<sup>147</sup> and some of these compounds have been synthesised.<sup>174,179</sup> Evidence from biosynthetic feeding experiments indicate that the nudibranchs likely synthesise these molecules *de novo*.<sup>173</sup>

The Antarctic nudibranch *Austrodoris kerguelensis* (*Doris kerguelensis*)<sup>410</sup> has yielded a number of diterpene glycerides with a variety of skeletons, even within one population,<sup>181</sup> including *ent*-labdane,<sup>182,183</sup> labdane,<sup>184</sup> halimane,<sup>184,185</sup> clerodane<sup>184,186,187</sup> and isocopalane<sup>188</sup> frameworks.<sup>186,189</sup> Some norsesquiterpenes<sup>190</sup> have also been isolated from this well-studied species. Of the compounds isolated, some of the diterpene diacylglycerides had feeding deterrent activity against the predatory seastar *Odontaster validus*,<sup>191</sup> some of the clerodane (palmadorins A and B) and labdane (palmadorins M–O) diterpenes were growth inhibitory to human erythroleukemia (HEL) cells and palmadorin M (50) was shown to be apoptotic to these cells.<sup>184</sup> Not surprisingly, as for *Archidoris*, it is thought likely that the above compounds are biosynthesised *de novo* by the nudibranch.<sup>191,192</sup>

The verrucosins are also diterpenoid acid glycerides obtained from *Doris verrucosa*,<sup>193,194</sup> and in addition to ichthyotoxicity, verrucosins A and B (51 and 52) were shown to be potent activators of protein kinase C and to promote tentacle regeneration in the freshwater hydrozoan *Hydra vulgaris*.<sup>195</sup> Biosynthetic feeding experiments with <sup>14</sup>C labelled mevalonic acid and glycerol resulted in poor incorporation into the verrucosins so *de novo* biosynthesis was not proven but good incorporation into sterols did establish that the mevalonate pathway was operative in the nudibranch.<sup>196</sup> A xylosyl thioether, 9-[5'-deoxy-5'(methylthio)- $\beta$ -D-xylofuranosyl]adenine was also obtained from *D. verrucosa*<sup>197–199</sup> and biosynthetic studies indicated that it

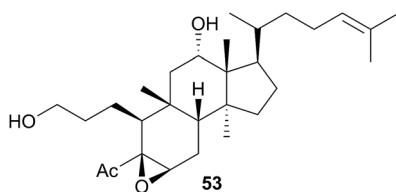


arises in *D. verrucosa* from isomerisation of endogenous 5'-deoxy-5'-methylthioadenosine (MTA).<sup>200</sup>

### 5.3 Onchidoridoidea

The Onchidoridoidea consists of five families but only representatives of the Onchidorididae and the Goniadorididae have been examined for natural products.

**5.3.1 Onchidorididae.** The family Onchidorididae comprises five genera and has been little studied chemically. Only one species from each of two genera (*Acanthodoris* and *Adalaria*) has been examined. *Acanthodoris nanaimoensis* from British Columbia yielded three sesquiterpenoid aldehydes with novel skeletons, nanaimoal,<sup>201</sup> acanthodorol<sup>202</sup> and isoacanthodorane.<sup>202</sup> Biosynthetic studies involving injecting the animals with [1,2-<sup>13</sup>C<sub>2</sub>]acetate, indicated that the compounds were biosynthesised *de novo* by the nudibranchs and a biosynthetic scheme was proposed.<sup>203</sup> A degraded triterpenoid, love-none (53) was isolated from skin extracts of a Norwegian collection of *Adalaria loveni* and displayed modest cytotoxicity to two HTCLs. A dietary origin was suspected, given the lack of any such metabolites in a closely related species.<sup>204</sup>



**5.3.2 Goniadorididae.** The Goniadorididae family comprises eight genera of which only one, *Hopkinsia*, has been examined for natural products. *Hopkinsia rosacea* (*Okenia rosacea*<sup>411</sup>) yielded a seemingly unique apocarotenoid, hopkinsianthin which is similar to the carotenoid fucoxanthin found in marine plants.<sup>205,206</sup> The alkaloid 2,5,6-tribromo-*N*-methylgramine was obtained from the nudibranch *Okenia zoobotryon* and from its bryozoan prey, *Zoobotryon verticillatum*<sup>137</sup> (*Amathia verticillata*<sup>207</sup>).

### 5.4 Phyllidoidea

The Phyllidoidea superfamily comprises three families (Dendrodoridae, Mandeliidae and Phyllidiidae) and is very well studied, although no representatives of the Mandeliidae have been studied to date. All metabolites isolated thus far from this superfamily have been terpenes.

**5.4.1 Dendrodoridae.** Two of the three genera comprising the Dendrodoridae family (*Dendrodoris* and *Doriopsilla*) have been chemically examined. The discovery of *de novo* synthesis of the drimane sesquiterpene polygodial (54) in *Dendrodoris limbata* was the first proven example of biosynthesis in a nudibranch.<sup>208</sup> The antifeeding properties of 54, in conjunction with its localisation solely within the mantle, indicated its defensive role.<sup>208</sup> Surprisingly, 54 was found to be toxic to *D. limbata* if injected directly into the hepatopancreas,<sup>209,210</sup> presumably due to its reactivity with free amino groups.<sup>208,210</sup> It was speculated that a protected form of 54 must be produced in order to facilitate transport throughout the nudibranch. Olepupane

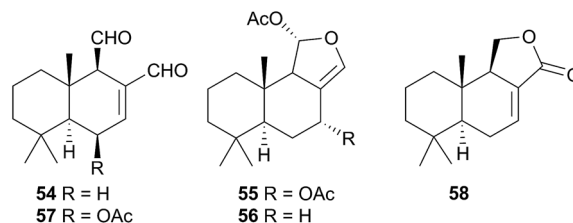
(55) was also found in *D. limbata* and was converted to 54 in the presence of aqueous acid, suggesting that 55 was the protected form.<sup>210</sup> A mixture of three fatty acid esterified sesquiterpenoids isolated from *D. limbata* may offer an alternative storage or handling method of the toxic 54 for the nudibranch.<sup>211</sup>

Biosynthesis of 54 and related compounds has been proven in *Dendrodoris grandiflora* through radiolabelling experiments.<sup>212,213</sup> Whilst 54 was extracted from the mantle, the fatty acid esterified sesquiterpenoids were found in the digestive glands along with a series of known spongian terpenes.<sup>212</sup> Other studies have reported drimane sesquiterpenes from *Dendrodoris carbunculosa*,<sup>214</sup> *D. nigra*, *D. tuberculosa* and *D. krebsii*.<sup>215,216</sup> The anatomical distribution and role that such terpenes may play has been investigated in Mediterranean *Dendrodoris* nudibranchs.<sup>217</sup> The presence of sequestered sponge metabolites might indicate a dual defence for *Dendrodoris* species but they were completely absent from the mantle, where one would expect to find defence allomones. Unlike *Cadlina luteomarginata*, in which it appears *de novo* synthesis is downregulated when sequestered metabolites are available,<sup>48</sup> *D. grandiflora* still utilises its own natural products for defence.

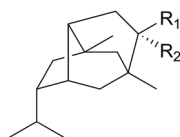
Drimane biosynthesis has also been reported in *Dendrodoris arborescens*, in the form of 56, following radiolabelling studies and another drimane, 6 $\beta$ -acetoxy polygodial (57), was also isolated from the mantle of *D. arborescens*.<sup>213</sup> Feeding experiments with <sup>14</sup>C- and <sup>13</sup>C-labelled glucose on *D. limbata* and *D. grandiflora* indicated that glucose was incorporated into the terpenoid portion of drimanes *via* the standard mevalonate pathway.<sup>218</sup> A more recent study identified the presence of symbiotic bacteria in the outer tissues of *D. nigra* and it was suggested that they could be implicated in defence from predators.<sup>219</sup>

In a New Zealand study, the sesquiterpene cinnamolide (58) was detected in all specimens of *D. denisoni* examined, regardless of geographic location or age, potentially indicating that it was biosynthesised by the nudibranch.<sup>61</sup> Cinnamolide (58) has previously only been obtained from terrestrial plants.<sup>220</sup>

Studies of species of the related *Doriopsilla* genus including *D. albopunctata*<sup>215,216</sup> *D. janaina*,<sup>215</sup> *D. pelseneri*<sup>221</sup> and *D. areolata*<sup>211,222-224</sup> indicated that they also contained drimane sesquiterpenoids, as well as enantiomerically related sesquiterpenoids of the *ent*-palescensin A skeleton.<sup>221-224</sup> Biosynthetic investigations of *D. areolata*<sup>222,223</sup> and *D. pelseneri*<sup>225</sup> indicated that they produce both drimane sesquiterpenoids and sesquiterpenoids with the *ent*-palescensin A skeleton *de novo* and their presence in the mantle of *D. areolata* indicated that they too were involved in the chemical defence of the nudibranch.<sup>222,223</sup>

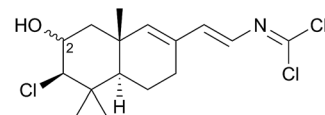


**5.4.2 Phyllidiidae.** Representatives of four of the five genera comprising the Phyllidiidae family (*Phyllidia*, *Phyllidiella*, *Phyllidiopsis* and *Reticulidia*) have been chemically studied. Despite *de novo* synthesis being well documented among the superfamily Phyllidioidea, sequestering of metabolites still occurs, especially within the genus *Phyllidia*. A number of highly bioactive metabolites have been reported from this genus following the isolation of 9-isocyanopupukeanane (**59**) from *P. varicosa*.<sup>226</sup> Evaluating the prey of the nudibranch revealed that **59** was sequestered from a sponge of the *Hymeniacidon* genus. The mucus secreted by *P. varicosa* is concentrated with respect to **59** and is known to be toxic to fish and crustaceans.<sup>226</sup> 2-Isocyanopupukeanane was later isolated from the nudibranch and again shown to be sequestered from a *Hymeniacidon* sp.<sup>227</sup> *epi*-9-Isocyanopupukeanane (**60**) has been reported to co-occur with **59** in *P. bourgini*<sup>228</sup> (*Phyllidiella rosans*<sup>412</sup>). Thiocyno derivatives of these metabolites, **61–62**, have also been isolated from *P. varicosa* and its sponge prey *Axinyssa aculeata* and were noted to be moderately antibacterial.<sup>229</sup> Subsequent studies have found a number of related nitrogenous mono-, bi- and tricyclic sesquiterpenes from *Phyllidia* sp.,<sup>230</sup> *P. varicosa*,<sup>231,232</sup> *P. ocellata*,<sup>232–234</sup> *P. coelestis*,<sup>235</sup> and *P. pustulosa*.<sup>231,232,236,237</sup> *Phyllidia pustulosa* has been reclassified as *Phyllidiella pustulosa*<sup>413</sup> so unsurprisingly, several studies of the animal reported as *Phyllidiella pustulosa* also yielded nitrogenous sesquiterpenes,<sup>238–242</sup> although one additionally yielded nitrogenous diterpenes,<sup>240</sup> which had also been isolated previously from a sponge.<sup>240</sup> *Phyllidiopsis krempfi* also yielded nitrogenous sesquiterpenes and a sesquiterpene peroxide.<sup>232</sup> Potent antifouling activity has been reported for some of these compounds against barnacle larvae<sup>232,237,243,244</sup> and several also possess antimalarial activity against *Plasmodium falciparum*.<sup>234,239</sup> The lipid content of *Phyllidia coelestis*<sup>245</sup> and the fatty acid content of *P. varicosa*<sup>246</sup> and *Phyllidiella pustulosa*<sup>246</sup> have also been examined.

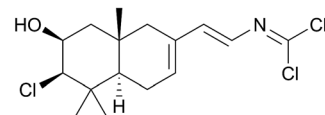


**59** R<sub>1</sub> = NC, R<sub>2</sub> = H  
**60** R<sub>1</sub> = H, R<sub>2</sub> = NC  
**61** R<sub>1</sub> = SCN, R<sub>2</sub> = H  
**62** R<sub>1</sub> = H, R<sub>2</sub> = SCN

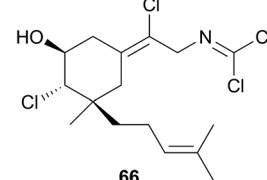
A series of cytotoxic, antifouling sesquiterpenes (**63–66**) was isolated from *Reticulidia fungia*<sup>247</sup> which possess an unique carbonimidic dichloride functionality. Two of the metabolites, reticulidins A (**63**) and B (**64**) are novel to the nudibranch and were moderately cytotoxic to two HTCLS,<sup>247</sup> whilst the other two metabolites (**65** and **66**) had previously been isolated from the sponge *Pseudaxinyssa pitys*.<sup>248,249</sup> The structural similarities to **65**, and the rarity of the carbonimidic dichloride functionality, suggests that **63** and **64** are also likely sequestered from an, as yet unidentified, *Pseudaxinyssa* sponge.



**63** 2(*R*)  
**65** 2(*S*)



**64**

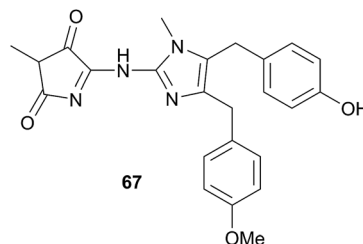


**66**

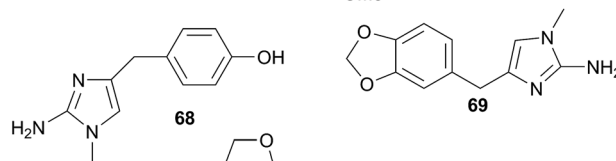
## 5.5 Polyceroidea

Although only three of the five families in the Polyceroidea have been chemically examined, the superfamily represents a remarkably diverse range of dorids that have attracted considerable attention from researchers.

**5.5.1 Aegiridae.** Two genera (*Aegires* and *Notodoris*) comprise the Aegiridae family but only *Notodoris* species have been examined to date. Nudibranchs of this genus, are specialist feeders, known to prey predominantly on sponges of the genus *Leucetta*,<sup>250</sup> and are bright yellow, matching the colour of their sponge prey. The colouration in the sponges is caused by a range of at least 13 imidazole alkaloids<sup>250–253</sup> of which naamidine A (**67**) is a representative metabolite. Many of these compounds have also been isolated from *Notodoris citrina*<sup>250</sup> and *N. gardineri*<sup>251</sup> after feeding on *Leucetta*. In addition, three metabolites only present in the nudibranch were obtained; dorimidazole A (**68**),<sup>251</sup> preclathridine A (**69**) and clathridine B

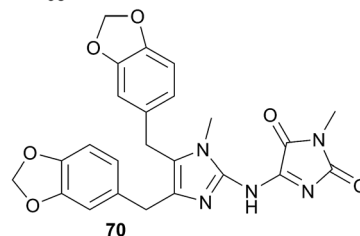


**67**



**68**

**69**



**70**

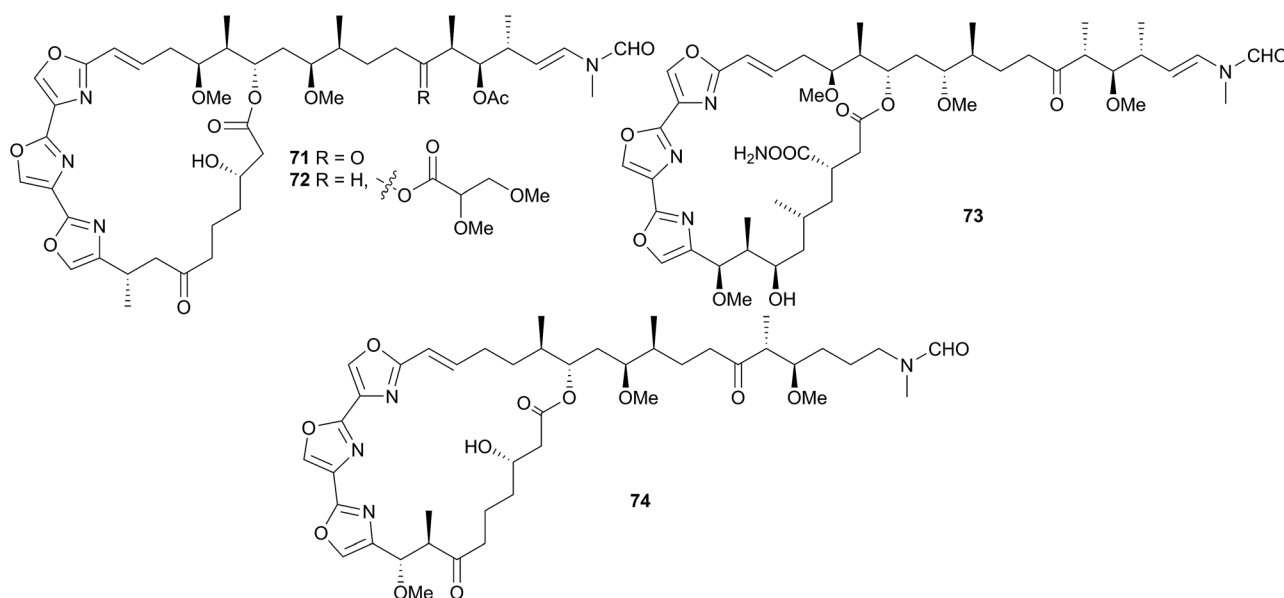


(70).<sup>252</sup> Biosynthesis of these compounds is unlikely, due to structural similarities with other sponge metabolites.<sup>251</sup> Some of these compounds have been found to be antiparasitic<sup>251</sup> and are presumably sequestered by *Notodoris* for this activity.<sup>251</sup>

**5.5.2 Hexabranthidae.** The family Hexabranthidae contains one genus, *Hexabranthus*, which has predominantly, but not exclusively, yielded macrolides. Hawaiian specimens of the bright red “Spanish dancer” nudibranch, *Hexabranthus sanguineus*, have yielded a number of bioactive macrocyclic lactones (macrolides). Ulapualide A (71) and B (72) were isolated from egg masses, in high concentration, and were both cytotoxic (against leukaemia) and antifungal in nature.<sup>254</sup> They were also detected in the nudibranch itself, although at much lower concentrations.<sup>254</sup> Three additional related macrolides, ulapualides C–E were isolated from egg masses of *H. sanguineus*, also obtained from Hawaii. Only ulapualide C was isolated in sufficient quantity for

compounds), is derived from potent depolymerisation of the actin cytoskeleton within cells.<sup>262</sup>

Most of these macrolides are strongly suspected of being of dietary origin as they were found in both the mantle and digestive tracts of the nudibranch.<sup>258</sup> Furthermore, halichondramide<sup>261</sup> and derivatives have been isolated from *Halichondria* sponges and these sponges are known prey species of *H. sanguineus*. Halichondramide itself, is absent in all specimens of *H. sanguineus*, despite being the major metabolite of the sponge,<sup>258,261</sup> so it has been suggested that the nudibranch is either secondarily converting halichondramide into compounds such as 74, or selectively excluding it.<sup>258</sup> Since halichondramide is very cytotoxic (LD<sub>50</sub> in mice when injected subcutaneously is 1.4 mg kg<sup>-1</sup>),<sup>261</sup> it may be too potent for use by *H. sanguineus*.



bioactivity testing and although it exhibited cytotoxicity against several HTCLs, it was 2–4 fold less potent than ulapualides A 71 and B 72.<sup>255</sup>

Other macrolides have also been isolated from *H. sanguineus* and its egg masses from various locations. These include kabiramide C (73)<sup>256–258</sup> and related compounds<sup>256,258–260</sup> and halichondramide derivatives<sup>258,260,261</sup> such as dihydrohalichondramide (74). Ulapualides, kabiramides and halichondramide derivatives possessed a range of bioactivities, including cytotoxicity<sup>254,255,260,261</sup> and antifungal properties<sup>254,256,259,261</sup> and the latter two macrolide families have been shown to deter feeding in both fish (*Thalassoma lunare*) and crabs (*Dardanus megistos*).<sup>258</sup> Macrolides have been found at higher concentrations in egg masses than in the adult nudibranchs,<sup>254,258</sup> suggesting that their main function is to protect these vulnerable egg masses, although it has been postulated that the macrolides are also secreted in the mucus of *H. sanguineus* thus conferring protection on the adult as well.<sup>258</sup> One investigation has highlighted that the bioactivity of 71 (and hence presumably that of related

Hurghadin (75), the red pigment responsible for the colouration of *H. sanguineus*, has been isolated from an Egyptian specimen<sup>263</sup> and as it is a carotenoid, it is almost certainly sequestered. The occurrence of 75 in the mantle follows an inverse relationship with the known macrolides, indicating that it may provide an alternative chemical defence, in addition to acting as a visual warning to potential predators,<sup>263</sup> although with no bioactivity studies conducted on 75, this is only conjecture. The apocarotenoid apoastacenal was isolated from *H. sanguineus* egg masses from Japan<sup>264</sup> as a new natural product (but known synthetic compound).<sup>265</sup>

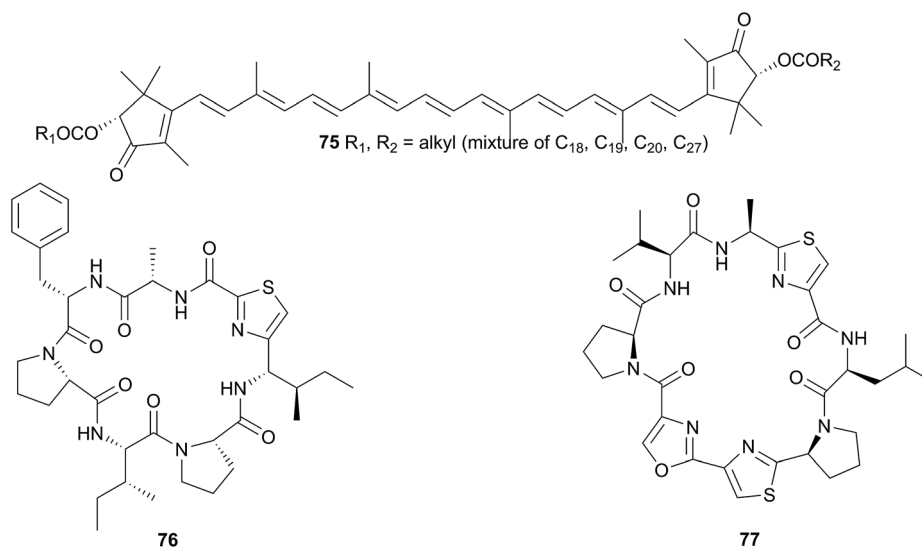
*H. sanguineus* is a generalist feeder on many species of sponge. An adult specimen from the South China Sea was found to contain a mixture of nitrogenous sesquiterpenoids rather than macrolides,<sup>266</sup> two of which were known metabolites from *Axinella*, *Acanthella* and *Dysidea* sponges, and two were novel.<sup>266</sup> However, as both novel compounds were found in the digestive tract of the nudibranch, this suggests that they too are of dietary origin.



A Fijian specimen of *H. sanguineus* analysed by very sensitive NMR spectroscopy (600 MHz spectrometer with a 1 mm high-temperature superconducting cryoprobe), yielded, in addition to a number of related macrolides, two thiazole cyclic peptides, sanguinamide A (76) and sanguinamide B (77).<sup>259</sup> Both 76 and 77 were present at extremely low concentrations across the whole individual (0.0023% and 0.011% dry weight respectively) suggesting that the compounds were not major components in *H. sanguineus* defence and likely represented metabolites of an as yet unidentified prey species.<sup>259</sup> Although no dietary source has been identified for the sanguinamides, the structures suggest that cyanobacteria or tunicates may be their original source.<sup>259</sup> Both 76 (ref. 267) and 77 (ref. 68) have been synthesised; synthesis of the former revised the configuration to (76). Sanguinamide B analogues were active against *Pseudomonas aeruginosa*, reducing twitching motility.<sup>268,269</sup>

predatory nudibranch, feeds upon smaller nudibranchs, preferentially *Tambja abdere* and *T. eliora*, which in turn prey on the bryozoan *Sessibugula translucens*. Tambjamines A–D 78–81 were found in all four organisms, indicating their production by the bryozoan then sequestration and concentration up the food chain.<sup>270</sup>

Tambjamines have also been noted to deter feeding in fish, and thus likely act as a defence against both generalist and specialist feeders.<sup>271</sup> Conversely, the *Tambja* nudibranchs and *R. tigris* have developed the ability to track their respective prey through chemoreception of these same compounds.<sup>271</sup> In the slime trails of *T. abdere*, 78–81 were present at low concentrations, as well as being released in a mucus at relatively high concentrations when *T. abdere* was molested.<sup>270,271</sup> *R. tigris* was noted to track the slime trail of *T. abdere*, but would sometimes break off attack if the mucus was released,<sup>270</sup> indicating that the

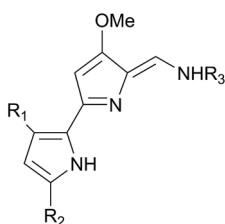


The implication of these studies, is that *H. sanguineus* can sequester a variety of metabolites to utilise in defence and can seemingly do so from a range of prey species.<sup>259,266</sup>

**5.5.3 Polyceridae.** The Polyceridae is comprised of three subfamilies, the Nembrothinae, the Polycerinae and the Triophinae. The Nembrothinae contains three genera, *Nembrotha*, *Tambja* and *Roboastra*, all of which utilise a series of antimicrobial and cytotoxic alkaloids, the tambjamines, which are known to be sequestered metabolites.<sup>270</sup> *Roboastra tigris*, a large

antifeeding properties of the tambjamines still affected *R. tigris* if their concentration was sufficient.<sup>271</sup> In the event that *T. eliora* was attacked, it would attempt to flee rather than secrete a defence, suggesting that the lower concentration of tambjamines in *T. eliora* prevents release of a mucus.<sup>271</sup> Similarly, *T. eliora* preferentially selected low concentrations of tambjamines (consistent with natural concentrations in *S. translucens*) in a Y maze, but was deterred if concentrations were high.<sup>271</sup> Thus the tambjamines, in addition to being an anti-feedant, in *Tambja* species, act as a tracking pheromone at low concentrations and an alarm pheromone at higher concentrations.<sup>271</sup>

Tambjamines, including 78–81 and new variants, have since been reisolated from *T. eliora*<sup>272</sup> and from a bryozoan.<sup>273</sup> A related yellow pigment was obtained from a bacterium<sup>274</sup> and a related blue tetrapyrrole pigment was isolated independently from *Nembrotha kubaryana*,<sup>98</sup> a compound ascidian,<sup>275</sup> a bryozoan<sup>276</sup> and from the predator-prey pairing *Nembrotha* spp. and the ascidian *Atapozoa* sp.<sup>277</sup> and was identical to that produced by a mutant bacterium,<sup>278</sup> indicating that it is likely of bacterial



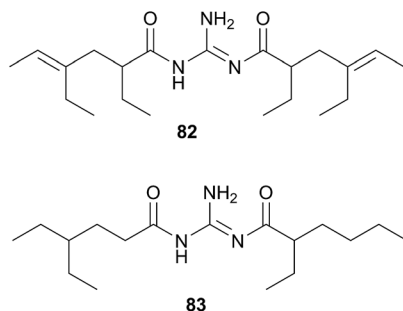
- 78 R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
 79 R<sub>1</sub> = R<sub>3</sub> = H, R<sub>2</sub> = Br  
 80 R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = *i*Bu  
 81 R<sub>1</sub> = Br, R<sub>2</sub> = H, R<sub>3</sub> = *i*Bu



origin in all cases. Tambjamines have also been isolated from several predator-prey pairings; *Tambja ceutae* and the bryozoan *Bugula dentata*,<sup>279</sup> *Tambja stegosauriformis* and *B. dentata*<sup>137</sup> and from *Nembrotha* spp. and the ascidian *Atapozoa* sp.<sup>277,280</sup> Some tambjamines, especially **81**, have been investigated for pharmaceutical uses as they have been shown to be cytotoxic against a number of tumour cell lines.<sup>272,275</sup> Proposed mechanisms for the cytotoxicity include intercalation into DNA as well as the promotion of single-strand DNA oxidative cleavage, although a lack of selectivity for tumour cells over healthy cells has been noted as a prominent obstacle to drug development.<sup>281</sup>

The Triophinae subfamily consists of nine genera of which only two (*Triopha* and *Limacia*) have been chemically examined. Two temperate nudibranchs from this subfamily, *Triopha catalinae* and *Limacia clavigera* also feed exclusively on bryozoans.<sup>282,283</sup> The structurally related triophamine (**82**)<sup>282</sup> and limaciamine (**83**)<sup>283</sup> have been isolated from *T. catalinae* and *L. clavigera* respectively. Unlike the tambjamines, triophamine **82** has been shown to be *de novo* synthesised by *T. catalinae*<sup>284,285</sup> and has also been isolated from a nudibranch in the closely related Polycerinae subfamily, *Polycera tricolor*.<sup>152</sup> The geometry of the double bonds has been determined by total synthesis.<sup>286</sup>

The structural similarities between triophamine **82** and limaciamine **83** has led to speculation that **81** is also biosynthesised,<sup>283</sup> but this has yet to be proven. As no bioactivity studies were conducted on these metabolites, their biological roles can only be speculated upon. The carotenoid triophaxanthin was first isolated as the main pigment of *Triopha carpenteri*<sup>287</sup> (*T. catalinae*<sup>414</sup>) but subsequent isolations from a tunicate<sup>288</sup> and a cuttlefish<sup>289</sup> and its presence in the gut of *T. carpenteri*,<sup>287</sup> indicate that it is dietary in nature.



## 6 Cladobranchs

### 6.1 Aeolidioidea

The superfamily Aeolidioidea, comprises seven families but only two (Aeolidiidae and Facelinidae) have been studied. Despite this, the superfamily has attracted much attention from researchers, largely due to the genus *Phyllodesmium*, the only aeolid genus known not to sequester cnidocysts or nematocysts.<sup>290</sup>

**6.1.1 Aeolidiidae.** Of the nine genera comprising the Aeolidiidae family, a single species of each of three, *Aeolidia*, *Aeolidiella* (*Berghia*<sup>415</sup>) and *Spurilla* has been chemically examined. When *Aeolidia papillosa* ate the sea anemone *Anthopleura elegantissima*, the alarm pheromone from *A. elegantissima*,

anthopleurine, persisted in the nudibranch tissues for over five days. After this time, *Aeolidia papillosa* could evoke alarm responses in anemones without touching them, stimulating them to withdraw the tentacles and oral disk and to leave the body regions with the highest anthopleurine concentrations open to attack.<sup>291</sup> *Aeolidiella stephanieae* (*Berghia stephanieae*<sup>415</sup>) exclusively feeds on glass anemones of the *Aiptasia* genus which usually contain endosymbiotic dinoflagellates that provide nutrients such as fatty acids to their host. A study where breeding pairs of *Berghia stephanieae* were fed with either symbiotic or aposymbiotic *Aiptasia pallida*, revealed differences in the fatty acid profiles of their egg masses.<sup>292</sup> An Argentinian collection of a number of individuals of *Spurilla* sp. revealed that the prey cnidocysts in the nudibranch cerata were highly variable in type and abundance and thus from a variety of sea anemone species.<sup>293</sup>

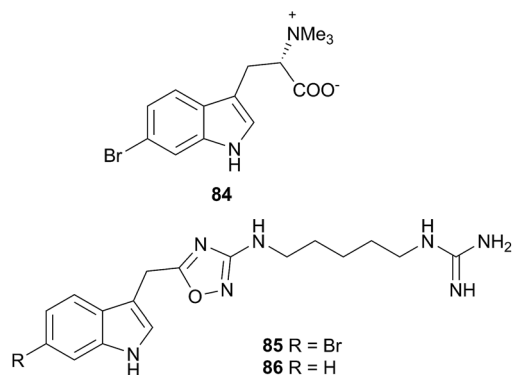
**6.1.2 Facelinidae.** Facelinidae is a large family of nudibranchs comprised of 34 genera. Representatives of just four of these genera (*Cratena*, *Hermisenda*, *Phidiana* and *Phyllodesmium*) have been studied chemically. Some prenylphenols were isolated from the skin of *Cratena peregrina*,<sup>294</sup> two of which were found previously in a brown alga<sup>295</sup> and in the digestive glands of another nudibranch, *Dendrodoris grandiflora*,<sup>212</sup> indicating their dietary origin. Chitin was found in *C. peregrina* (and *Flabellina affinis*) as intracellular granules in skin epidermal cells and the epithelial cells of the stomach.<sup>296</sup> These nudibranchs prey on Cnidaria and the chitin granules are released in response to nematocysts fired by prey tentacles and form aggregates with the nematocyst tubules, thus protecting the animals from the effects of the tentacles. In granular form, the chitin maintains skin flexibility while still conferring protection.<sup>296</sup>

1-6-Bromohypaphorine (**84**) was isolated from *Hermisenda crassicornis* and found to be an agonist of human  $\alpha 7$  nicotinic acetylcholine receptor.<sup>297</sup> A dietary origin of **84** is likely, as the compound has been found in the sponges *Pachymatisma johnstoni*<sup>298</sup> and *Aplysina* sp.,<sup>299</sup> as well as the tunicate *Aplidium conicum*.<sup>300</sup> Whilst *H. crassicornis* is largely considered a generalist feeder, a recent report noted a preference for colonial tunicates in its diet, especially *Aplidium solidum*.<sup>301</sup> It would therefore seem likely that the source of **84** in the nudibranch is from either *A. conicum* itself or another *Aplidium* species.

Two indole alkaloids, phidianidines A (**85**) and B (**86**), were isolated from *Phidiana militaris* and were cytotoxic against a number of cell lines, including C6 and HeLa tumour cells.<sup>302</sup> They remain to date, the only known marine natural products with the 1,2,4-oxadiazole core. The rarity of this backbone, coupled with the total lack of any precursor metabolite in a known prey species, precludes the possibility of *P. militaris* sequestering **85** and **86**. Whilst *de novo* synthesis might therefore be suspected, isotope studies are needed for confirmation. If isotope studies fail to show evidence of biosynthesis, then an unidentified prey species must possess the metabolites, or precursors thereof, or the source could potentially be a symbiotic organism. The biological activity of **85** and **86** coupled with their structural rarity, have led to syntheses of the natural



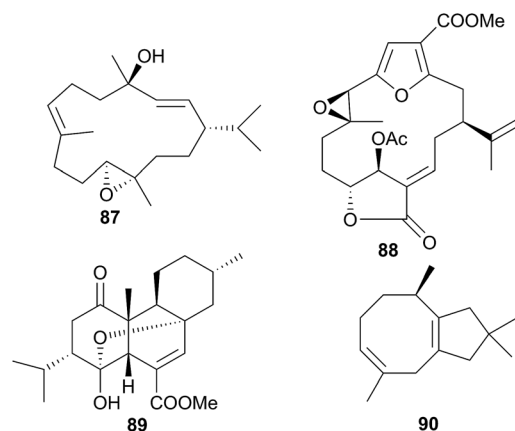
products<sup>303–306</sup> and analogues<sup>307–309</sup> for exploration of their neuroprotective effects.<sup>303–309</sup>



The genus *Phyllodesmium* is the only aeolid genus known not to sequester cnidocysts or nematocysts.<sup>290</sup> Without the physical defence utilised by many aeolids, it might be expected that *Phyllodesmium* sp. would obtain a chemical defence in its place and indeed, this has been shown to be the case.<sup>290,310–312</sup> The cytotoxic diterpene trocheliophorol (**87**) was isolated from *Phyllodesmium longicirra* (*P. longicirrum*<sup>418</sup>) and the soft coral *Sarcophyton trocheliophorum*, upon which it was found.<sup>310</sup> The cerata of the nudibranch were concentrated with **87** and were noted to detach when molested, suggesting that *P. longicirra* was sequestering a defensive metabolite.<sup>310</sup> Similarly, *Phyllodesmium guamensis* (*P. guamense*<sup>416</sup>) was also found grazing upon soft corals; *Sinularia maxima*, *S. polydactyla* and an unidentified *Sinularia* species.<sup>311</sup> The diterpene 11 $\beta$ -acetoxypukalide (**88**) was sequestered from these corals by *P. guamense* and concentrated in its cerata. Diterpene **88** deterred feeding by the predatory pufferfish *Canthigaster solandri* at concentrations lower than those found in the cerata.<sup>311</sup> Four polycyclic diterpenes were isolated from a single specimen of *Phyllodesmium longicirrum* from the Great Barrier Reef, Australia, of which 4-oxochatancin (**89**) deterred feeding by *Canthigaster solandri*.<sup>313</sup> Although the food source of the nudibranch was not collected, it was noted that *P. longicirrum* usually feeds on soft coral of the *Sarcophyton* genus.<sup>313</sup> This, coupled with **89** possessing a planar structure the same as that of isosarcophytin from Indian Ocean *S. elegans*<sup>314</sup> but stereochemistry the same as that of chatacin<sup>315</sup> from an Okinawan *Sarcophyton* sp., means that **89** is very likely a sequestered metabolite.

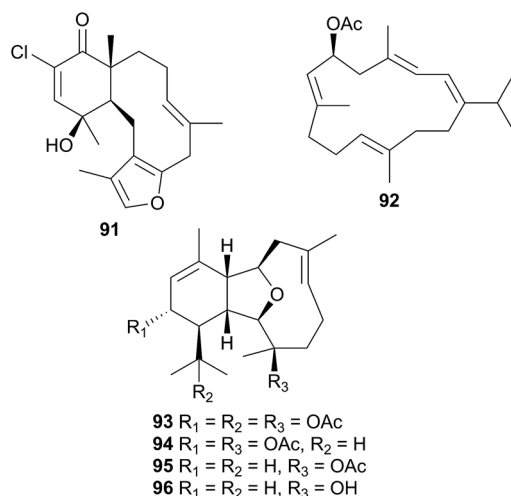
Sesquiterpenes are also sequestered by *Phyllodesmium* aeolids. Those obtained from *P. lizardensis* (*P. lizardense*<sup>417</sup>), were also found at an elevated concentration in the cerata<sup>290</sup> and their dietary source was found to be a coral of the *Heteroxenia* genus. Although these sesquiterpenes were inactive in anti-fungal, antibacterial or anti-algal assays and were not tested for feeding deterrence, a related compound, (+)-6-hydroxy- $\alpha$ -muurolene, has been found to be lethal to brine shrimp.<sup>312</sup> A mixture of eight diverse sesquiterpenes was also isolated from *P. magnum*, including a novel asteriscane terpene (**90**).<sup>316</sup> Of the remaining seven metabolites, four were known from corals of the *Sinularia* genus and three were known from the brown alga *Dictyopteris divaricata*,<sup>316</sup> suggesting sequestration and that *P. magnum* may graze upon corals as well as brown algae. Whilst

**90** was a novel natural product, a more recent study of *Sinularia capillosa* highlighted compounds with similar backbones,<sup>317</sup> indicating that **90** may be a metabolite of an unidentified *Sinularia* sp., or be otherwise secondarily modified, as opposed to being biosynthesised *de novo*.



## 6.2 Arminoidea

Consisting of the two families, Arminidae (seven genera) and Doridomorphidae (one genus), this superfamily has received minimal attention from natural products researchers, with only two species of the Arminidae (*Armina* and *Dermatobranchus*) being investigated to date. A series of seven briarane diterpenes, including the chlorinated example **91**, was isolated from the nudibranch *Armina maculata* and its octocoral prey *Veretillum cynomorium*<sup>318–320</sup> as was a cembranoid, prevrecynarmin (**92**),<sup>320</sup> highlighting that all were of dietary origin for the nudibranch. Similarly, four related diterpenoids, ophirin (**93**), calicophirin B (**94**), 13-deacetoxy calicophirin B (**95**) and 13-deacetoxy-3-deacetyl calicophirin B (**96**), were isolated from the nudibranch *Dermatobranchus ornatus*.<sup>321</sup> Of these, **94** and **95** were subsequently found within a prey species, a gorgonian of the *Muricella* genus.<sup>321</sup> This indicated that these compounds may be of dietary origin, with **93** and **96** being sourced from an unidentified prey species or otherwise secondarily modified.

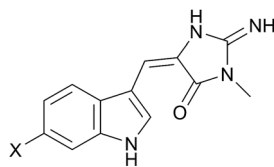


### 6.3 Doridoxoidea

Of the unassigned Cladobranchs, there has been one superfamily designated, the Doridoxoidea which in turn consists of one family (the Doridoxidae) containing one genus (*Doridoxa*). Under former classification systems,<sup>12</sup> Doridoxoidea was not strictly a cladobranch, but evidence emerged to suggest that this superfamily should be included under Cladobranchia,<sup>15</sup> and it is now classified as such.<sup>13</sup> There have been no natural product studies of Doridoxoidea species, possibly as they, like the Bathydoridoidea, are polar, deep water nudibranchs and are thus considerably more difficult to collect.<sup>12</sup>

### 6.4 Fionoidea

This superfamily contains the families Fionidae and Pseudo-vermidae but has barely been examined. A study of *Phestilla melanobranchia* (*Tenellia melanobranchia*<sup>419</sup>) (Fionidae) which feeds on the coral *Tubastrea coccinea*, yielded the known sponge alkaloids, 4'-de-*N*-methylaplysinopsin (**97**) and 6-bromo-4'-de-*N*-methylaplysinopsin (**98**), which were also obtained from the prey coral.<sup>322</sup> A study of *Phestilla sibogae* (*Tenellia sibogae*<sup>420</sup>) highlighted that the nudibranch can track its coral prey through chemoreception using its rhinophores<sup>4</sup> but the study did not involve isolating any metabolites that could potentially be implicated. The researchers noted that the rhinophores responded to various amino acids, with the most intense responses to aspartic and glutamic acids,<sup>4</sup> so suggested that *P. sibogae* tracked corals through amino acids.<sup>4</sup> However, as no natural product investigations have been conducted, the possibility remains that the nudibranch may detect and respond to secondary metabolites in corals that it wishes to sequester. After all, tracking of metabolites is not unprecedented in nudibranchs, as the response of *Roboastra tigris* to the tambjamins highlights (see Section 5.5.3 above).<sup>270</sup>



**97** X = H  
**98** X = Br

### 6.5 Flabellinoidea

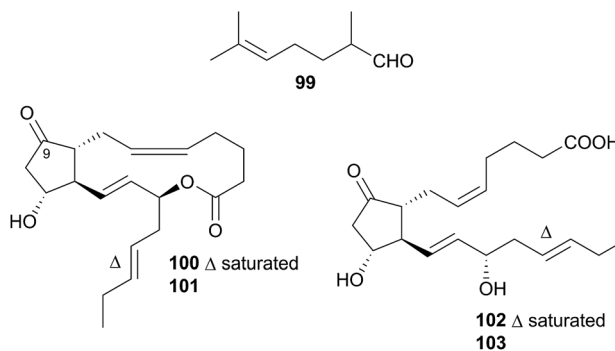
The Flabellinoidea is divided into two families, the Flabellinidae (eight genera including *Flabellina* and *Flabellinopsis*) and the Notaeolidiidae (one genus) but there has been very little chemical research into these nudibranchs. As noted above, chitin was found in skin epidermal cells and the epithelial cells of the stomach of *Flabellina affinis* as intracellular granules.<sup>296</sup> *F. affinis* was also noted to feed and lay its eggs upon several species of hydroid of the *Eudendrium* genus and to contain the same polyhydroxylated sterols as the hydroid but only the major component of this sterol mix was isolated and only from the hydroid.<sup>323</sup> The ubiquitous carotenoid astaxanthin<sup>324</sup> was found in *Flabellinopsis iodina* and its sponge diet.<sup>287</sup>

### 6.6 Tritonioidea

Nudibranchs of this superfamily, sometimes referred to as dendronotoids, are further separated into nine families, of which only two, the Tethydidae (two genera) and the Tritoniidae (nine genera) have received any attention from natural product chemists.

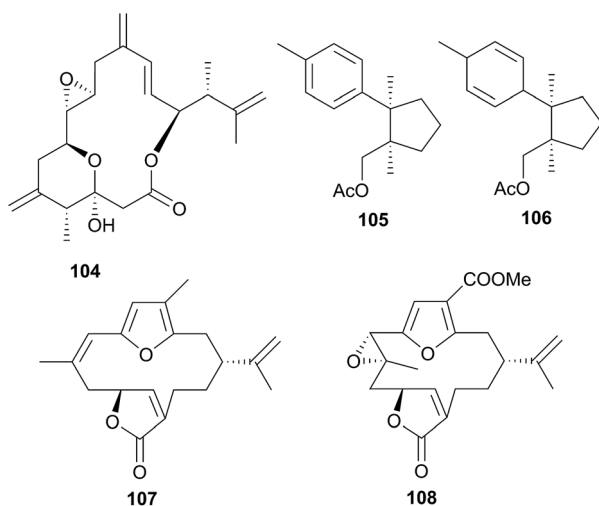
**6.6.1 Tethydidae.** Tethydidae, comprises two genera; (*Melibe* and *Tethys*) and natural product biosynthesis has been observed in both.<sup>325,326</sup> Nudibranchs of this family are unusual in that they do not feed on sessile, benthic organisms, but rather on free swimming planktonic crustaceans.<sup>7,325</sup> They have developed an extended oral veil which acts as a net to sweep up their prey, and are noted to swim freely in the water column.<sup>325</sup> *Melibe leonina* is found along the entire coastline of Northern America and is noted to have a fruity aroma.<sup>327</sup> Degraded terpenoids, 2,6-dimethyl-5-heptenoic acid (a known synthetic compound)<sup>328</sup> and 2,6-dimethyl-5-heptenal<sup>325</sup> (**99**), were isolated from the nudibranch, of which **99** was found to be the source of this scent. *De novo* synthesis was confirmed *via* stable isotope feeding studies.<sup>325</sup> Whilst no bioactivity studies of **99** were conducted, a potential sea star predator (*Pyncnopodia helianthoides*) was repelled upon contact with *M. leonina*.<sup>325</sup> The complete mitochondrial genome of *M. leonina* has recently been determined.<sup>329,330</sup>

Prostaglandin (PG) lactones have been isolated from the related species *Tethys fimbria*<sup>326,331</sup> which is known to synthesise some of these *de novo*.<sup>326,332</sup> These are synthesised from, and act as protected forms of, the free PG acids,<sup>326</sup> compounds known to promote a range of hormonal responses in many organisms. PG molecules are classified by the structure of their central ring system, denoted by a letter, which indicates the membrane protein that the PG will interact with.<sup>333</sup> A subscript indicates the number of double bonds present in the aliphatic side chains. *T. fimbria* synthesises and stores PG lactones of the E class, PGE<sub>2</sub>-1,15-lactone (**100**) and PGE<sub>3</sub>-1,15-lactone (**101**), in its cerata.<sup>326</sup> When molested, *T. fimbria* emits a mucus from its body and cerata and if the cerata become detached, they can continue to release mucus for a number of hours. When molested, the nudibranch converted **100** and **101** back to the free acid forms PGE<sub>2</sub> (**102**) and PGE<sub>3</sub> (**103**) respectively,<sup>326</sup> suggesting that the free acid forms **102** and **103** were being utilised in the nudibranch's defence. PG-lactones of the F series have also been detected in *T. fimbria* (not pictured, but 9(*S*)-hydroxy derivatives of **100** and **101**)<sup>332</sup> but are only present in the ovotestis (hermaphroditic gland of the nudibranch) and not the cerata, indicating that they may play a role in reproduction as opposed to defence.<sup>332</sup>





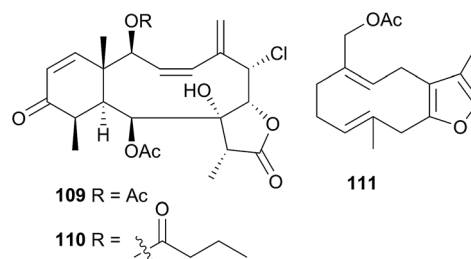
**6.6.2 Tritoniidae.** The most diverse of the Tritinoidea families is Tritoniidae. Comprising nine genera, these nudibranchs are noted to sequester metabolites from their prey.<sup>334,335</sup> The macrolactone amphidinolide P (**104**), was isolated from the octocoral *Stragulum bicolor* and its nudibranch predator *Marionia limceana* from Brazil.<sup>335</sup> Prior to this isolation, **104** has only been isolated from laboratory cultures of the marine dinoflagellate *Amphidinium* sp.<sup>336</sup> but *S. bicolor* appears to host a diverse but so far uncultivable dinoflagellate community and **104** was present in much higher concentration in the octocoral than was reported in *Amphidinium* sp. Although **104** was passed up trophic levels to *Marionia limceana*, no evidence was presented that it was actively sequestered and despite it having been reported as possessing moderate cytotoxicity,<sup>336</sup> **104** was found to be inactive when tested against the HCT-116 cell line in this study.<sup>335</sup>



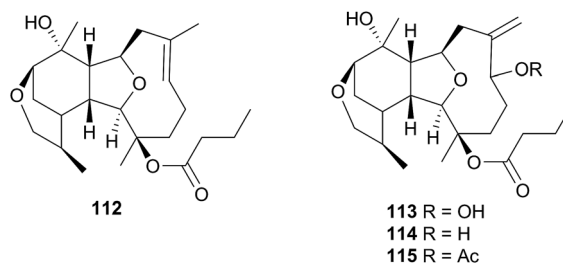
A series of six terpenoid metabolites has been isolated from two nudibranch populations of *Tochuina tetraquetra*<sup>337</sup> (*T. gigantea*<sup>423</sup>). Specimens from Port Hardy, British Columbia were noted to contain tochuinyl acetate (**105**), dihydrotochuinyl acetate (**106**), rubifolide (**107**) and pukalide (**108**). Analysis of a prey species, the soft coral *Gersemia rubiformis*, present at Port Hardy, indicated that **105** and **106** were minor metabolites of this species. Rubifolide **107** had been previously detected in *G. rubiformis*.<sup>338</sup> Whilst a known source of **108** was not found at Port Hardy, it has been previously reported from tropical corals, *Sinularia*,<sup>339</sup> and gorgonians of the genus *Lophogorgia*.<sup>337</sup> A second collection of *T. tetraquetra*, from Bamfield, British Columbia, revealed the diterpenoid ptilosarcenone (**109**) and its butanoate analogue (**110**).<sup>337</sup> The sea pen *Ptilosarcus gurneyi*, a prey species of *T. tetraquetra* in Bamfield waters, is known to produce **109**.<sup>340</sup> As it appears that the nudibranch sequesters natural products from various prey species,<sup>337</sup> it is therefore not surprising that the geographically separated populations possess different compositions of natural products.

*Tritonia hamnerorum* was observed on its prey, the sea fan *Gorgonia ventalina* at very high densities, in the Florida Keys, U.S.A., resulting in the isolation of the furano-germacrene julieannafuran (**111**) from both sea fan and nudibranch. *T. hamnerorum* concentrated **111** relative to other sea fan

metabolites and **111** either significantly reduced or entirely prevented reef fish feeding on the nudibranch in both natural and laboratory environments.<sup>341</sup>



1-O-Hexadecyl glycerol (chimyl alcohol) was detected in the Antarctic nudibranch *Tritoniella belli* and its usual prey, the stoloniferan coral *Clavularia frankliniana*. The common predatory Antarctic sea star *Odontaster validus*, showed feeding deterrence to both *T. belli* mantle tissue and to chimyl alcohol.<sup>342</sup> A series of sesquiterpenes, tritoniopsins A–D (**112**–**115**), were isolated from the nudibranch *Tritoniopsis elegans* and its soft coral prey *Cladiella krempfi*.<sup>334</sup> The major metabolites in both species were found to be **112** and **113** but the relative ratio of these was inverted in the predator-prey pair, such that **112** dominated the *T. elegans* extract and **113** dominated the extract of *C. krempfi*. Tritoniopsin A **112** was concentrated within the mantle tissue of *T. elegans*, to a greater degree than were **113**–**115**, suggesting that **112** plays a defensive role for the nudibranch and that it was preferentially sequestered from the coral. No bioassays were conducted for **112**, but weak to moderate cytotoxicity was observed for tritoniopsin B **113** against a selection of rat cell lines.<sup>334</sup>



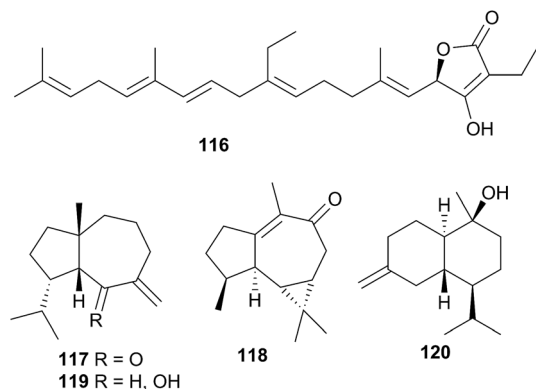
## 6.7 Unassigned families

**6.7.1 Charcotiidae.** Only three of the nine unassigned families have been subject to natural products investigations. The first, Charcotiidae, contains three genera (*Charcotia*, *Leminda* and *Pseudotritonia*) and only the Antarctic nudibranch *Charcotia granulosa* and the tropical nudibranch *Leminda millecra* have been examined chemically. Granuloside (**116**), a homosesterterpene lactone, was isolated from the Antarctic nudibranch *Charcotia granulosa*.<sup>343</sup> Whilst sesquiterpenes are known in some dorid nudibranchs, granuloside (**116**) is the only known linear homosesterterpene in all of nature.<sup>343</sup> It was isolated from the lipophilic extract of the external part of the nudibranch and was absent in the gut and the digestive gland. Additionally, neither **116** nor any related compound was found in the specialist prey of the nudibranch,

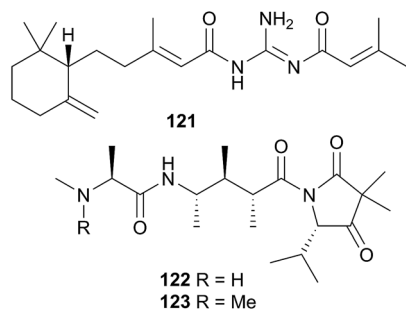


the bryozoan *Beania erecta*, strongly suggesting a *de novo* biosynthetic origin.<sup>344</sup>

*L. millecra* is known to sequester sesquiterpenes.<sup>345,346</sup> Millecrones A (**117**) and B (**118**), as well as millecrols A (**119**) and B (**120**), were isolated from a South African population of *L. millecra*.<sup>345</sup> Analysis of the nudibranch's stomach contents revealed spicules from the soft corals *Alcyonium foliatum*, *A. valdiviae* and *Capnella thyrsoidea*.<sup>345</sup> Limited antimicrobial activity was noted for **117**, **119** and **120**. A separate analysis of another South African population of *L. millecra* and its local prey, identified the dietary origin of **117** and **118**.<sup>346</sup> GC analysis indicated that **117** originated from the soft coral *Alcyonium fauri*, whilst **118** was from the gorgonian *Leptogorgia palma*.<sup>346</sup> At least eleven other sesquiterpenes were detected (structures not shown) in the latter study by GC. These were also expected to be of dietary origin, from various octocoral prey species, due to the backbone common with typical octocoral metabolites.<sup>346</sup> Some of the triprenylated toluquinones and toluhydroquinones obtained from *Leminda millecra* induced apoptosis in oesophageal cancer cell lines.<sup>347</sup>



**6.7.2 Dotidae.** Members of the Dotidae family (comprising four genera) have been reported to feed exclusively on hydrozoans.<sup>348</sup> Only one species from this family has been chemically studied. A Spanish collection of *Doto pinnatifida* yielded dotofide (**121**), a guanidine-interrupted terpenoid<sup>348</sup> but **121** was not found in the hydrozoan *Nemertesia antennina*, the exclusive prey of *D. pinnatifida*, suggesting the likelihood of *de novo* biosynthesis.<sup>348</sup> A new species, *D. carinova* has recently been described and compared with *D. antarctica* but as yet, no chemistry has been reported for either species.<sup>349</sup>



**6.7.3 Proctonotidae.** Of the five genera comprising the Proctonotidae family, only *Janolus* has been studied. The tripeptide janolusimide (**122**) was isolated from the

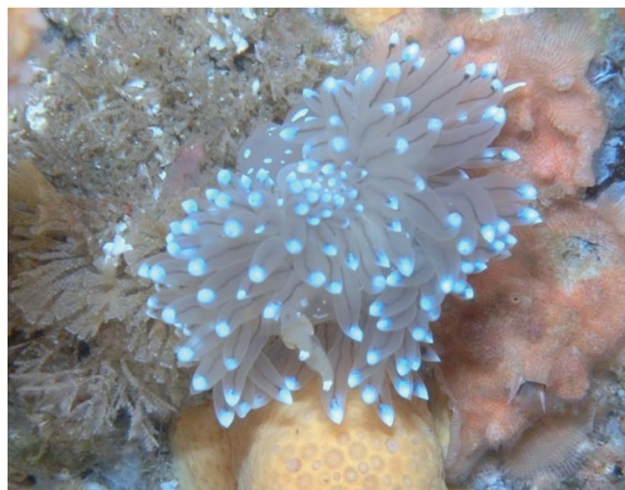


Fig. 3 *Janolus cristatus* feeding on *Bugulina flabellata* in the Shetland Islands. Photograph courtesy of Joanne Porter.

Mediterranean nudibranch *Janolus cristatus*.<sup>350</sup> Janolusimide (**122**) was toxic to mice (LD 5 mg kg<sup>-1</sup>; i.p.) and antagonism of its neurotoxic action at lower concentrations by atropine suggested that **122** affects the acetylcholine receptors.<sup>350</sup> More recently, an *N*-methyl analogue of **122**, janolusimide B (**123**) was isolated from a New Zealand population of the bryozoan, *Bugula flabellata*<sup>351</sup> (*Bugulina flabellata*<sup>352</sup>) from Stewart Island. This bryozoan is native to the British Isles but has since spread to Australasia, the western coastline of the U.S.A. and throughout the Atlantic and Mediterranean. In New Zealand at least, it is considered a fouling "weed" for all intents and purposes.<sup>353</sup> The structural similarity between **122** and **123** suggested an ecological interaction between *J. cristatus* and *B. flabellata*.<sup>351</sup> Indeed, *J. cristatus* is known to feed predominantly on bryozoans, including *B. flabellata* (Fig. 3).<sup>354</sup> However, as **122** was never identified in the bryozoan, and **123** was never found in the nudibranch, it was unclear if *J. cristatus* sequestered **122** from its diet or secondarily modified it from **123**.

A subsequent investigation into a different New Zealand population of *B. flabellata* found evidence of both **122** and **123** within the bryozoan.<sup>355</sup> Small scale extraction of New Zealand collections of *Janolus novozealandicus* and *Bugulina flabellata* and screening of the extracts by tandem liquid chromatography mass spectrometry (LCMS) indicated the presence of both **122** and **123** and suggested the presence of a series of at least six related tripeptides. The relative abundance of **122** and **123** is inverted within *J. novozealandicus* (**122** dominant) with respect to *B. flabellata* (**123** dominant) suggesting preferential uptake of **122**. An egg mass of *J. novozealandicus* was also extracted and screened and of the two tripeptides, only **122** was found (as the main metabolite), highlighting its potential role as a defensive compound,<sup>355</sup> although further studies are needed to confirm this.

## 7 Nematocysts and zooxanthellae

Sequestration of whole organisms (zooxanthellae) or nematocysts by some aeolid nudibranchs has been given its own



section as, strictly speaking, it is not natural products chemistry. Nevertheless these processes deserve a brief mention. As has already been noted, virtually all aeolid species except those of the *Phyllodesmium* genus are known to sequester the stinging cells from their cnidarian prey.<sup>9,290</sup> The nematocysts are taken up by the aeolids and transported to the tips of cerata where multiple cells are incorporated into a single cnidosac.<sup>9</sup> The use of a cnidosac is almost certainly in defence, as aeolids which have had their cerata removed are considerably more likely to be consumed. In most species, the cerata are also known to regenerate, indicating that they serve an important function to the aeolids.<sup>9</sup> The exact mechanisms by which the nudibranch is able to protect itself from the sting of these cells are not fully understood.<sup>9,356</sup> The presence of epithelial linings within the viscera has been observed and noted to absorb the damage from a discharged nematocyst, thus protecting the nudibranch.<sup>9</sup> Application of aeolid mucus to the sea anemone *Anthopleura elegantissima* lowered the number of nematocyst discharges, with respect to mucus of other nudibranchs.<sup>9</sup> This highlighted that aeolids used multiple strategies to cope with the stinging cells. A relatively recent study tested the hypothesis that aeolids transfer immature nematocysts to the cnidosacs and then allow them to mature, thus avoiding the potential damage caused by transporting a charged nematocyst.<sup>356</sup> Utilising a fluorescent dye, researchers were able to show that there was a change in pH as the nematocysts were incorporated into the cnidosacs. As an accumulation of protons is necessary for nematocysts to mature, this supported the hypothesis that aeolids themselves were maturing the nematocysts.<sup>356</sup>

Whilst sequestration of nematocysts is common in all aeolids except those of *Phyllodesmium*, an interesting symbiotic relationship has been observed in a number of cladobranchs. Zooxanthellae, photosynthetic dinoflagellates, are frequently found within the cells of cladobranchs' branched digestive gland.<sup>357</sup> This symbiosis has been observed in a number of *Phyllodesmium* species and may highlight why this genus does not sequester nematocysts.<sup>357,358</sup> Aeolids of the *Phestilla* (*Tenellia*<sup>419,420</sup>) (Fionidae family) and *Pteraeolidia* (Facelinidae family) have also been noted to possess zooxanthellae symbionts. A number of non-aeolid cladobranchs also obtain these symbiotic organisms, namely the dendronotoids of *Melibe* and *Doto* genera as well as *Doridomorpha gardineri* (Doridomorphidae family) and *Pinufius rebus* (unassigned Cladobranchia, Superfamily Arminoidea, Family Pinufidae).<sup>357,358</sup> The advantages offered to these cladobranchs are obvious, in that the transfer of (primary) metabolites can enhance survivability if food is scarce.<sup>357</sup> Interestingly, there have been no reported cases of zooxanthellae symbiosis within any of the dorid nudibranchs. This is presumably because their unbranched digestive gland and lack of cerata (or similar projections) limits the available surface area for zooxanthellae photosynthesis.

## 8 Conclusions

The natural products chemistry of nudibranchs is extensive and well documented. Terpenes and sesquiterpenes in particular,

dominate those metabolites that have been isolated, although virtually all classes of natural products are represented. The sequestering of these metabolites from prey species is seemingly the most common source of nudibranch natural products. Indeed, metabolites have been sequestered from sponges, corals, tunicates, gorgonians and bryozoans. Whilst *de novo* synthesis is rarer than sequestration of natural products, it can still be found throughout all of Nudibranchia. Secondary modification is also suspected in a number of cases. Unsurprisingly, terpenes still dominate the types of structures observed.

It is certainly true that dorids have received considerably more research attention than their cladobranch counterparts. This is perhaps due to a perceived notion that cladobranchs, especially aeolids, utilise a physical defence (cnidosacs) over a chemical one. Furthermore, many dorids are known to feed exclusively on sponges, and sponges themselves are known to be the most prolific producers of marine natural products,<sup>36c</sup> so the natural products chemistry of those dorids that feed on sponges might also be expected to be rich in metabolites. However, as this review has highlighted, natural products are found within all branches of Cladobranchia (that have been studied). *De novo* synthesis is known within the dendronotoids and suspected in some aeolids. There have even been reports of unprecedented novelty, including the first examples of marine metabolites with a 1,2,4-oxadiazole core (**85** and **86**)<sup>302</sup> as well as the first known linear homosesterterpene (**116**).<sup>343</sup> These examples challenge the historical notion that the dorids represent the greatest source of nudibranch natural products. In light of this, more investigations into cladobranchs should be conducted moving forwards.

Even within the dorid nudibranchs, there has been an uneven allocation of research attention. Certainly the Doridoidea are well represented but many of these investigations are from species of a single genus, *Chromodoris*. Similarly, *Hexabranchnus sanguineus*, has received considerable attention but no reports into other *Hexabranchnus* species have been carried out. This preference of some superfamilies and some species over others means that there are still many nudibranchs to be properly studied. Perhaps the biggest message to be gained from this review, is that very few natural products have proven ecological roles. Indeed in some cases, only structures have been reported with absolutely no consideration for their bioactivity. Of all the metabolites presented within this review for which an ecological role is known or suspected, all but the PGF-lactones isolated from *Tethys fimbria*, are used in defence. Although the defensive capabilities of natural products are assumed in many cases, very few have been shown to actually deter predation. However, proving a chemical ecological role is not a simple task. Typically this requires dissection of the nudibranch into its mantle, viscera and other parts, instead of whole organism extraction, as well as conducting a number of antifeeding tests and bioassays. In many cases, natural product investigations are pharmaceutically driven and the chemical ecology is only of secondary interest. Thus, extensive ecological studies are relatively rare in the literature, given the time and amount of metabolite required to adequately perform these experiments.



Table 1 Current classification (WoRMS) of nudibranchs covered in this review

Reported					
Superfamily	Family	Subfamily	Genus	Species	Reclassification or (correction)
<b>Dorids</b>					
Bathydoridoidea	Bathydorididae		<i>Bathydoris</i>	<i>hodgsoni</i>	
Doridoidea	Actinocyclusidae		<i>Actinocyclus</i>	<i>papillatus</i>	
	Cadlinidae		<i>Aldisa</i>	<i>andersoni</i>	
				<i>sanguinea cooperi</i>	<i>Aldisa cooperi</i> <sup>359</sup>
				<i>smaragdina</i>	
			<i>Cadlina</i>	<i>laevis</i>	
				<i>luteomarginata</i>	
				<i>pellucida</i>	
	Chromodorididae		<i>Ardeadoris</i>	<i>egretta</i>	
			<i>Casella</i>	<i>atromarginata</i>	<i>Doriprismatica atromarginata</i> <sup>360</sup>
			<i>Ceratosoma</i>	<i>amoena</i>	<i>Ceratosoma amoenum</i> <sup>361</sup>
				<i>brevicaudatum</i>	
				<i>gracillimum</i>	
				<i>trilobatum</i>	
			<i>Chromodoris</i>	<i>albonotata</i>	
				<i>albopunctata</i>	<i>Goniobranchus albopunctatus</i> <sup>362</sup>
				<i>annulata</i>	<i>Goniobranchus annulatus</i> <sup>363</sup>
				<i>cavae</i>	<i>Goniobranchus cavae</i> <sup>364</sup>
				<i>elisabethina</i>	
				<i>epicura</i>	
				<i>funerea</i>	<i>Chromodoris lineolata</i> <sup>365</sup>
				<i>geminus</i>	<i>Goniobranchus geminus</i> <sup>366</sup>
				<i>geometrica</i>	<i>Goniobranchus geometricus</i> <sup>367</sup>
				<i>gleniei</i>	<i>Goniobranchus gleniei</i> <sup>368</sup>
				<i>hamiltoni</i>	
				<i>inopinata</i>	
				<i>inornata</i>	<i>Chromodoris aspersa</i> <sup>369</sup>
				<i>kuniei</i>	<i>Goniobranchus kuniei</i> <sup>370</sup>
				<i>lochi</i>	
				<i>luteorosea</i>	<i>Felimida luteorosea</i> <sup>371</sup>
				<i>macfarlandi</i>	<i>Felimida macfarlandi</i> <sup>372</sup>
				<i>maridadilus</i>	<i>Hypselodoris maridadilus</i> <sup>373</sup>
				<i>marislae</i>	<i>Felimida marislae</i> <sup>374</sup>
				<i>michaeli</i>	
				<i>norrisi</i>	<i>Felimida norrisi</i> <sup>375</sup>
				<i>obsoleta</i>	<i>Goniobranchus obsoletus</i> <sup>376</sup>
				<i>petechialis</i>	<i>Goniobranchus petechialis</i> <sup>377</sup>
				<i>quadricolor</i>	
				<i>reticulata</i>	<i>Goniobranchus reticulatus</i> <sup>378</sup>
				<i>sedna</i>	<i>Doriprismatica sedna</i> <sup>379</sup>
				<i>sinensis</i>	<i>Goniobranchus sinensis</i> <sup>380</sup>
				<i>tinctoria</i>	<i>Goniobranchus tinctorius</i> <sup>381</sup>
				<i>willani</i>	
				<i>youngbleuthi</i>	<i>Glossodoris rufomarginata</i> <sup>382</sup>
			<i>Felimida</i>	<i>grahami</i>	<i>(Felimare grahami)</i> <sup>383</sup>
			<i>Glossodoris</i>	<i>atromarginata</i>	<i>Doriprismatica atromarginata</i> <sup>360</sup>
				<i>averni</i>	<i>Ardeadoris averni</i> <sup>384</sup>
				<i>cincta</i>	
				<i>dalli</i>	<i>Felimida dalli</i> <sup>385</sup>
				<i>hikuerensis</i>	
				<i>pallida</i>	
				<i>quadricolor</i>	<i>Chromodoris quadricolor</i> <sup>386</sup>
				<i>rufomarginata</i>	
				<i>sedna</i>	<i>Doriprismatica sedna</i> <sup>379</sup>
				<i>tricolor</i>	<i>Felimare tricolor</i> <sup>387</sup>
				<i>valenciennesi</i>	<i>Felimare picta</i> <sup>388</sup>
				<i>vespa</i>	
			<i>Goniobranchus</i>	<i>albonares</i>	
				<i>collingwoodi</i>	
				<i>daphne</i>	
				<i>splendidus</i>	



Table 1 (Contd.)

Reported					
Superfamily	Family	Subfamily	Genus	Species	Reclassification or (correction)
			<i>Hypselodoris</i>	<i>verrieri</i> <i>agassizii</i> <i>californiensis</i> <i>cantabrica</i> <i>daniellae</i> <i>fontandraui</i> <i>ghiselini</i> <i>godeffroyana</i> <i>infucata</i> <i>jacksoni</i> <i>lajensis</i> <i>orsinii</i> (i) <i>porterae</i> <i>tricolor</i> <i>villafranca</i> <i>webbi</i> <i>zebra</i>	<i>Felimare agassizii</i> <sup>389</sup> <i>Felimare californiensis</i> <sup>390</sup> <i>Felimare cantabrica</i> <sup>391</sup> <i>Thorunna daniellae</i> <sup>392</sup> <i>Felimare fontandraui</i> <sup>393</sup> <i>Felimare ghiselini</i> <sup>394</sup> <i>Risbecia godeffroyana</i> <sup>395</sup>  <i>Felimare lajensis</i> <sup>396</sup> <i>Felimare orsinii</i> <sup>397</sup> <i>Felimare porterae</i> <sup>398</sup> <i>Felimare tricolor</i> <sup>387</sup> <i>Felimare villafranca</i> <sup>399</sup> <i>Felimare picta</i> <sup>400</sup> <i>Felimare zebra</i> <sup>401</sup>
			<i>Miamira</i>	<i>magnifica</i> <i>miamirana</i>	
	Discodorididae		<i>Risbecia</i> <i>Tyrinna</i> <i>Anisodoris</i>	<i>tryoni</i> <i>nobilis</i> <i>nobilis</i> <i>fontainei</i>	<i>Hypselodoris tryoni</i> <sup>402</sup> <i>Tyrinna delicata</i> <sup>403</sup> <i>Peltodoris nobilis</i> <sup>404</sup> <i>Doris fontainii</i> <sup>405</sup>
			<i>Asteronotus</i> <i>Diaulula</i> <i>Halgerda</i>	<i>cespitosus</i> <i>sandiegensis</i> <i>aurantiomaculata</i> <i>gunnessi</i> <i>rubicunda</i> <i>stricklandi</i> <i>theobroma</i> <i>willeyi</i>	<i>Sclerodoris rubicunda</i> <sup>406</sup>
	Dorididae		<i>Jorunna</i> <i>Peltodoris</i> <i>Platydorid</i> <i>Sclerodoris</i> <i>Archidoris</i> <i>Neodoris</i> <i>Archidoris</i>	<i>funebri</i> <i>atromaculata</i> sp. <i>tanya</i> <i>carvi</i> <i>carvi</i> <i>montereyensis</i> <i>odhneri</i> <i>pseudoargus</i> <i>tuberculata</i>	<i>Doris fontainii</i> <sup>405</sup> <i>Doris fontainii</i> <sup>405</sup> <i>Doris montereyensis</i> <sup>407</sup> <i>Doris odhneri</i> <sup>408</sup> <i>Doris pseudoargus</i> <sup>409</sup> <i>Doris pseudoargus</i> <sup>409</sup> <i>Doris kerguelenensis</i> <sup>410</sup>
Onchidoridoidea	Goniodorididae		<i>Austroдорis</i> <i>Doris</i> <i>Hopkinsia</i> <i>Okenia</i>	<i>keruelenensis</i> <i>verrucosa</i> <i>rosacea</i> <i>zoobotryon</i>	<i>Okenia rosacea</i> <sup>411</sup>
	Onchidorididae		<i>Acanthodoris</i> <i>Adalaria</i>	<i>nanaimoensis</i> <i>loveni</i>	
Phyllidioidea	Dendrodorididae		<i>Dendrodoris</i>	<i>arborescens</i> <i>carbunculosa</i> <i>denisoni</i> <i>fulva</i> <i>grandiflora</i> <i>krebsii</i> <i>limbata</i> <i>nigra</i> <i>tuberculosa</i>	
			<i>Doriopsilla</i>	<i>albopunctata</i> <i>areolata</i> <i>janaina</i> <i>pelseneeri</i>	
	Phyllidiidae		<i>Phyllidia</i>	<i>bourgini</i> <i>coelestis</i>	<i>Phyllidiella rosans</i> <sup>412</sup>



Table 1 (Contd.)

Reported										
Superfamily	Family	Subfamily	Genus	Species	Reclassification or (correction)					
Polyceroidea	Aegiridae	Nembrothinae	<i>Phyllidiella</i> <i>Phyllidiopsis</i> <i>Reticulidia</i> <i>Notodoris</i>	<i>ocellata</i>	<i>Phyllidiella pustulosa</i> <sup>413</sup>					
				<i>pulitzeri</i>						
	<i>pustulosa</i>									
	<i>varicosa</i>									
	<i>rosans</i>									
	<i>kremphi</i>									
	<i>fungia</i>									
	<i>citrina</i>									
	<i>gardineri</i>									
	<i>sanguineus</i>									
Hexabranthidae	Polyceridae	Polycerinae	<i>Hexabranthus</i> <i>Nembrotha</i> <i>Roboastra</i> <i>Tambja</i>	<i>kubaryana</i>	<i>Triopha catalinae</i> <sup>414</sup>					
				<i>tigris</i>						
<i>abdere</i>										
<i>ceutae</i>										
<i>eliora</i>										
<i>stegosauriformis</i>										
<i>tricolor</i>										
<i>clavigera</i>										
<i>carpenteri</i>										
<i>catalinae</i>										
Cladobranchs	Aeolidioidea	Aeolidiidae	<i>Aeolidia</i> <i>Aeolidiella</i> <i>Spurilla</i>	<i>papillosa</i>	<i>Berghia stephanieae</i> <sup>415</sup>					
				<i>stephanieae</i>						
Aeolidioidea	Facelinidae	Polycerinae	<i>Cratena</i> <i>Hermisenda</i> <i>Phidiana</i> <i>Phylloidesmium</i>	sp.	<i>(Phylloidesmium guamense)</i> <sup>416</sup> <i>(Phylloidesmium lizardense)</i> <sup>417</sup> <i>(Phylloidesmium longicirrum)</i> <sup>418</sup>					
				<i>peregrina</i>						
				<i>crassicornis</i>						
				<i>militaris</i>						
				<i>guamensis</i>						
				<i>lizardensis</i>						
				<i>longicirra</i>						
				<i>magnum</i>						
				Arminoidea		Arminidae	Doridomorphae	<i>Pteraeolidia</i> <i>Armina</i> <i>Dermatobranchus</i> <i>Doridomorpha</i>	<i>maculata</i>	<i>Tenellia melanobranchia</i> <sup>419</sup> <i>Tenellia sibogae</i> <sup>420</sup>
									<i>ornatus</i>	
Doridoxoidea	Fionoidea	Fionidae	<i>Phestilla</i>	<i>melanobranchia</i>						
				<i>sibogae</i>						
Flabellinoidea	Flabellinidae	Tethydoidea	<i>Flabellina</i> <i>Flabellinopsis</i>	<i>affinis</i>	<i>Flabellina iodinea</i> <sup>421</sup>					
				<i>iodinea</i>						
Tritonioidea	Tethyidae	Tritoniidae	<i>Melibe</i> <i>Tethys</i> <i>Marionia</i> <i>Tritonia</i>	<i>leonina</i>	<i>Tritonia tetraquetra</i> <sup>422</sup>					
				<i>fimbria</i>						
	<i>limceana</i>									
	<i>diomedea</i>									
Tritonioidea	Tritoniidae	Tritoniidae	<i>Tritoniella</i> <i>Tritoniopsis</i> <i>Tochuina</i>	<i>hammerorum</i>	<i>Tochuina gigantea</i> <sup>423</sup>					
				<i>belli</i>						
Unassigned Families	Charcotiidae	Dotidae	<i>Charcotia</i> <i>Leminda</i> <i>Doto</i>	<i>granulosa</i>	<i>granulosa</i> <i>millecra</i> <i>antarctica</i> <i>carinova</i> <i>pinnatifida</i> <i>rebus</i> <i>cristatus</i> <i>novozelandicus</i>					
				<i>millecra</i>						
Unassigned Families	Dotidae	Pinufidae	<i>Pinufius</i> <i>Janolus</i>	<i>antarctica</i>						
				<i>carinova</i>						
Unassigned Families	Proctonotidae	Pinufidae	<i>Pinufius</i> <i>Janolus</i>	<i>pinnatifida</i>						
				<i>rebus</i>						
Unassigned Families	Proctonotidae	Pinufidae	<i>Pinufius</i> <i>Janolus</i>	<i>cristatus</i>						
				<i>novozelandicus</i>						



## 9 Conflicts of interest

There are no conflicts to declare.

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