REVIEW

Natural-Product Diversity of the New Caledonian Marine Ecosystem Compared to Other Ecosystems: A Pharmacologically Oriented View

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Dedicated to the memory of *Jean-Pierre Guemas*

In comparison with other ecosystems, biodiversity and natural-product diversity of the New Caledonian marine ecosystem, comprising lagoons, barrier reefs, and deep waters in seamount regions, are described here phylogenetically with the aid of molecular drawings and tabulation of data. Admittedly, since the inception of these studies in 1977, the comparison is biased by selection of New Caledonian organisms on the basis of positive pharmacologically oriented bioassays. However, we show that these and other distortions must be accepted to draw any comparison on a regional basis, which, nonetheless, turn out to be useful for the progress of knowledge, particularly in directing future explorations of biodiversity in the search for new pharmacologically active metabolites.

1. Introduction. – New Caledonia and its economic dependencies constitute a peculiar marine ecosystem that lies on the eastern edge of the Indo-Australian continental plate, 1,500 km away from the coast of Queensland, extending for more than 1,700,000 km^2. The morphology of the seabed in this region is extremely multifaceted, and varied structures occur. The main island, Grande Terre, and the adjacent islands, Pines Island to the southeast and Belep Islands to the northwest, are an emerged portion of the Norfolk Ridge, a geosyncline, dating from the Mesozoic that extends to New Zealand (*Figure*) [1]. Far to the west of the Grande Terre lies the Lord Howe Ridge. This is an underwater and emergent relief of volcanic origin that comprises the Chesterfields, Bellona, Nova, Argo, Kelso, and Capel banks. The Lansdowne and Fairway banks, which are forms of submerged atolls, lie in between. Northeast of the Grande Terre, the Loyalty Islands Ridge, made up of Ouvéa, Lifou, Maré, and Walpole Islands, borders the subduction zone where the Indo-Australian plate sinks beneath the Pacific plate. A trench as deep as 7,000 m separates the Loyalty Islands Ridge from the volcanic archipelago of Vanuatu (*Figure*).

The geological events that shaped the earth, from about 180 million years ago – when Laurasia started separating from the sole existing continent, Pangea, in the uninterrupted Panthalassa that circled the earth – until 15 million years ago, when India became fused to Asia and Australia moved to its present position, help us to understand the decrease in biodiversity and natural-product diversity on moving eastward from the Great Barrier Reef [2a]. Consequently, the stable conditions of southwestern Pacific

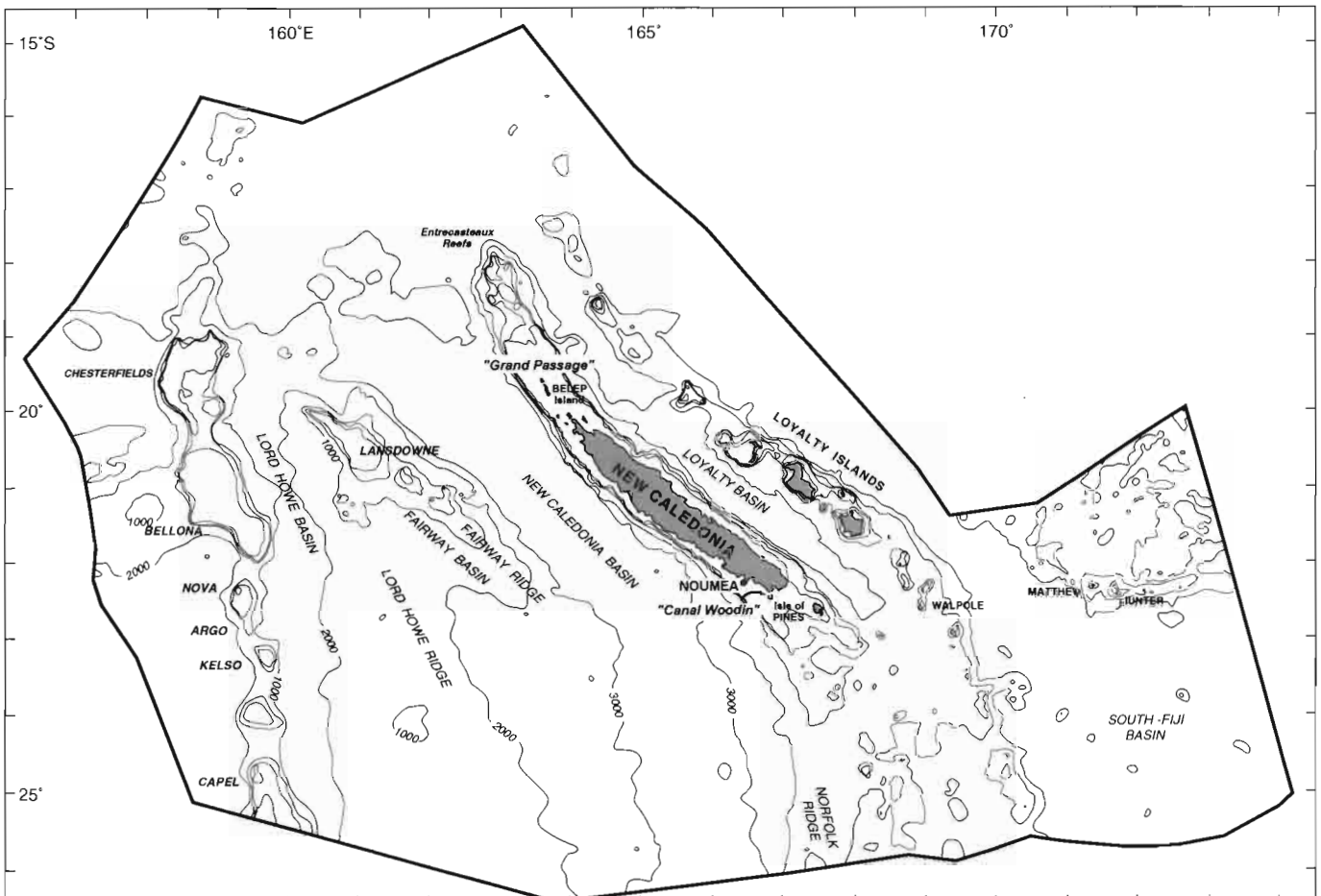

Figure. *Bathymetric map of the exclusive economic zone of New Caledonia* (depths in meters), *adapted from 'Carte bathymétrique de la Zone Economique Exclusive de la Nouvelle-Calédonie', 3 coupures, échelle 1/1 095 708 à l'équateur, projection Mercator WGS 72* (F. Missegue, J. Dupont, J. Daniel) [1]

seamounts along a line from New Zealand to the Philippines [2b] favored the conservation of a fauna of early invertebrates that are rich in long-living endemic biodiversity, including 'living fossils' [3a], in contrasts to the ephemeral life of hydrothermal vents [2b].

The New Caledonian Economic Zone is also an area of lagoons and barrier reefs. The lagoon of the Grande Terre has a surface of 40,000 km^2 and a barrier reef that extends for 1,600 km. Second in size only to the Great Barrier Reef, it is more accessible, with the external barrier lying only 10–12 km from the coast. Depths in the lagoon do not exceed 50 m. This allows diving with normal scuba equipment all year long.

The first marine natural product research program in New Caledonia (*SNOM, Substances Naturelles d'Origine Marine*) was started by *Pierre Potier* in 1977. This tripartite program between a research-oriented pharmaceutical company, *Rhône Poulenc*, and research institutions, *CNRS* and *ORSTOM*[1]), was aimed at isolating metabolites of pharmacological interest from the lagoon's marine invertebrates. Five years later, it was superseded by *SMIB* (*Substances Marines d'Intérêt Biologique*), a program involving mainly *ORSTOM* and *CNRS*, in collaboration with other national research institutions (*CEA*, *INSERM*, and *MNHN*)[1]), and French and foreign universities. Although bioactivity remained the central theme, this multidisciplinary program was extended to studying the biodiversity and natural-product diversity of invertebrates from the lagoon, reefs, and seamounts. The biologists of the Oceanography Laboratory of *ORSTOM* in Nouméa, *MNHN* in Paris, and foreign institutions, aided by the *ORSTOM* team of professional divers for shallow-water exploration and vessels for deep-water dredging campaigns[2]), started a taxonomic evaluation that is documented in handbooks on echinoderms [5a], ascidians [5b], sponges [3a], and gorgonaceans [5c], while that on alcyonaceans is in preparation. Many novel secondary metabolites were isolated, in particular from sponges and echinoderms, reflecting their rich diversity in New Caledonia.

The third phase of these studies, currently under way, is fully characterized by pharmaceutical interest, with *Pierre Fabre* as an industrial partner.

These studies are reviewed here in two sections. In the first section, the New Caledonia marine ecosystem is compared with other ecosystems in terms of natural product chemistry organized per taxa of invertebrates, ending with a brief note about microbial and algal products. Natural products and analogues made available by total synthesis are also reviewed, with emphasis on situations where shortage of products from nature has been overcome, or where structures have been completed or revised. The second section encompasses the biological activity and technological potential of the above products in comparison with the same compounds or analogues – or pointing out sharp differences – for other ecosystems along a time span, 1977 to date, during which there have been vast changes in the pharmacological approach. The bioactivity

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[1]) *ORSTOM:* now *IRD, Institut de Recherche pour le Développement*; *CEA: Centre à l'Energie Atomique*; *CNRS: Centre National de la Recherche Scientifique*; *INSERM: Institut National de la Santé et de la Recherche Médicale*; *MNHN: Muséum National d'Histoire Naturelle.*

[2]) *MUSORSTOM* cruises [4] made it possible to investigate specimens collected at depths of 200–2,000 m, most frequently at *ca.* 400 m. The value of these samples led ORSTOM to conduct deep dredging cruises within the *SMIB* program, relying on its oceanographic vessels, *Vauban* and *Alis.*

data are summarized in the *Table* (*Appendix*) for quick review alongside those for other ecosystems.

2. Natural Product Chemistry. – *Deeper- and Deep-Water Sponges.* From the introductory discussion about the geological events that shaped the earth, it follows that extant sponges of deeper waters (> 400 m depth [3a]) in seamount areas evolved from Panthalassa entrapped sponges. Conservation of the morphological traits of those Cretaceous sponges, during the 80–100 million years that they have been separated, is best documented by lithistid sponges that have a firm body with desma spicules. Collected by dredging in the Norfolk Ridge area (*Figure*), they closely resemble both the fossil lithistids found in western Europe and extant members from both the Azores [3a] and New Zealand seamounts [6], as relicts, or evolved relicts, of sponges from the sea that encircled the earth in those early times.

Morphological comparisons can also be drawn for spiculose, soft-bodied (thus non-lithistid) deeper-sea, extant sponges from New Caledonia, which, according to the similarity of isolated spicules found in uplifted sediments in New Zealand [3a][6][3]), appear to have evolved from Eocene species (58–37 million years ago).

As a consequence of these geological events, deeper-water sponges of New Caledonia are less widely distributed than shallow-water sponges. This also holds true for the Caribbean, where there is less diversity of lithistid sponges and many, such as in the genera *Corallistes* and *Discodermia*, have largely speciated [7].

It is in this biogeographical[3]) and evolutive [8] scenario that natural-product diversity of sponges living far below the range of scuba diving is examined in the following section. The data are summarized in the *Table* in the *Appendix*.

Deeper- and Deep-Water Lithistid Sponges. Nitrogenous compounds, macrolides, and steroids have been reported from eight lithistid sponges of New Caledonia, mostly from deeper waters (> 400 m depth [3a]), in the families Corallistidae, Phymatellidae, and Pleromidae, as representatives of 'living fossils'. Nitrogenous compounds include a bis-imidazole alkaloid (corallistine (**1**) from *Corallistes fulvodesmus* LÉVI, C. & LÉVI, P. [9]), indole alkaloids (ethyl 6-bromo-1*H*-indole-3-carboxylate (**2**) and 6-bromo-3-(hydroxyacetyl)-1*H*-indole (**3**) from *Pleroma menoui* LÉVI C. & LÉVI P., 1983 [10]), pteridines (**4** from *C. fulvodesmus* [9] and **5** from *Corallistes undulatus* LÉVI C. & LÉVI P., 1983 [11]), and free porphyrines (corallistins A–E (**6**–**10**; isolated as methyl esters,

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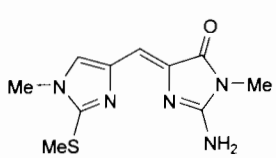
[3]) Shallow-water sponges have been the subject of study preferred by the marine-natural-product chemist. Less attention has been given to deep-water sponges, which stem mainly from New Caledonia, the Caribbean, and southern Australian waters. Comparisons with New Caledonia are nevertheless difficult because taxa differ widely between the three ecosystems [6]. Morphological analogies may not correspond to secondary metabolites, and are faced with the difficulty of static Linnaean taxonomic definitions that stand in contrast with restless evolution of the organisms. On the other hand, comparative genomic studies for sponges and other marine invertebrates are in their infancy. Even when these are made available in corroborating phylogenetic and taxonomic schemes, the concern is, as for all other eukaryotes, with coding regions of rRNA (for long phylogenetic distances) that have little or nothing to do with genes for secondary metabolites. This is also true for ITS data (for population dynamics), because ITS are faster-evolving non-coding regions of rRNA. Thus, genomic observations, based on average time of nucleotide replacement, and natural-product observations, which depend on the evolution of genes for secondary metabolites, are relegated into separate worlds and are destined to remain so until functional genomics of the secondary metabolism receives adequate attention [8].

such as **6a**) from *Corallistes* sp. [12]), as well as a cyclodepsipeptide (neosiphoniamolide A (**11**) from *Neosiphonia superstes* SOLLAS [13], which is a valine analogue of geodiamolide D (**12**) [14]). Total synthesis confirmed the structures of corallistins A (**6**) [15a] and B–E (**7**–**10**) [15b], while a protocol was provided for the synthesis of novel porphyrins – potentially useful in the photo-therapeutical treatment of tumors – consisting of formylation of the Ni^{II} complexes of corallistins **6**–**10** [12b].



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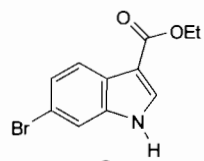

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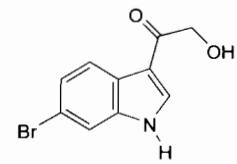

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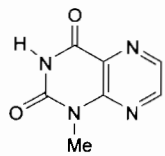

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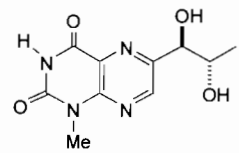

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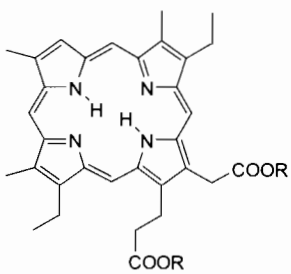
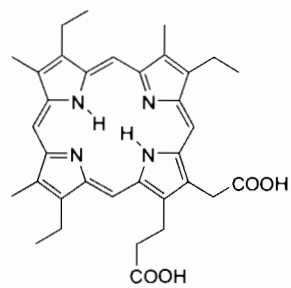


6 R = H
6a R = Me



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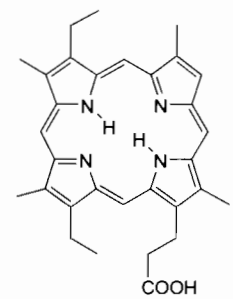

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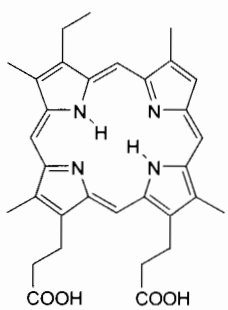

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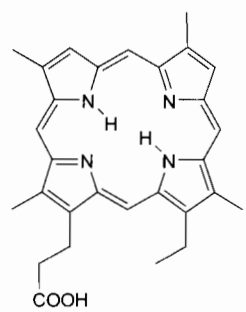

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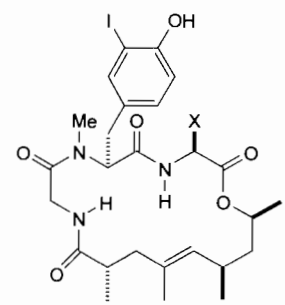

11 X = i-Pr
12 X = Me

Macrolides of two types were isolated from deeper-water Phymatellidae lithistids (*Table*). Decalin-fused 16-membered macrolides, such as superstolide A (**13a**) [16a] and B (**13b**) [16b], isolated from *Neosiphonia superstes* SOLLAS, constitute one group. The other group comprises 26-membered polyoxygenated macrolides, such as sphinxolide (**14a**) [17a,b][18a] and sphinxolide D (**14d**) [17a][18b], first isolated from a Hawaiian nudibranch [18][4]), as well as new sphinxolides B (**14b**), C (**14c**) [17a], and E–G (**14e**–**14g**) [17c] from *Neosiphonia superstes* SOLLAS and reidispongiolides A and B (**14h** and **14i**) [17b,d] and C (**14j**) [17c] from *Reidispongia coerulea* LÉVI, C. & LÉVI, P. Structurally belonging to the sphinxolide family, reidispongiolides, according to precedence rules, should have been named sphinxolides. Deriving product names from the productive sponge was, in this case, both redundant and confusing. The diverse origins of sphinxolide-type macrolides, from a nudibranch mollusk [18] and lithistid sponges [17], and the structures suggest *de novo* bacterial synthesis.

Few stereochemical details were allowed by the 12 mg of sphinxolide (**14a**) [18a], and even less of sphinxolide D (**14d**) [18b], isolated from a mollusk. Later, sphinxolides made available in huge amounts from sponges allowed better stereochemical insight into sphinxolide (**14a**) [17b]. Although the stereochemical definition is still limited to sectors of sphinxolide, synthetic chemists who specialize in bioactive complex marine macrolides (*Table*) should be stimulated to complete the structure of this molecule by total synthesis.

Steroids are represented by 24,26-dialkylated cholestanes isolated from *Neosiphonia superstes* SOLLAS, such as β-sitosterol [19], typical of plants, and 24(28)-dehydroaplysterol [19], characteristic of shallow-water verongid sponges.

Some of these products from 'living fossil' lithistids, or analogues, have been found in shallow-water marine organisms as well. Sphinxolide (**14a**) and sphinxolide D (**14d**), as mentioned above, were also found in a Hawaiian nudibranch mollusk [18]. Geodiamolide D (**12**), an analogue of neosiphoniamolide A (**11**), was found in a halichondrid sponge from Papua New Guinea [14]. Pteridines were found in widely distributed diatoms [11]. Bromoindoles are widespread in marine organisms. In other cases, the lithistid products, albeit new, belong to known classes, such as free porphyrins **6**–**10** [12], which are also present in bathypelagic scyphozoans and hydrozoans [20][5]). A few lithistid products have no precedent, like the bis-imidazole alkaloid called corallistine (**1**) [9] and decalin-fused macrolides called superstolides (**13a** and **b**) [16].

Metabolites from Azoricidae and Scleritodermidae lithistids from New Caledonian deep waters (<400 m depth [3a]) have also been reported. *Microscleroderma* sp. (Scleritodermidae) yielded microsclerodermins A and B (**15a** and **15b**) [22a] in a group of cyclic hexapeptides that includes analogues from shallow-water lithistids from the

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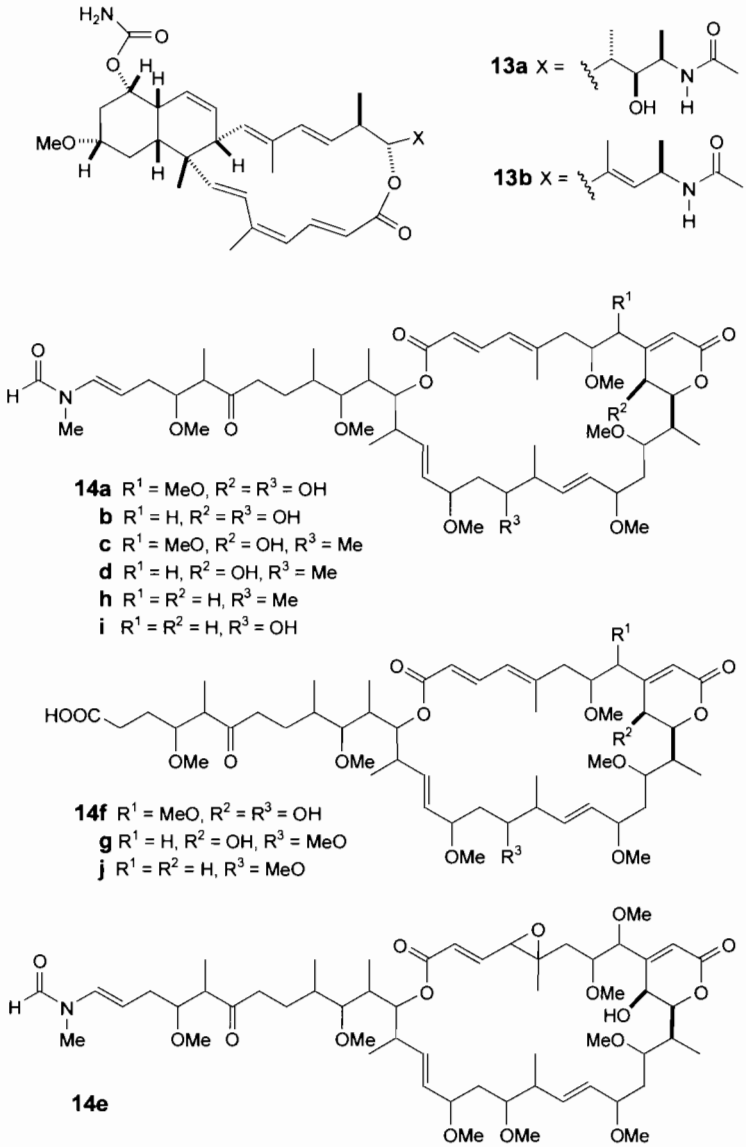
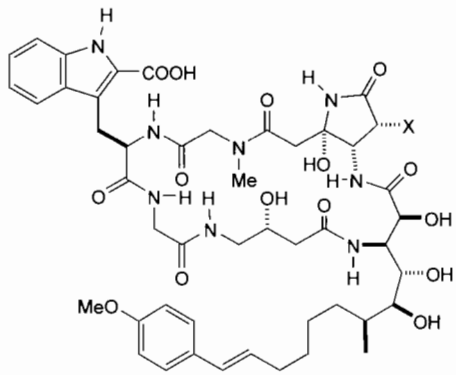
[4]) Compound **14d** was first reported without a name [18b].

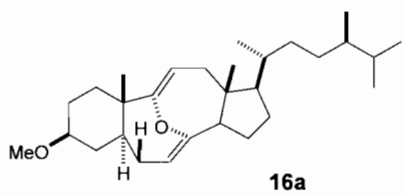
[5]) A light screening role was tentatively attributed to the free porphyrins of bathyal schyphozoans and hydrozoans, which should protect these invertebrates from luminescent predators [20]. The extrapolation went farther, as it was judged as 'probable that free porphyrins are restricted to the deep-sea medusae' [20]. Corallistins **6**–**10**, which account for an amazing 60% of the EtOH extract from the deeper-water New Caledonian lithistid sponge *Corallistes* sp. [12], disprove the point. Such failures in accounting for the function of metabolites, in the absence of a dedicated study, justify our position in refraining from carrying out ecologically-oriented bioassays about predation in deep, remote, inaccessible waters under normal laboratory conditions [21].



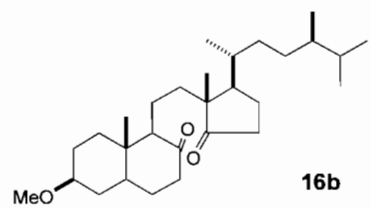
Philippines [22b] and deep-water lithistids from Micronesia [22c]. The antifungal [22a] and antiproliferative activities [22e] of these peptides are reported in the *Table.* Circumstantial evidence suggests a bacterial origin for these peptides [22d]. In addition, *Jereicopsis graphidiophora* LÉVI, C. & LÉVI, P. (Azoricidae, formerly Leiodermatiidae) yielded 9,11-*seco*-3β-*O*-methyl-sterols, jereisterols A and B (**16a** and **16b**) [23a], unique for a combination of methoxylation and ring opening, besides ring-intact analogues [23b].



15a X = OH
b X = H



16a



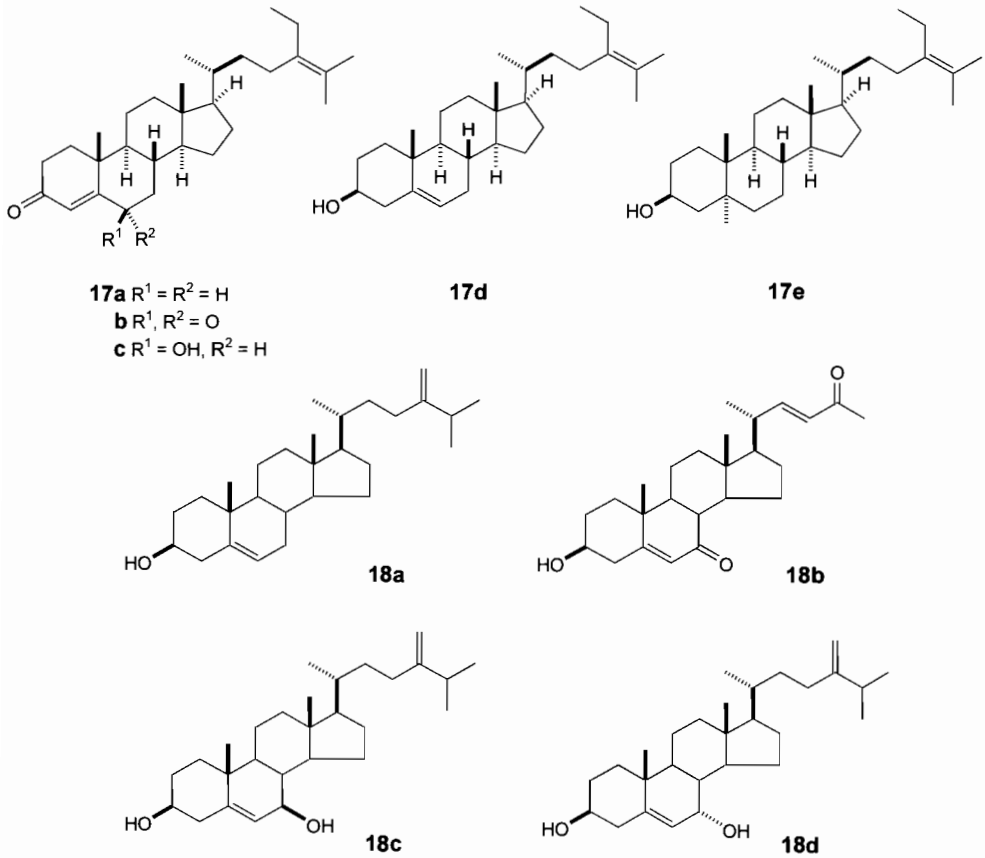
16b

Few studies of deep-water lithistids from other ecosystems have appeared, concerning *Discodermia polydiscus* DUBOCAGE 1879 (Theonellidae) [24a], and two other species in this genus from the Caribbean, and *Aciculites pulchra* (Scleritodermidae) from New Zealand [25]. *D. polydiscus* furnished a brominated (aminoimidazolinyl)indole alkaloid, called discodermindole [24a]. *Discodermia* sp. from St. Lucia gave a depsipeptide called polydiscamide A [24b,c]. Several *Discodermia* sp. from the Bahamas provided cyclic peptides called discobahamins [24d] and new discodermolide analogues [24e]. *A. pulchra* gave a side-chain polyalkylated cholestane called pulchrasterol [25].

In conclusion, lithistid sponges from New Caledonia, either recent or 'living fossils', are unique, from a biological point of view, but revealed little new natural-product chemistry. Similarity of secondary metabolites to those of other invertebrates may result from either diet, microbial associates, or convergent evolution [2a]. However, comparisons with lithistids of New Zealand seamounts, which bear much morphological similarity with those of New Caledonian seamounts, are eagerly awaited [6].

Deeper- and Deep-Water Non-Lithistid Sponges. Deeper-water (>400 m depth [3a]) New Caledonian sponges in the orders Astrophorida, Dictyoceratida, Haplosclerida, and Poecilosclerida yielded isoprenoids and polypropionates. Steroids were secured from the astrophorid *Stelletta* sp. and the poecilosclerid *Stelodoryx chlorophylla* LÉVI. Along a complex characterization involving chemical transformations, the first was shown to contain stigmastane sterones **17a**–**17c** and a 4:1 mixture of stigmastane sterols **17d** and **17e** [26]. Stigmastanes, although unprecedented in the sea, are widespread in terrestrial plants. *S. chlorophylla* gave twenty-two side-chain-oxygenated C_{27}–C_{29} Δ^5-mono- and di-unsaturated cholestane- and degraded cholestane-sterols, classified in four groups according to the nature of the nucleus, with side

chains of various lengths and C-branching, like **18a – 18d**, as the most abundant in each group [27a].



17a $R^1 = R^2 = H$
b $R^1, R^2 = O$
c $R^1 = OH, R^2 = H$

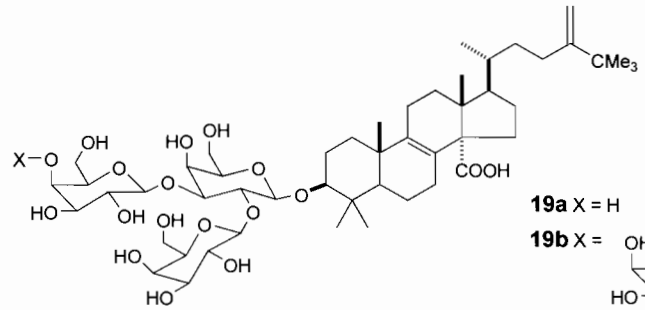
17d **17e**

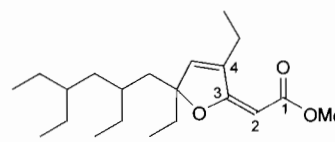
18a **18b**

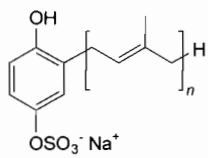
18c **18d**

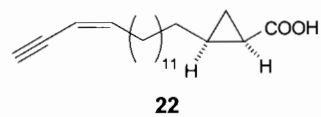
Eryloside C (**19a**) and D (**19b**), glycosylated isoprenoids from the New Caledonian astrophorid sponge *Erylus* sp. [28a], find analogues from *Erylus lendenfeldi* SOLLAS from shallow waters in the Red Sea [28b], as well as *Erylus goffrilleri* WIEDENMAYER, 1977 [28c], and *Erylus formosus* SOLLAS, 1886 [28d], from shallow waters of the Bahamas. Several other oligoglycosides based on the same triterpene nucleus were obtained from shallow-water Caribbean [28e] and northwestern Pacific [28f] sponges of the genus *Erylus*, while oligoglycosides based on related triterpene nuclei were secured from shallow-water sponges, like halichondrid *Ulosa* sp. from Madagascar [28g] and poecilosclerid *Ectyoplasia ferox* DUCHASSAING & MICHELOTTI from the Caribbean [28h]. Triterpene saponins are also known from shallow-water astrophorid sponges of other genera.

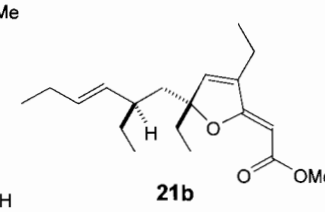
Prenyl sulfates of the type represented by compounds **20a – 20c**, isolated from a New Caledonian dictyoceratid sponge, *Ircinia* sp. [29a], are widely distributed in this sponge order, irrespective of family and ecosystem [29b – d].

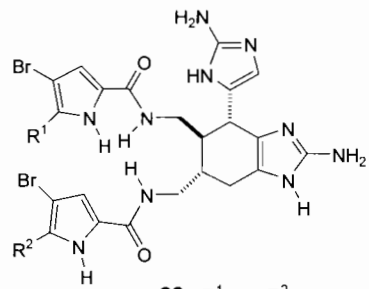


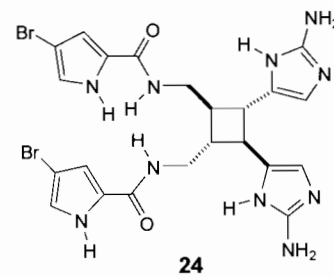








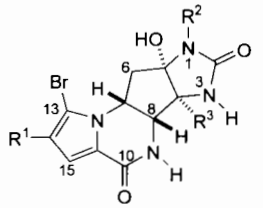




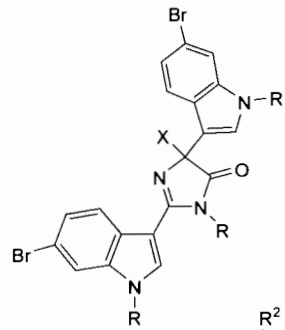
A polypropionate from the New Caledonian haplosclerid sponge *Cladocroce incurvata* LÉVI, C. & LÉVI, P., cladocrocin A (**21a**) [30a], albeit of uncertain configuration, bears some similarity to compound **21b** from the homosclerophorid sponge *Plakortis halichondrioides* of shallow Caribbean waters [30b]. Also, cladocrocic acid (**22**), isolated from *C. incurvata* [30a], finds analogy with other cyclopropane-bearing fatty acids from red seaweeds and shallow-water invertebrates [30c].

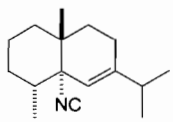
From deep-waters, New Caledonian sponges comprise species in the Agelasida, Halichondrida, and Poecilosclerida, collected at 235–300 m depth. Agelasid sponges gave C_{11}, and dimeric C_{11}, alkaloids, typical both of sponges in this order and

halichondrid sponges, like ageliferin (**23a**) and sceptrin (**24**) from *Agelas novaecaledoniae* LÉVI & LÉVI, 1983 [31a]. Ageliferin was also found in Western Pacific agelasid sponges [31c], while sceptrin was also found in Caribbean agelasid sponges [31b,d,e]. Agelastatin A (**25a**) [32a] and B (**25b**) [32b] from *Agelas dendromorpha* LÉVI, and agelastatin C (**25c**) and D (**25d**) from the shallow-water halichondrid sponge *Cymbastela* sp. of Western Australia [32d], although structurally related to polycyclic oroidin-related C_{11} alkaloids commonly found in both agelasid and halichondrid sponges, are unique in the cyclization mode.



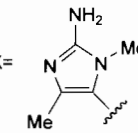
25a $R^1 = R^3 = H$, $R^2 = Me$
b $R^1 = Br$, $R^2 = Me$, $R^3 = H$
c $R^1 = H$, $R^2 = Me$, $R^3 = OH$
d $R^1 = R^2 = R^3 = H$



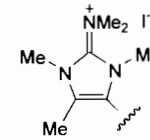


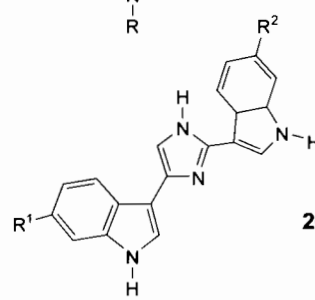
27

26a R = H, X=



26b R = Me, X =





26c $R^1 = R^2 = Br$
d $R^1 = Br$, $R^2 = H$
e $R^1 = H$, $R^2 = Br$

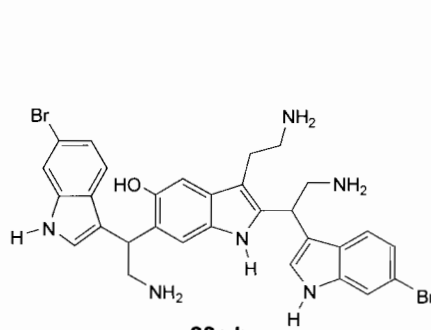
Structural transformations of agelastatin A (**25a**) established the absolute configuration and revealed the role of the functional groups and ring-junction configuration of this molecule (see *Sect. 3*) [32c]. This, coupled to the definition of agelastatin A as '*a molecule of enormous biological interest*' [32e] because of its selective inhibition of GSK-3β (see *Table* and *Sect. 3*), has garnered the attention of synthetic chemists. Total synthesis of agelastatin A in racemic form was performed in twelve steps, with *ca.* 7% overall yield, from cyclopentadiene [32f]. The key intermediate in this process has recently been provided in optically active form [32g]. The natural enantiomer **25a** was obtained *via* a multistep sequence in *ca.* 1% overall yield from an epoxyalkyne pure enantiomer [32h], and the process was unified and extended to yield (–)-agelastatin B (**25b**) [32i].

In New Caledonian halichondrids, *Dragmacidon* sp. gave nortopsentin D (**26a**) [33a], which should not be confused with a non-natural compound of the same name with a different structure, obtained by hydrogenolysis of nortopsentins A–C (**26c**–**26e**) [33b]. Nortopsentin D (**26a**) is a novel member, unique for bearing a 2-amino-1,4-dimethyl-1*H*-imidazol-4-yl moiety at the central 1*H*-imidazol-5*H*-one nucleus, in a family of bis-indole alkaloids represented by nortopsentins A–C (**26c**–**26e**), isolated

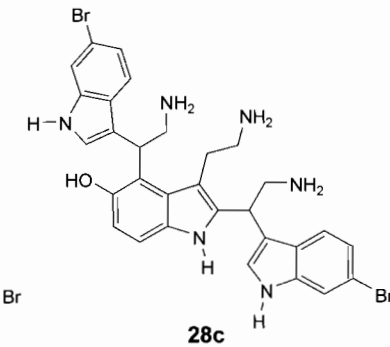
from the halichondrid sponge *Spongosorites ruetzleri* of deep Caribbean waters [33c]. The nortopsentins may be compared with other bis-indole alkaloids, called dragmacidins, where the imidazole central nucleus of nortopsentins is replaced by a pyrazine nucleus; they were isolated from deep-water sponges, *Dragmacidon* sp. from the Caribbean [33d] and *Spongosorites* spp. from both the Caribbean [33e] and the Great Australian Bight [33f].

The New Caledonian *Stylotella* sp., with stylotelline (**27**) [34a], showed the typical production of isonitrile terpenoids of halichondrid sponges [34b].

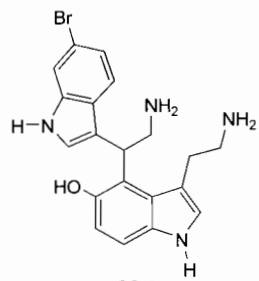
In the New Caledonian haplosclerids, *Orina* sp. gave racemic tris-indole alkaloids, gelliusine C (**28c**) [35b] and diastereoisomeric gelliusines A and B (**28a** and **b**) [35a], as well as bis-indole alkaloids, gelliusines D–F (**28d**–**28f**) [35b]. The only other known marine tris-indole alkaloids are represented by trisindoline (**29**) [35c] and other compounds [35d], all isolated from Okinawan and North Sea bacteria in culture.



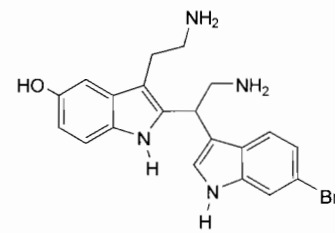
28a,b



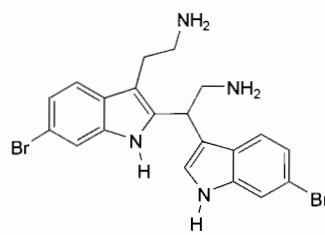
28c



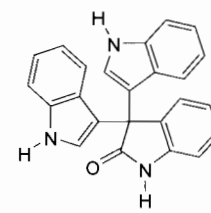
28d



28e

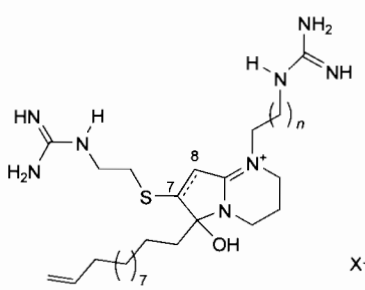


28f

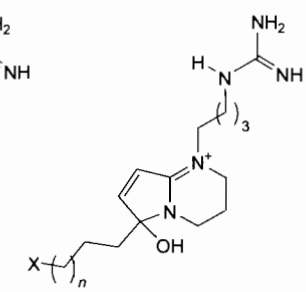


29

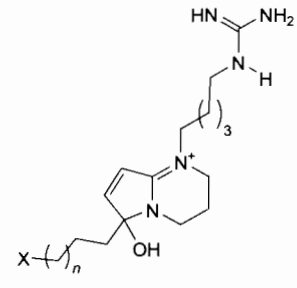
Another New Caledonia haplosclerid, *Phloeodictyon* (= *Oceanapia*) sp., gave the first examples of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium alkaloids, which can be grouped as follows. In the first group, phloeodictynes B (**30a**) [36a], C1 (**30b**), and C2 (**30c**) [36b] bear a thioethylguanidine side chain at C(7), while the second group, phloeodictynes A (**30d**) [36a], A2 (**30e**), A4 (**30f**), and A7 (**30g**) [36b], and third group, phloeodictynes A1 (**30h**), A3 (**30i**), A5 (**30j**), and A6 (**30k**) [36b], are characterized by a chain of four or five CH_2 units, respectively, connecting the guanidine moiety. Total synthesis of racemic phloeodictyne A1 has been reported [36c], confirming the structural assignment from spectroscopic data [36b].



30a $n = 3$, $\Delta^{7,8}$
b $n = 4$
c $n = 3$



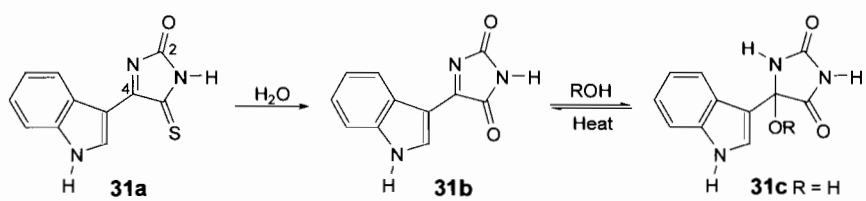
30d $n = 9$, X = CH_2=$CHCH_2$
e $n = 7$, X = CH_2=$CHCH_2$
f $n = 5$, X = CH_2=$CHCH_2$
g $n = 8$, X = i-Pr



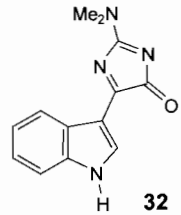
30h $n = 7$, X = CH_2=$CHCH_2$
i $n = 5$, X = CH_2=$CHCH_2$
j $n = 4$, X = CH_2=$CHCH_2$
k $n = 8$, X = i-Pr

A New Caledonian poecilosclerid sponge, *Zyzza massalis* (DENDY) (Acarnidae, formerly Cornulidae), gave a yellow-colored indole alkaloid, zyzzin (**31a**, *Scheme*) [37a]. It is structurally related to ascidian products, like 3-(1*H*-indol-3-yl)imidazol-4(4*H*)-one (**32**) [37b] from the English-Channel ascidian *Dendrodoa grossularia*, which, however, lacks activation at C(4)=N. Related to **31a**, structure **31d** (*Scheme*) was assigned to polyandrocarpamide D, isolated upon MeOH workup from the ascidian *Polyandrocarpa* sp. of the Philippines [37c], which is likely to be an artifact, although published data [37c] do not clarify whether zyzzin (**31a**) or its keto derivative **31b** is the naturally occurring form. In contrast, zyzzin (**31a**) is structurally unrelated to pyrroloiminoquinone alkaloids from *Zyzzya fuliginosa* CARTER, 1879, from the Fiji islands [37d], although tryptophan is likely to be at the origin of all these alkaloids.

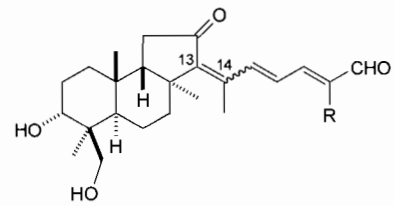
Scheme. *A Thermochromic System*, **31b**⇌**31c** (*or* **31d**), *arising from zyzzin* (**31a**), *isolated from the poecilosclerid sponge* Zyzza massalis [37a]



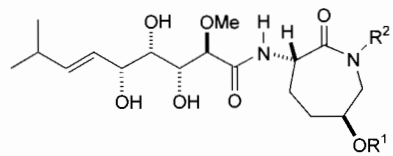
31a **31b** **31c** R = H
d R = Me



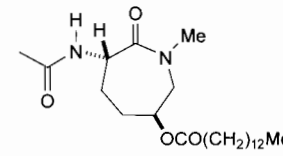
32



33a $\Delta^{13}Z$, R = Me
b $\Delta^{13}E$, R = Me
c $\Delta^{13}Z$, R = H
d $\Delta^{13}E$, R = H



34a $R^1 = CH_3(CH_2)_{12}CO$, R^2 = H
b $R^1 = CH_3(CH_2)_{12}CO$, R^2 = Me
c $R^1 = CH_3(CH_2)_{11}CO$, R^2 = H
d $R^1 = CH_3(CH_2)_{11}CO$, R^2 = Me
e $R^1 = CH_3(CH_2)_{13}CO$, R^2 = H
f $R^1 = CH_3(CH_2)_{13}CO$, R^2 = Me



34g

In conclusion, little biodiversity was observed for deep-water (< 400 m) sponges of New Caledonia. Representatives of the Hadromerida, Homosclerophorida, Spirophorida, and Verongida were lacking, which widely occur in Caribbean deep waters [2a]. Based on chemical studies carried out to date, *Ircinia* and *Dragmacidon* are the only genera common to both deep-water ecosystems.

Shallow-Water Sponges. The absence of paleontological evidence throws much speculative character on any inference about origin and comparative biogeography for shallow-water sponges of New Caledonia [3a]. In light of this absence and the paucity of genomic data, even assignments of the same species from different ecosystems, expressed by the static Linnaean terminology[3]), may be dubious. Judging from morphological traits, endemism for shallow-water sponges in New Caledonia, estimated at 45%, is much lower than for deeper-water (> 400 m depth [3a]) sponges, estimated at 72%. Also, there was little or no genetic mixing between the two groups [3a]. Morphologically, shallow-water New Caledonian sponges resemble species from the Great Barrier Reef, New Guinea, southern Indonesia, and Micronesia, suggesting that they originate from the same gene pool. This also hints at a relatively recent colonization of New Caledonian shallow waters, unlike the deeper waters [3a]. Resemblance to species from New Zealand is surprisingly very low.

It should be acknowledged that the limited natural-product diversity that has emerged from sponges may reflect only a small sample of the shallow-water sponge diversity from New Caledonia [3a]. No species of shallow-water Agelasida is represented, and none at all of Homosclerophorida and Hadromerida. Although the order Agelasida comprises only a few species, shallow-water representatives from Papua New Guinea, Fiji, Vanuatu, and Indonesia have furnished a vast array of

biologically active secondary metabolites, such as C_{11} and C_{10} oroidin-related alkaloids, polyketide peroxides [38a], and pyrrolo-acridine alkaloids [38b]. Homosclerophorida from the tropics, mainly represented in the family Plakinidae [38c], are known for polyketide peroxides. The Hadromerida have never proved particularly productive; latrunculins, microfilament-disrupting macrolides from *Latrunculia magnifica* of the Red Sea, are an exception, triggering much interdisciplinary interest [38d].

Very few calcareous sponges from New Caledonia, or from other marine ecosystems, have been studied.

Shallow-Water Demosponges. Shallow-water astrophorid sponges are widely distributed in the tropics, but the most-prolific natural product sources, in the genera *Epipolasis*, *Erylus*, *Jaspis*, *Pachastrella*, *Penares*, *Poecillastra*, and *Stelletta* were harvested from temperate Japanese waters. They gave sesquiterpenes and alkaloidal sesquiterpenes, isomalabaricane triterpenes, triterpene saponins, fatty acid tetrasaccharides, macrocyclic bis-pyridinium alkaloids, bis-guanidinium alkaloids, *N*-nitroso alkanes, unusual purine bases, styryl sulfates, and long-chain polyamines [40c]. Shallow-water New Caledonian astrophorids are represented in chemical studies by *Rhabdastrella globostellata* (CARTER, 1883) and *Jaspis carteri* (RIDLEY, 1884) only. The first gave truncated isomalabaricanes, aurorals 1–4 (**33a**–**33d**) [39a], in a triterpene class that has been taken as chemotaxonomic marker of this species [39b]. *J. carteri* gave bengamides G–K (**34c**–**34g**) [40a], as structural variants of bengamides A and B (**34a** and **34b**), first isolated from *Jaspis* sp. from the Fiji islands [40b].

The sole, though remarkable, example of New Caledonian shallow-water sponges in the family Axinellidae, recently merged into the order Halichondrida [3b], is *Cymbastela* (= *Pseudaxinyssa*) *cantharella* (LÉVI, 1983). Production fits its phylogeny with nor-A-cholestanes [41] and oroidin-related C_{11} alkaloids. The latter include odiline (**35a**), dibromocantharelline (**35b**) and known dibromophakellin, or degraded forms of them, like aldisin and 2-bromoaldisin [42a]. Girolline (**35c**), from the same sponge [42b–d][6]), may also be viewed as a truncated form of oroidin-related C_{11} alkaloids, although the side chain functionalization is unusual. Total synthesis of girolline has been carried out, both enantioselective [43a] and of the racemate [43b]. In contrast, pyraxinine (**36**) from this sponge [44] has no easily recognizable phylogenetic significance, in spite of being composed of common structural fragments.

In New Caledonian sponges of the family Dysideidae, recently merged into the order Dendroceratida [3b], *Dysidea fusca* RIDLEY gave drimane sesquiterpenes typical of this genus [45]. *Euryspongia* sp. proved more interesting for unusually polyhydroxylated 9,11-secosterols, called euryspongiol A1 (**37a**) and A2 (**37b**) [46a]. They are compared with xestobergsterol A (**38a**) and B (**38b**) [46c] in the *Table*.

In New Caledonian dictyoceratids, *Petrosaspongia nigra* (BERGQUIST, 1995), initially incorrectly assigned as *Dactylospongia* sp. [47a], gave cheilanthane sesterpenes and norsesterterpenes called petrosaspongiolides A (**39a**), B (**39b**) [47a,b], C–L (**39c**–**39l**) [47b], M and N (**39m** and **39n**), and P–R (**39p**–**39r**) [47c]. Cheilanthanes, which were novel to the *Petrosaspongia* genus, had been first isolated from ferns in the

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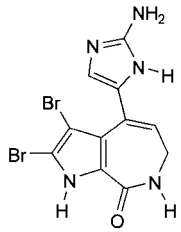
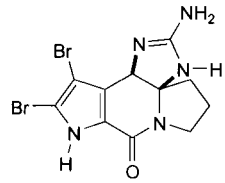
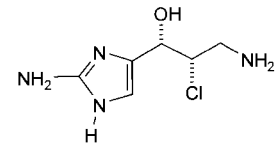
[6]) It can be appreciated from the structure of oroidin (**35d**), or oroidin-related C_{11} alkaloids [42a], widely present in members of the Axinellidae and the Agelasidae, that girolline (**35c**) [42b–d] appears to be degraded from the opposite side with respect to aldisin and 2-bromoaldisin truncation.



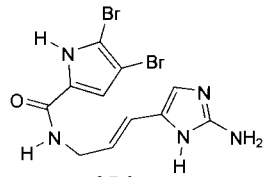
35a



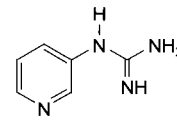
35b



35c



35d



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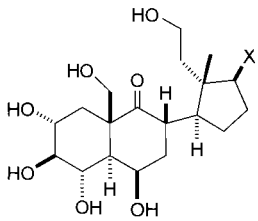
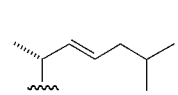
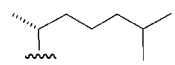
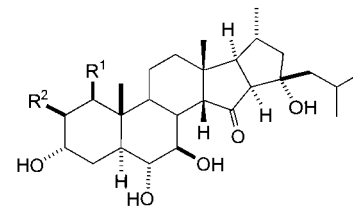


37a X =



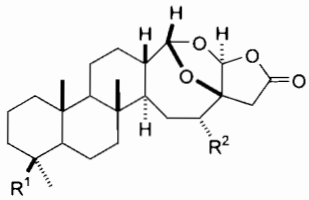
37b X =



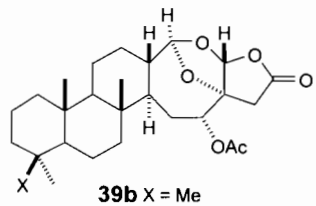


38a $R^1 = R^2 = H$
b $R^1 = R^2 = OH$

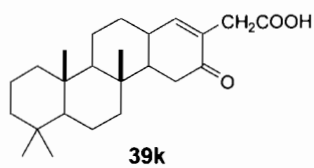
genus *Cheilanthes* and then, like **40**–**42**, also from dictyoceratid sponges (as likely biogenetic precursors of scalaranes) and nudibranch mollusks that feed on them [48]. Luffolide (**42**), found in Micronesian dictyoceratid sponges of the genus *Luffariella*, is a likely biogenetic intermediate *en route* to petrosaspongiolides [47a]. Another representative of this genus, the Micronesian *Petrosaspongia metachromia* de LAUBENFELS, gave merosesquiterpenes [47d]. Other New Caledonian dictyoceratid sponges in the genera *Hyrtios* and *Fasciospongia* gave scalarane (**43a** and **43b**) [49a] and manoalide (**45**) like sesterterpenes, called thorectolide (**44a**), thorectolide monoacetate (**44b**) [50a], fasciospongide A (**46a**), B (**46b**), and C (**46c**) [50c], as well as the known merosesquiterpene puupehenone (**47a**), which represent product classes typical of Dictyoceratida, and a new red-colored dimer, dipuupehenone (**47b**) [51a]. They also furnished other merosesquiterpenes of the phenolic type, like **48** [52], a class widely distributed in marine organisms. The variability of metabolic production by *Hyrtios erecta* (KELLER, 1889) with the ecosystem (**43c** and β-carboline alkaloids) is illustrated in the *Table*. The limited variety of Dictyoceratida from New Caledonia contrasts with their biological position as '*the most diverse of the so-called keratose sponge orders*' [3a], a statement that is still valid even after the family Dysideidae was merged into Dendroceratida [3b]. From the Great Barrier Reef alone, chemical studies of 17 genera of dictyoceratids have been reported.



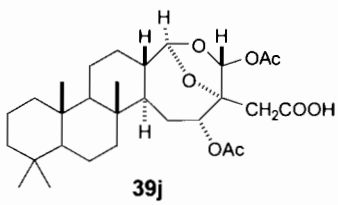
39a R^1 = Me, R^2 = AcO
c R^1 = $AcOCH_2$, R^2 = AcO
d R^1 = $HOCH_2$, R^2 = AcO
e R^1 = CHO, R^2 = AcO
f R^1 = COOH, R^2 = AcO
g R^1 = $HOCH_2$, R^2 = OH
h R^1 = COOH, R^2 = OH



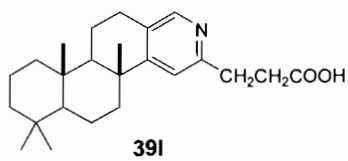
39b X = Me
i X = $AcOCH_2$



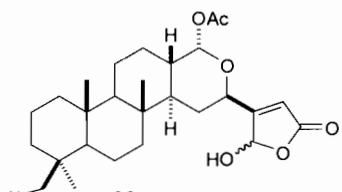
39k



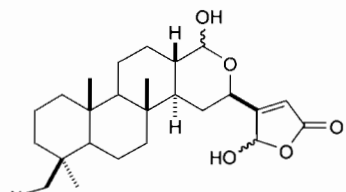
39j



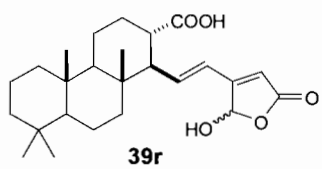
39l



39m X = H
n X = AcO

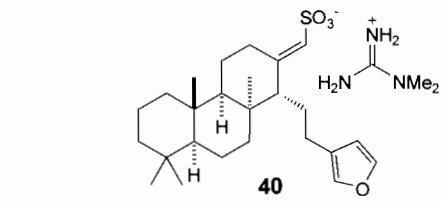


39p X = H
q X = AcO



39r

New Caledonian shallow-water lithistid sponges are scanty in these studies. *Callipelta* sp. is a rare example. Depsidecapeptides isolated from this sponge, callipeltin A (**49a**) [53a] (related to ascidian aplidine (**50**)) and callipeltins B and C (**49b** and **49c**) [53b], have also been found, besides acyclic, truncated, callipeltins D and E (**49d** and **49e**), in the hadromerid sponge *Latrunculia* sp. of the Vanuatu [53c]. Taxonomic unrelatedness of these two sponges may suggest a microbial origin for the callipeltins. *Callipelta* sp. is more representative of New Caledonia for a series of glycosidic macrolides, callipeltosides A–C (**51a**–**51c**) [54a,b]. Full stereochemical details for callipeltoside A (**51a**) were clarified by total synthesis [54f–h]. These molecules have no precedents; if anything, some resemblance to glycosidic macrolides



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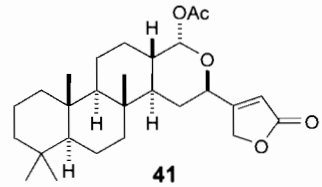

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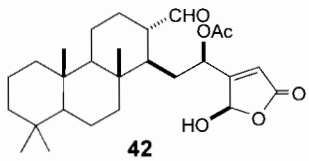
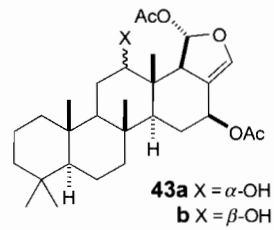
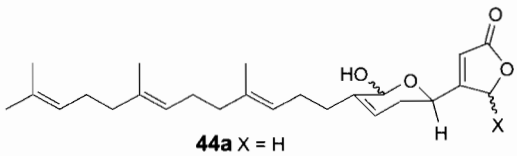


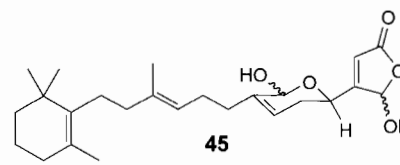
42



43a X = α-OH
b X = β-OH
c X = α-AcO



44a X = H
b X = AcO



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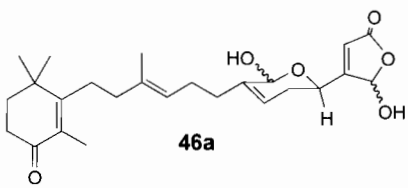
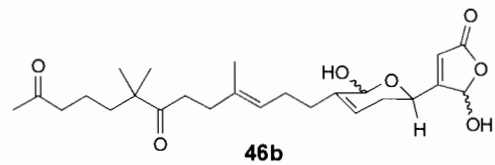
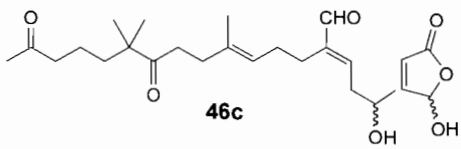


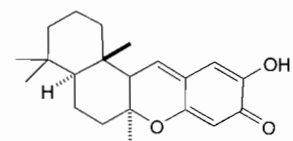
46a



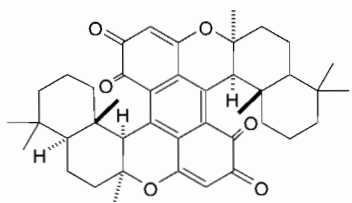
46b



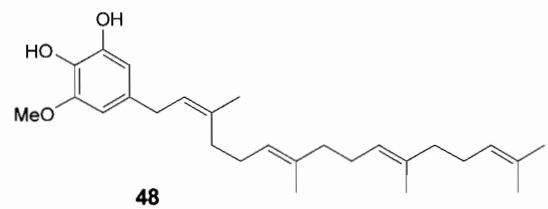
46c



47a

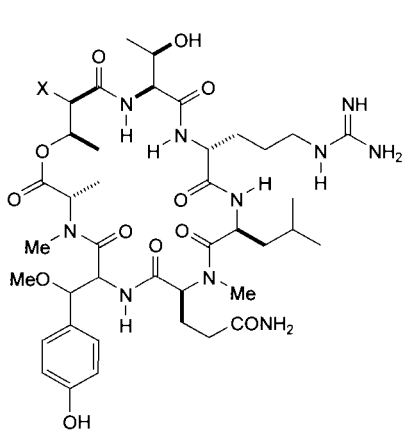


47b

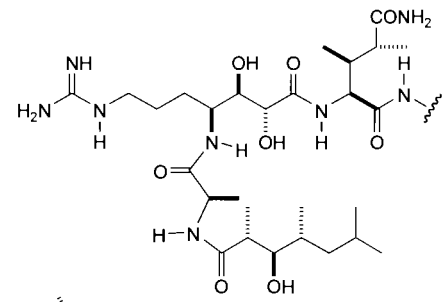


48

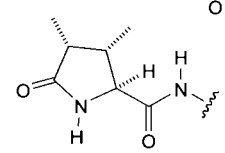
from cyanobacteria (**54**), red seaweeds (**52**), and opisthobranch mollusks (**53**) may be noted. No structural analogy is seen with any other lithistid product, although several shallow-water lithistids have been investigated from other marine ecosystems, like

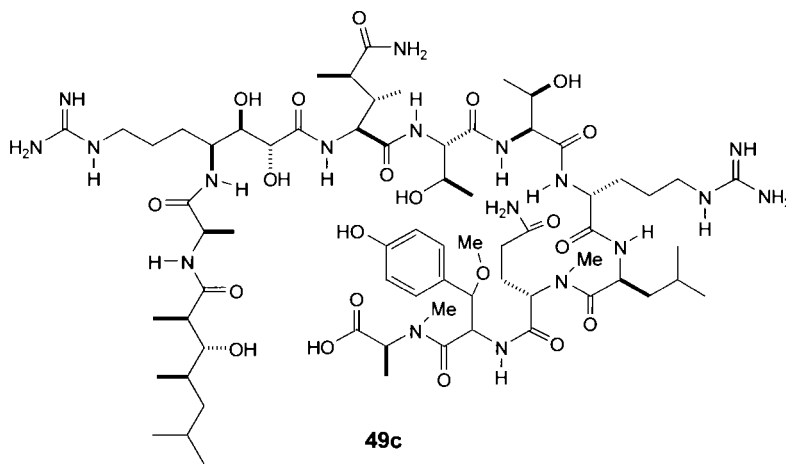


49a X =

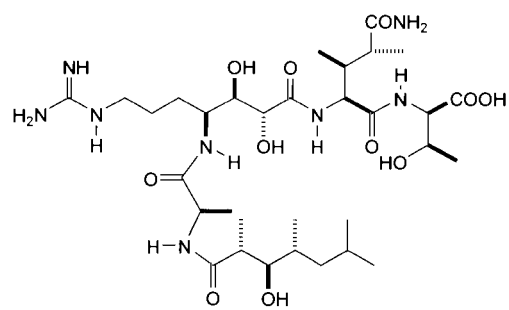


49b X =





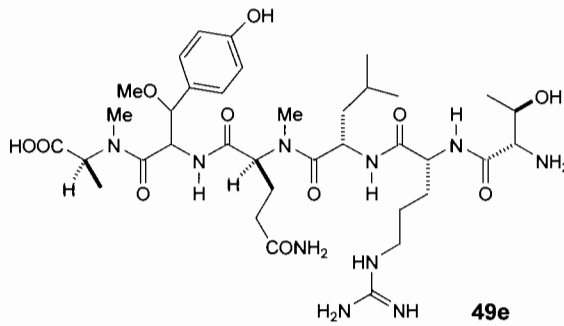
49c



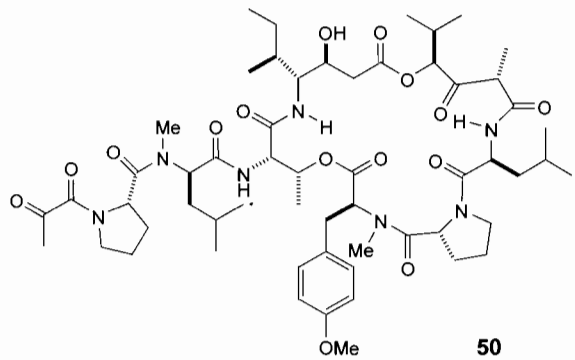
49d

Discodermia sp. from the Caribbean and several species of *Theonella* from the tropical and north-western Pacific, Indian Ocean, and the Red Sea.

The order Poecilosclerida comprises as many as 25 widely investigated families of sponges, from the Caribbean, in the genera *Batzella*, *Ectyoplasia*, *Iotrochota*,



49e



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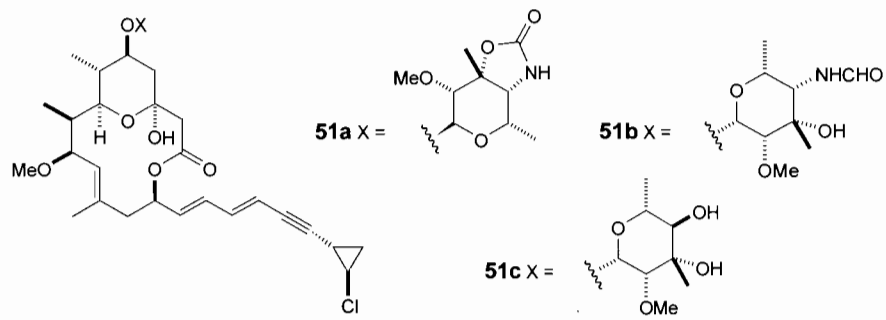
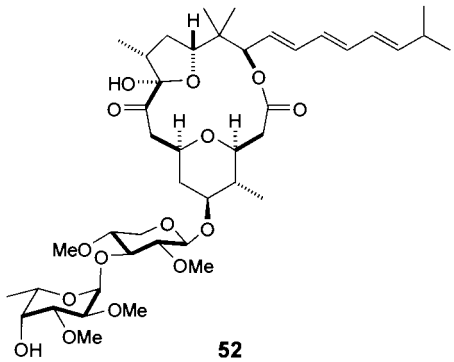


Desmapsammia, *Hemimycale*, *Forcepia*, *Monanchora*, *Mycale*, *Pandaros*, *Tedania*, *Thalysia*, and *Topsentia*. They have yielded pyrroloiminoquinone, guanidine, and macrocyclic alkaloids, as well as polyether macrolides. Poecilosclerids from New Caledonian shallow waters include *Echinochalina mollis* LÉVI, which gave polyunsaturated 12-hydroxy C_{20} and C_{22} fatty acids [55a], in lipid classes widely distributed in marine invertebrates and algae. Another recently established species, *Echinochalina* (= *Protophlitaspongia*) *bargibanti* HOOPER & LÉVI, 1993, has given low-polarity polyarsenic metabolites, in a class of compounds unprecedented in nature [56]. However, because of unusual difficulties encountered, their structure elucidation is still under



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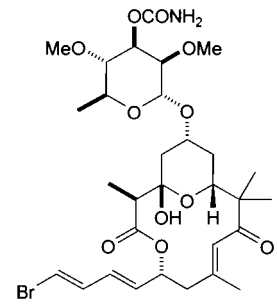

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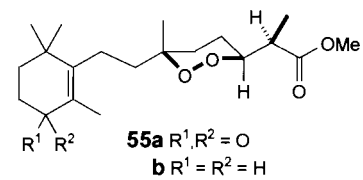
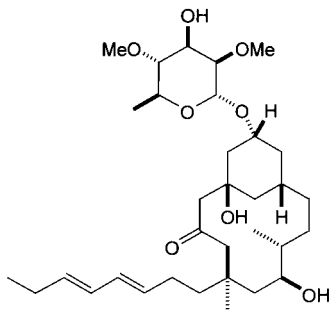
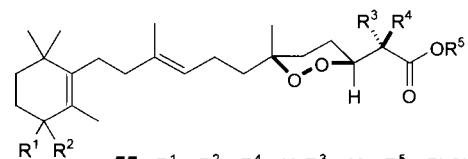


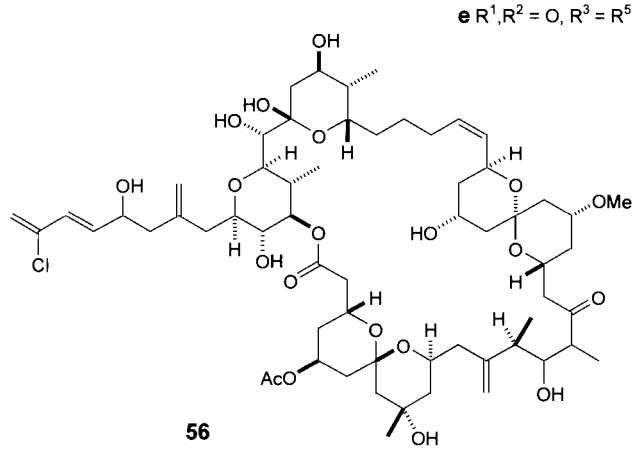
55a $R^1,R^2 = O$
b $R^1 = R^2 = H$



54



55c $R^1 = R^2 = R^4 = H$, $R^3 = Me$, $R^5 = PhCH_2$
d $R^1,R^2 = O$, $R^3 = H$, $R^4 = R^5 = Me$
e $R^1,R^2 = O$, $R^3 = R^5 = Me$, $R^4 = H$



56

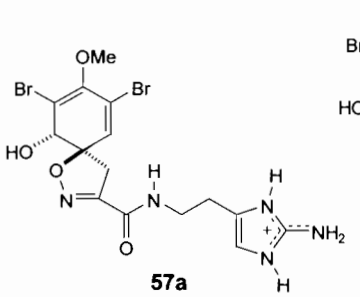
[58a]. This macrolide belongs to a class first represented by spongistatins (=altohyrtins), isolated from a group of taxonomically unrelated sponges, the hadromerid *Spirastrella spinispirulifera* from southeastern Africa [58b], and the dictyoceratids *Hyrtios altum* from Okinawa [58c] and *Hyrtios* sp. from the Maldives [58d]. Steroids [59a] and fatty acids of phospholipids [59b,c] were characterized for a New Caledonian spirophorid, *Cinachyrella* aff. *schulzei* KELLER (1891). They are compared in the *Table* with the production by sponges in this genus from other ecosystems.

Sponges of the order Verongida are characterized by tyrosine metabolites. There are no exceptions from New Caledonia, where *Pseudoceratina verrucosa* BERGQUIST, 1995 gave pseudoceratinines A–C (**57a–57c**) – which are built on one or two dibromotyrosine residues and incorporate a 2-aminohistamine residue – and known aplysamine 1 and 2, purealin, and purealidins A and B [60]. In addition, *Verongia* sp. gave, alongside **58b** and **58c**, a bis-dibromotyrosine metabolite, hemifistularin 3 (**58a**). The latter is derived from 11-oxofistularin 3 (**58d**) along a peculiar base-induced degradation [61a]. A practical high-yield synthesis, *via* anodic oxidation of a dibromophenolic precursor, was devised for dibromoverongiaquinol (**58e**) [61b], isolated from the above *Verongia* sp. [61a] and other verongids, like the New Caledonian *Suberea creba* [61c] and the Mediterranean *Aplysina aerophoba*, both from the wild sponge and from *in vitro* cultivated fragments of the latter [61d]. The synthetic study of dibromoverongiaquinol (**58e**) also led to the discovery of a new case of NHI-like rearrangement [61b].

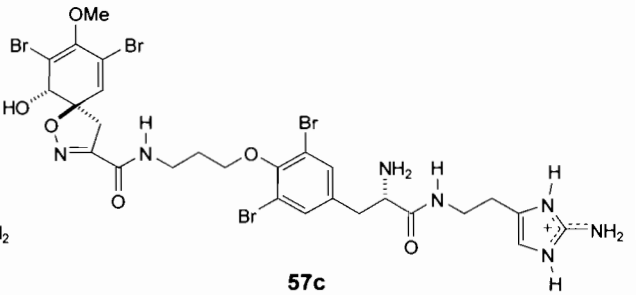
Sponges of the order Haplosclerida are very common in shallow-water coral reefs. Natural product studies have particularly flourished with species from Papua New Guinea, Micronesia, Okinawa, the Red Sea, and the Caribbean. Polyacetylenes were most commonly found, particularly from species of the genera *Callyspongia, Crybrochalina, Haliclona,* and *Petrosia*. Species in the genera *Petrosia* and *Xestospongia* also gave a variety of polycyclic polyketide alkaloids – notably the manzamines – that were most imaginatively envisaged to arise from acyclic aldehyde precursors and ammonia *via* macrocyclic 3-alkylpyridinium alkaloids [62]. Related products, like the very unusual trimeric pridinium alkaloid visosamine [62b], were also discovered.

In this order, *Petrosia* and *Xestospongia* sponges from New Caledonia were investigated, but polyketide pyridinium alkaloids, or their cyclized forms, were not found. *Petrosia* sp. is a rare example of an invertebrate collected under favorable circumstances by scuba diving at the top of a seamount in the Norfolk Ridge area. It gave two C-branched polyacetylenes, aztèquynol A (**59a**) and B (**59b**). The position of C-branching for **59a** was clearly defined, as the first example in this class of metabolites, by tandem soft mass spectrometry [63]. *Xestospongia exigua* (KIRKPATRICK, 1900), preliminarily assigned as *Xestospongia* sp. [64a], furnished bis-1-oxaquinolizidine alkaloids, **60a–d**, related to **61** [64c], and a new β-carboline alkaloid, both belonging to well known alkaloid classes (see *Table*) [64c–d].

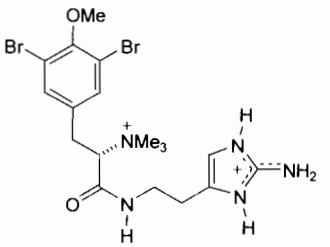
Another haplosclerid sponge from the eastern lagoon of the Grande Terre, *Oceanapia fistulosa* (BOWERBANK, 1873), gave 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium alkaloids, including those described above for the deep-water *Phloeodictyon* (=*Oceanapia*) sp. [36a,b] and others [36d]. In addition, ceramides called oceanapins (**62a–62f**), unique for C-branching on both the sphingosine and the fatty-acid chains, were secured from *Oceanapia* cf. *tenuis* DESQUEYROUX-FAUNDEZ, 1987 [65].



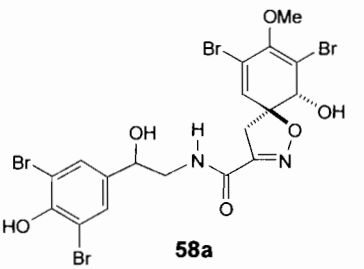
57a



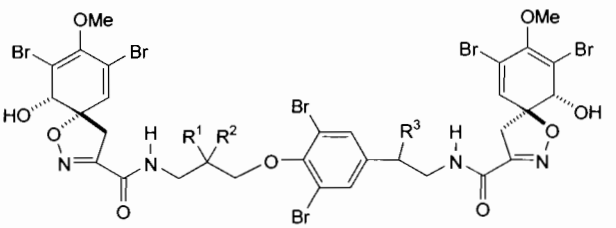
57c



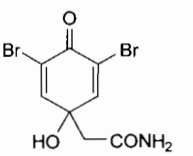
57b



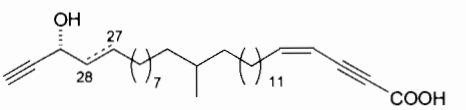
58a



58b R^1 = OH, R^2 = R^3 = H
c R^1,R^2 = O, R^3 = H
d R^1,R^2 = O, R^3 = OH

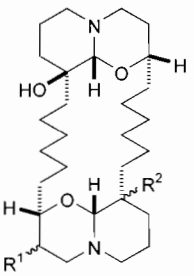


58e

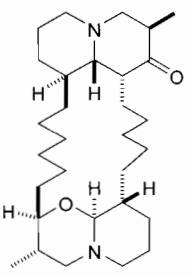


59a C(27)=C(28)
b C(27)-C(28)

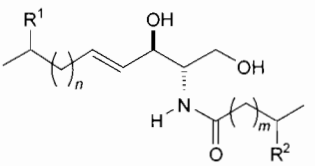
Calcareous Sponges. The class Calcarea comprises only shallow-water sponges of the orders Clathrinida and Leucosoleniida [3a]. The first are characterized by the production of imidazole alkaloids, both in the family Leucettidae, which includes *Leucetta* spp. from the Great Barrier Reef [66a], Micronesia [66b], Fiji [66c], Papua New Guinea [66d], and the Red Sea [66e,f], and the family Clathrinidae, which includes *Clathrina* spp. from the Mediterranean [66g]. Metabolites from Clathrinida also include polyunsaturated nitrogenous and non-nitrogenous polyketides, the first from *Clathrina* aff. *reticulum* from the southwestern Indian Ocean [67a] and *Leucetta*



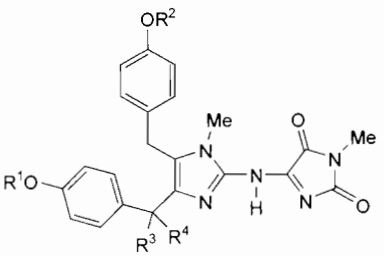
60a R^1 = H, R^2 = β-H
b R^1 = β-Me, R^2 = β-H
c R^1 = H, R^2 = α-H
d R^1 = α-Me, R^2 = β-H



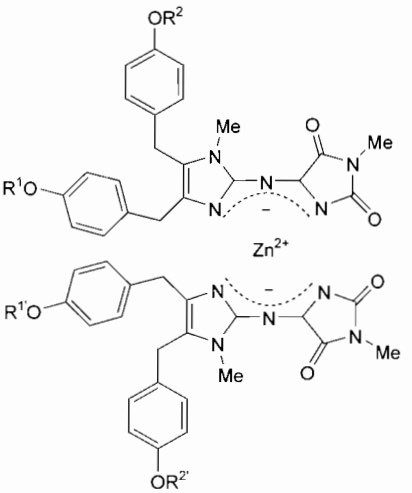
61



62a n = 9, m = 19, R^1 = H, R^2 = Me
b n = 9, m = 19, R^1 = R^2 = Me
c n = 9, m = 20, R^1 = Me, R^2 = H
d n = 10, m = 19, R^1 = R^2 = Me
e n = 10, m = 19, R^1 = Et, R^2 = H
f n = 10, m = 19, R^1 = Et, R^2 = Me



63a R^1 = Me, R^2 = R^3 = R^4 = H
b R^1 = R^2 = Me, R^3 = R^4 = H
c R^1 = Me, R^2 = R^3 = H, R^4 = OH
d R^1 = R^2 = Me, R^3 = H, R^4 = OH
e R^1 = Me, R^2 = R^3 = H, R^4 = MeO
f R^1 = R^2 = Me, R^3 = H, R^4 = MeO
g R^1 = R^2 = Me, R^3,R^4 = O



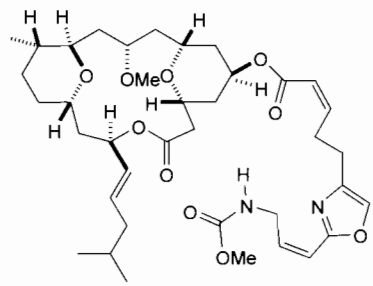
63h R^1 = $R^{1'}$ = Me, R^2 = $R^{2'}$ = H
i R^1 = $R^{1'}$ = R^2 = $R^{2'}$ = Me
j R^1 = $R^{1'}$ = R^2 = Me, $R^{2'}$ = H

leptorhapsis from Antarctica [67b], and the second from *Leucetta microraphis* from Okinawa [67c].

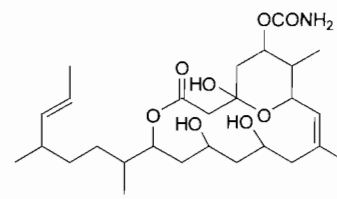
Clathrinida from New Caledonia are represented by *Leucetta* sp. with imidazole alkaloids, comprising the known naamidine A (**63a**) [66c,f], a close new analogue, naamidine G (**63b**) [66h], and a novel series characterized by oxidation at the benzylic position, such as 14-hydroxynaamidines A (**63c**) and G (**63d**), 14-methoxynaamidines A (**63e**) and G (**63f**), and 14-oxonaamidine G (**63g**) [66h]. This sponge also provided the first examples of same-ligand–Zn^{II} complexes of naamidines (**63h** and **63i**) and the first example of a mixed-imidazole-ligand–Zn^{II} complex (naamidinato A)(naamidinato G)zinc(II) (**63j**) [66h]. Related production by sponges in this genus from other marine ecosystems is illustrated in the *Table*.

In the Leucosoleniida, represented in the Caribbean by *Leucosolenia canariensis* with phospholipids [68a], New Caledonia emerged with, at the time, a breakthrough in

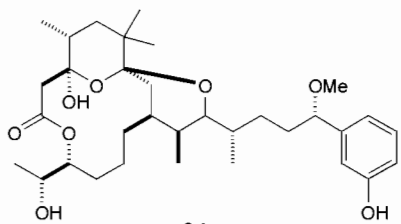
the natural-product diversity from calcareous sponges. It was a macrolide, leucascandrolide A (**64a**), isolated from a newly established species and genus, *Leucascandra caveolata* BOROJEVIC & KLAUTAU, 1998, from the eastern lagoon of the Grande Terre [68b]. Later, leucascandrolide B (**64b**) [68c] was also isolated from the same sponge. By looking at structural analogies, leucascandrolide A (**64a**) may be viewed as a member of the group of polyether macrolides represented by aplysiatoxin (**64c**), which was isolated from tropical cyanobacteria in the family Oscillatoriaceae [69]. However, leucascandrolide A is unique due to its oxazole-bearing side chain. During subsequent expeditions, *L. caveolata* was no longer found at the original site, and samples from northern sites did not contain these alkaloids [68c]. This suggests that the leucascandrolides were derived from adventitious bacteria colonizing dead portions of the sponge [68c].



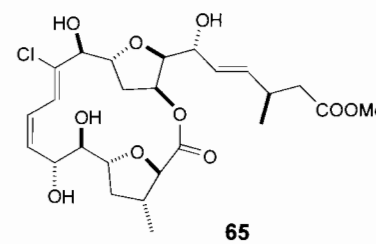
64a



64b



64c



65

The disappearance of leucascandrolide A (**64a**) from nature, and its challenging structure and pharmacological potential (*Sect. 3*), have stimulated the synthetic chemists [70]. Total synthesis of the optically active macrolide moiety of **64a**, which was also obtained by degradation of the natural product [68b], was carried out along sequences ending in macrocyclization of either *Mitsunobu* type [70a,b], classical *Yamaguchi* type [70c,h,i], or either the *Yonemitsu* type [70d] or polar-solvent [70e] variants of the latter. The first *Mitsunobu* route above [70a], and the latter two routes [70d,e], were completed with the attachment of the oxazole-bearing chain, which was also provided in separate synthetic experiments [70f], the first in a stereospecific manner with an astonishing 5.3% overall yield of **64a** from an easily prepared diene by a longest linear sequence of 23 steps [70a], and the latter two ending in a 7:1 mixture of **64a** and the (*E*)-isomer [70d,e]. A short, efficient synthesis of racemic leucascan-

drolide A from commercial precursors was based on spontaneous macrolactolization and *Mitsunobu* attachment of the side chain [70g].

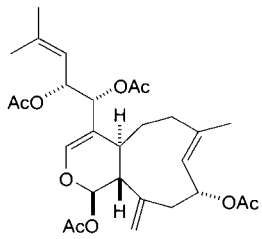
At the time, these were the sole macrolides isolated from calcareous sponges. A recent paper has reported another polyether (tetrahydrofuran) macrolide, chagosensine (**65**), isolated from *Leucetta chagosensis* from the Red Sea [68d]. Surprisingly, the importance of this finding in relation to the unusual macrolides from *Leucascandra caveolata* has been ignored [68d].

Apart from these findings, our search for new metabolites from calcareous sponges has been quite deceiving. We did not find any unusual metabolites in *Leuconia* sp. and *Grantia compressa* from various locations in Brittany [71a], *Leucetta* sp. from Tahiti [71b], and *Ascaltis grisea* from New Caledonia [71c].

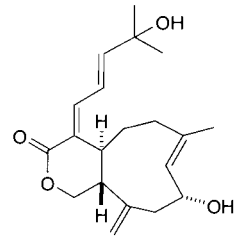
Cnidarians. The large diversity of alcyonaceans and gorgonaceans on coral reefs and in the colder waters of the northern and southern hemisphere, in addition to the presence of pennatulaceans, stoloniferans, and a few telestaceans, have made Cnidaria the second preferred phylum, after Porifera, for study by marine natural product chemists. Terpenoids were most commonly found either exclusively or typically of terrestrial plants. Polyhydroxylated steroids and guanidine, imidazole, macrolide, and isoprene alkaloids were also found [2a][72]. Deep-water species of gorgonaceans and pennatulaceans from Hawaii [73a], southern Indian Ocean [73b], and Mediterranean [73c], have yielded a similar variety of metabolites.

Studies of New Caledonian cnidarians have included a few alcyonaceans, gorgonaceans, and deep-water scleractinian corals. The alcyonaceans are represented by *Xenia garciae* BOURNE [74] and *Xenia membranacea* SCHENK [76], which gave diterpenes of the xenicin (**66**) group [75], like havannahine (**68a**) [76a], 11,19-desoxyhavannahine (**68b**), 11,19-deoxy-7-epihavannahine (**68c**), 11,19-desoxy-7,8,9-epihavannahine (**68d**) [76b], and other havannahine-related compounds. The configurations of these compounds [76c], and of a xeniolide A (**67**) type diterpene [77], 18,19-dichloro-7,10 : 8,11-diepoxyisoxeniolide A [76c], remain largely unknown. It should be possible to gain further insight into the nature of these compounds from molecular-mechanics calculations and NMR fitting, according to a protocol established for the xenicanes [78]. Both these and the studies described below concern only a very small percentage of the rich biodiversity of octocorals of New Caledonia [79].

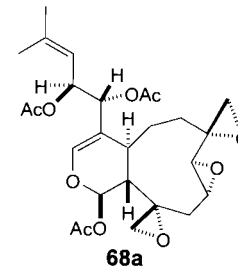
Briarane diterpenes **69a**–**69c** [80a] (related to **70** and **71**; *Table*) and **72a**–**72c** [81] were isolated, without assigning the position of the ester groups, from the New Caledonian pennatulacean corals *Pteroeides laboutei* HONDT, 1984, and *Cavernulina grandiflora* HONDT, 1984, respectively. As for the xenicanes, a deeper insight into the nature of these briaranes, which are characteristic of this group of corals, should be possible from molecular mechanics calculations and NMR fitting, according to protocols established for similar systems [73c]. As these briaranes are of stylatulide (**71**) type, they are expected to show temperature-dependent NMR signals [73c]. These, however, were not reported [80a]. It is possible that an inappropriate NMR frequency was used, or that the exchange phenomenon went unnoticed. Broadening of NMR signals for these stylatulide-type diterpenes is expected to arise from slow chair–chair inversion of the six-membered ring, resulting in unusual conformations with equatorial AcO–C(14) group and C(2) and C(9) in the *trans*-diaxial position, forced by repulsive interactions between β-substituents at the ten-membered ring [73c].



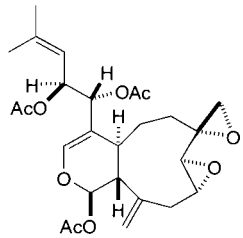
66



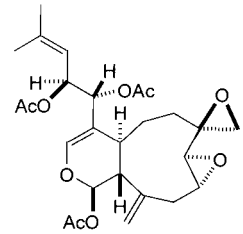
67



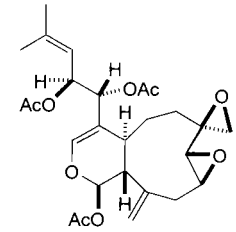
68a



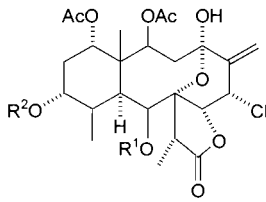
68b



68c

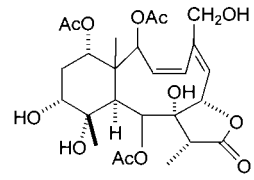


68d

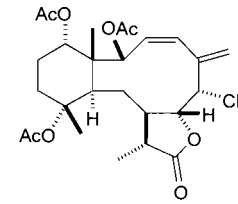


69a $R^1 = R^2 = Ac$

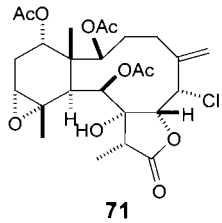
b $R^1 = Ac$, $R^2 = PhCO$



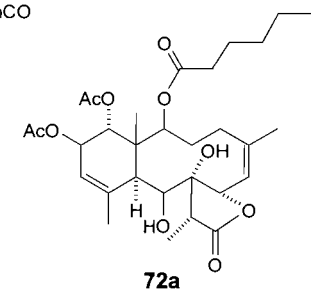
69c



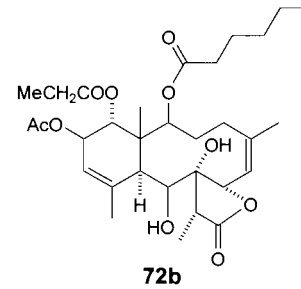
70



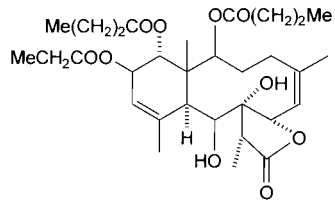
71



72a

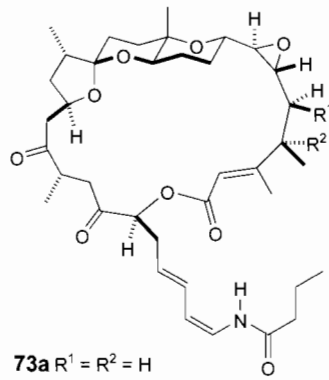


72b

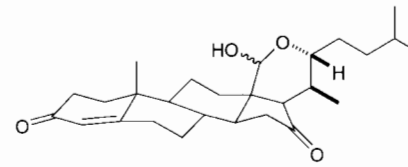


72c

Another New Caledonian pennatulacean, *Lituaria australasiae* (GRAY, 1970), digresses sharply from its taxonomic group due to the production of macrolides **73a**–**73c** [82]. As an isolated example from pennatulaceans, the polyether nature of these macrolides suggests bacterial biosynthesis.



73a $R^1 = R^2 = H$
b R^1 = AcO, R^2 = OH
c $R^1 = R^2$ = OH



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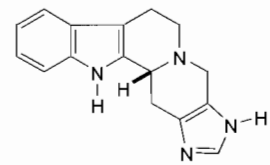

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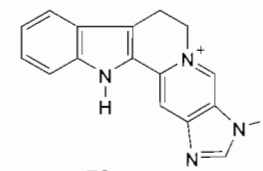


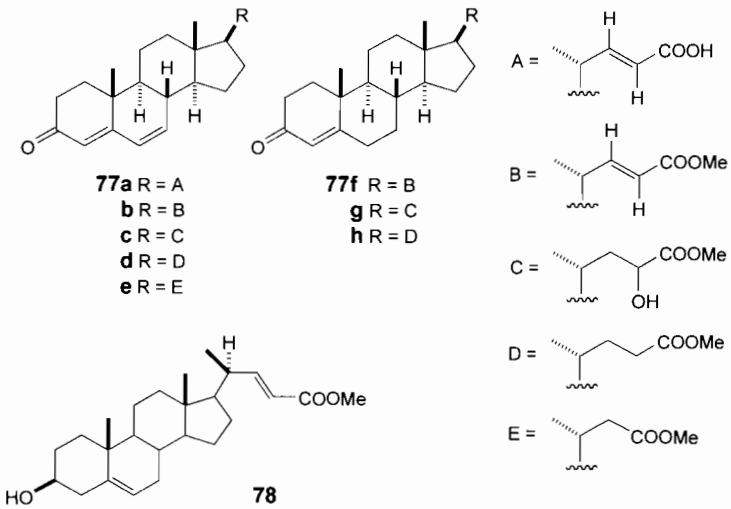
76

In New Caledonian gorgonaceas, *Ctenocella* sp. gave a mixture of sterone acetals (**74**) [83a]. Although these sterones closely resemble products from Western Australian *Ctenocella pectinata* [83b], taxonomic confirmation of the genus *Ctenocella* for the New Caledonian species is urged, because this genus is absent from authoritative taxonomic lists of New Caledonian gorgonaceans [5c][79]. As to other New Caledonian gorgonaceans, *Melithaea caledonica* GRASSHOFF, 1999 (originally erroneously reported as *Melithea* cf. *stormii*), gave a 21,159 Da protein that bears some sequence similarity to a product from a sea anemone, *Anemonia sulcata* [84]. Moreover, *Villagorgia nozzolea* GRASSHOFF, 1996 (originally erroneously reported as *Villagorgia rubra*), gave unique indoloquinolizidine alkaloids **75** and **76** in addition to caffeine [85a], typical of *Coffea arabica* L., and found in another gorgonacean coral [85b] as well. As with the alcyonaceans, the sample of gorgonacean diversity of New Caledonia [5c] is so small that trying to draw a biogeographical construct may be futile.

Hexacorallia, with the exception of actiniarian polypeptides, have received comparatively little attention from natural-product chemists. As recently summarized [2a], the family Dendrophylliidae, in the order Scleractinia, accounts for a large part of the unusual small metabolites isolated from Hexacorallia. In particular, they gave indole alkaloids called aplysinopsins, rich in chemistry and photochemistry. In contrast, the main coral-reef builders, the stony corals, are characterized by the presence of polyacetylenes in their organic extracts. Zoanthinarians, other than ecdysteroids, gave alkaloidal pigments called zoanthoxanthins, besides rearranged triterpene alkaloids called zoanthamines and high-molecular-weight toxic polyketides called palytoxins. Antipatharians from the southern Indian Ocean gave special hydroxydocosapentaenoic acids.

The first studies of deep-water scleractinian corals have been carried out on species from New Caledonia. Cholanic acid-type sterones **77a**–**77h** were found in *Deltocyathus*

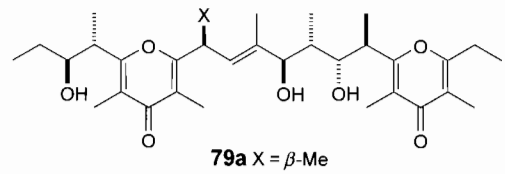
magnificus MOSELEY, 1876 [21]. Of these, **77e** is peculiar for loss of C(24), and **77c** and **77g** are unusual for hydroxylation on the side chain [21]. Similar steroids, including sterone **77f**, were found in mammalian and fish bile, as well as in the body of the marine gastropod *Aldisa sanguinea cooperi* from Pacific Canada [86a]. Sterones **77d** and **77h** were found in bacterial cultures on steroid precursors, and **77d** was also found in hepatoblastoma cells [21]. An unusual 20-epicholanic acid derivative, **78**, is known from the pennatulacean coral *Ptilosarcus gurneyi* GRAY from California [86b]. Unique polyhydroxycholanic acid derivatives, carolisterols A–C (**85a**–**85c**), have been found in the starfish *Styracaster caroli* from the deep waters around the Loyalty Islands [86c].



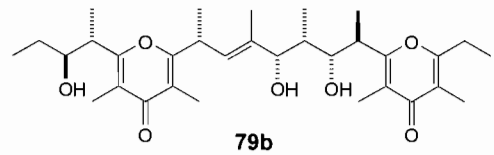
Molluscs. Opisthobranch mollusks, with a few exceptions of *de novo* synthesis, are known as rich sources of metabolites incorporated from cyanobacteria, algae, sponges, cnidarians, and bryozoans, according to their specific diet [2a]. Pulmonata have given a variety of acyclic polyketides, in particular polypropionates [2a]. Prosobranchs are best known for toxic polypeptides, called conotoxins, from tropical *Conus* spp. [2a].

Polypropionates and conotoxins were also isolated from New Caledonian molluscs. The prosobranch *Conus consors* gave the new conotoxins α-CnIA, α-CnIB, and CcTx [87], which are disulfide peptides built on 14, 12, and 30 amino acids, respectively. Structural analogies with other conotoxins are indicated in the *Table.*

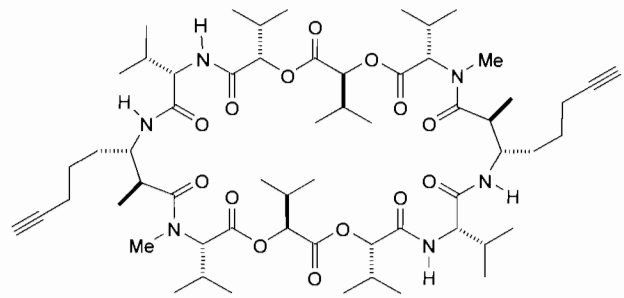
A New Caledonian pulmonate, *Onchidium* sp., gave polypropionates called onchitriols I and II, of assigned structures **79a** and **79b**, respectively [88]. From total synthesis, the latter was confirmed [89a], while the former was revised to **79c** [89b]. This mollusc also gave cyclic depsipeptides, onchidin (**80a**), characterized by uncommon C_2-symmetry [90a], and onchidin B (**80b**) [90b].



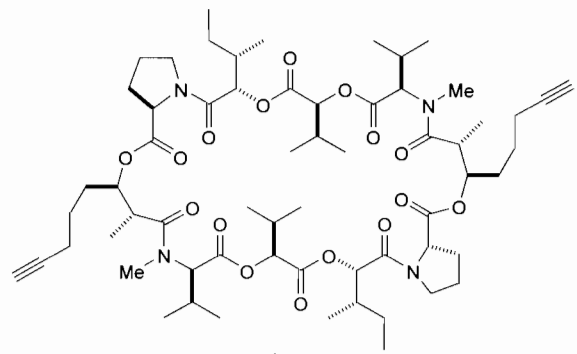
79a X = β-Me
79c X = α-Me



79b

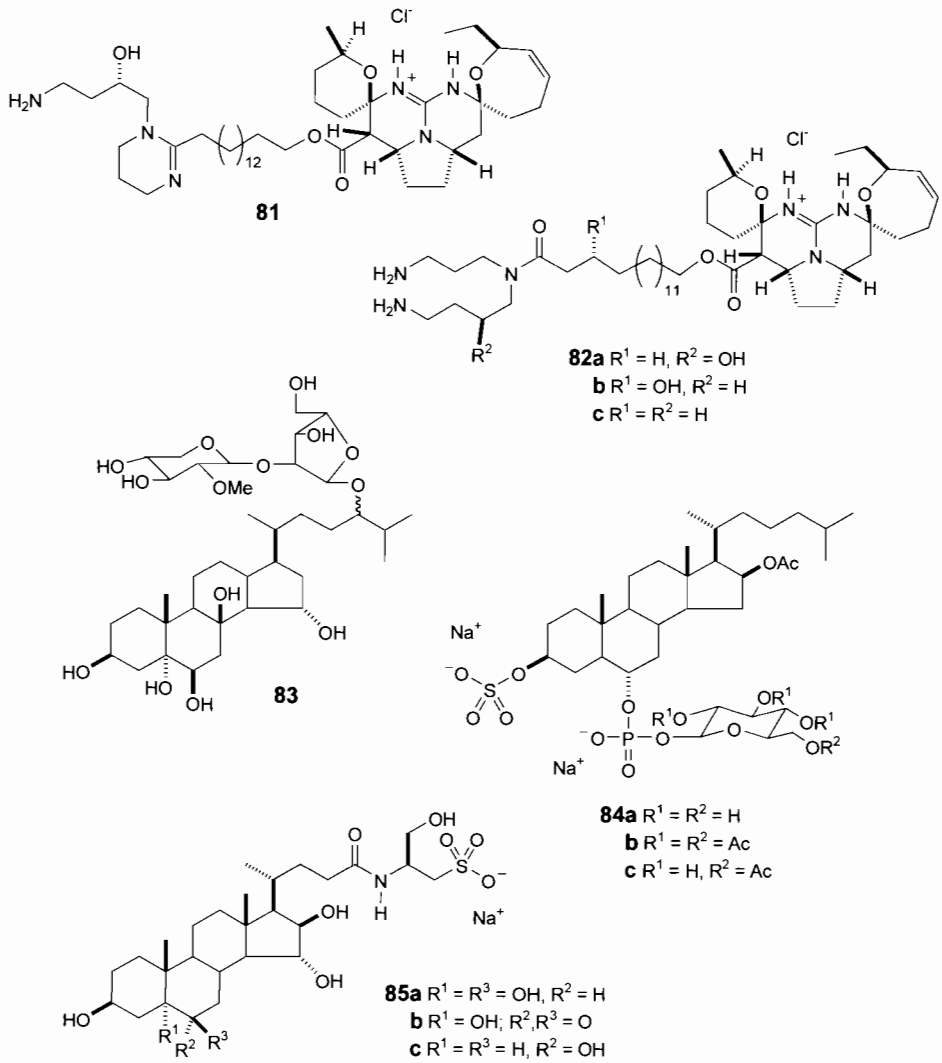


80a



80b

Echinoderms. Starfish are typified by the production of polyhydroxylated steroids and their glycosides [1]. A benzyltetrahydroisoquinoline alkaloid isolated from *Dermasterias imbricata* from British Columbia [91] was an isolated example of an unusual product from starfish. Recently, pentacyclic guanidinio alkaloids, like the new fromiamycalin (**81**) and celeromycalin (**82b**), and the known crambescidin 800 (**82a**) and ptilomycalin A (**82c**), were added to the oddities from starfish, with *Fromia monilis* PERRIER, 1875, and *Celerina heffernani* LIVINGSTONE, 1931, from New Caledonia [92a]. As typical products of sponges in the families Crambeidae and Mycalidae [92b], these

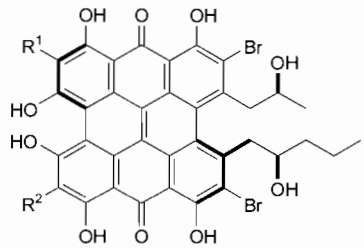


alkaloids may well be derived from the starfish feeding on a local, albeit mysterious, sponge.

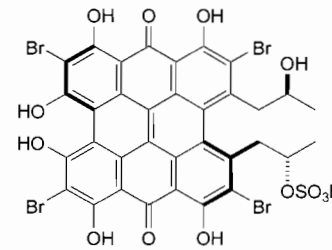
All other starfish studied from New Caledonia gave polyhydroxylated steroids and their glycosides, as recently reviewed [93]. The three most unusual species in this respect are reported in the *Table*. Thus, *Protoreaster nodosus* LINNÉ, 1758, gave nodososide (**83**), unusual because of a 2-*O*-methyl-3-D-xylopyranosyl-(1 → 2)-α-L-arabinofuranosyl moiety glycosidically attached at C(24) of a cholestane aglycon [94a]. Deep-water *Tremaster novaecaledoniae* (JANGOUX, 1982) gave tremasterols A – C (**84a** – **84c**), unusual cholestane steroids because of 3β-*O*-sulfated-6α-*O*-phosphated and 16β-*O*-acetylated groupings [94b]. *Styracaster caroli* LUDWIG is added to this list merely to show that abyssal depths (*Table*) do not confer any special metabolic

productivity, this species fitting its phylogeny with polyhydroxylated cholanic-acid-type sterols, called carolisterols A–C (**85a**–**85c**) [86c].

In addition to steroid sulfates from New Caledonian ophiures [95], attention was also paid to phenanthroperylenequinone pigments, gymnochrome A (**86a**), B (**86b**), C (**87**), D (**88**), and isogymnochrome D (**89**), isolated from a Norfolk Ridge deep-water 'living fossil' crinoid, *Gymnochrinus richeri* BOURSEAU, AMEGIANE-COMINARDI &



86a $R^1 = R^2 = Br$
b $R^1 = H$, $R^2 = Br$ or $R^1 = Br$, $R^2 = H$



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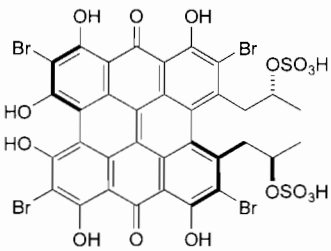
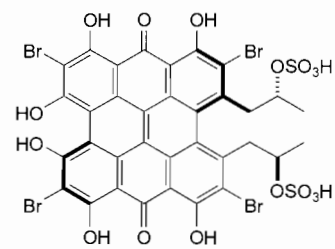


88



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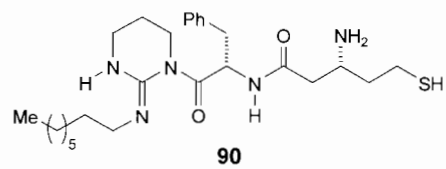

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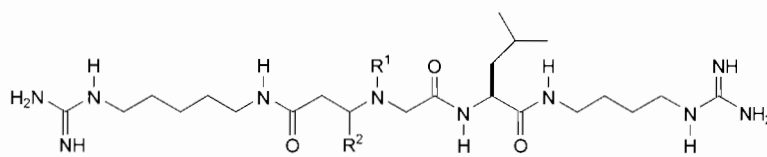


91a $R^1 = H$, $R^2 = Me(CH_2)_6$
b $R^1 = H$, $R^2 = Me(CH_2)_7$
c $R^1 = H$, $R^2 = Me(CH_2)_8$
d $R^1 = SO_3H$, $R^2 = Me(CH_2)_6$
e $R^1 = SO_3H$, $R^2 = Me(CH_2)_7$
f $R^1 = SO_3H$, $R^2 = Me(CH_2)_8$

ROUX, 1987 [96a]. These pigments represent a conserved trait from Jurassic crinoids, while the presence of non-brominated analogues in extant land plants and ciliates may be rationalized by convergent evolution [72].

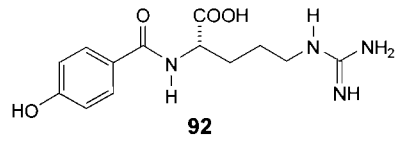
Tunicates. Production of unusual metabolites is typical of organisms that occupy low positions on the phylogenetic tree. Ascidians are an exception. Although the presence of a notochord in tadpoles places them very high on the phylogenetic tree, their metabolic production is as varied and unusual as that of the Demospongiae, which lie much lower along the tree. In particular, pyridoacridine and pyrroloiminoquinone alkaloids are characteristic of both groups of organisms [2a].

All ascidians investigated from New Caledonia are in the order Aplousobranchia. The family Didemnidae is specialized for modified peptides. Thus, *Didemnum rodriguesi* ROCHA & MONNIOT, 1993, gave a lipopetide, caledonin (**90**), which exhibits Zn^{II} and Cu^{I} complexing properties and peculiarly incorporates a penicillamine-like β-amino acid [97a]. This ascidian also gave sulfamic-acid-bearing analogues of guanidine peptides, called minaleimines A–F (**91a–91f**) [97b]. *Leptoclinides dubius* (SLUITER, 1909) gave a series of modified peptides that are unusual in that they contain an amino acid that has lost the amino group and two C-atoms, like *N*-(4-hydroxybenzoyl)-L-arginine (**92**), *N*-(1*H*-indol-3-ylcarbonyl)-D-arginine (**93**), *N*-(6-bromo-1*H*-indol-3-ylcarbonyl)-L-arginine (**94a**), *N*-(6-bromo-1*H*-indol-3-ylcarbonyl)-L-histidine (**94b**), and known L-enduracidinine (**94c**) [98a]. It also gave C^2-α-D-mannosylpyranosyl-L-tryptophan (**95a**), which is the first example of a C-glycoconjugate in non-humans, related to **95b** [98b], as will be discussed later. *Lissoclinum bistratum* (SLUITER) gave a series of lipopeptides, bistramides A (**96a**), B–D (**96b–96d**) and K (**96e**) [99e]. Bistramide A (**96a**) was also found (and called bistratene A) in both the same nominal species from the Great Barrier Reef and *Lissoclinum* sp. from the Fiji islands, allowing the revision [99a] of an erroneous structural deduction from the former studies [99b]. Synthesis of segments of the natural product, and total synthesis of one of its stereoisomers, coupled to chiroptical studies, allowed the assignment of the absolute configuration of a member of this family, bistramide C (**96c**) [99m].

All New Caledonian ascidians in the Polycitoridae family gave β-carboline alkaloids. Included are new eudistalbins A and B (**97a** and **97b**) and known eudistomin E (**98**) from *Eudistoma album* F. MONNIOT [100a], woodinine (**99**) from *Eudistoma fragum* F. MONNIOT [101a], and arborescidins A–D (**100a–100d**) from *Pseudodistoma arborescens* MILLAR [102].

Terpenoids were also isolated from New Caledonian Didemnidae, like *Lissoclinum voeltzkowi* MICHAELSON (dichlorolissoclimide (**101a**) [103a,c] and chlorolissoclimide (**101b**) [103b,c]) and deep-water Polyclinidae, like *Ritterella rete* MONNIOT C. & MONNIOT F., 1991. The latter gave a series of furanosesquiterpenes, 8-hydroxydendrolasin (**102a**), 6,7,8-trihydroxydendrolasin (**102b**), 8,10,11-trihydroxydendrolasin (**102c**), 8-hydroxy-6,7-epoxydendrolasin (**102d**), 8,15-dihydroxy-γ-butyrolactone dendrolasin (**102e**), and 8-hydroxy-1-methoxy-γ-butyrolactone dendrolasin (**102f**) [104], as well as *N*-α-methyl derivative of **95a** C^2-α-D-mannosylpyranosyl-L-tryptophan, **95b** [98b].

Microorganisms. Although little attention has been paid to marine microorganisms and seaweeds from New Caledonia, the few species studied warrant brief mention here to complete the scenario and pave the way for future opportunities. Bacteria isolated from sponges of the Grande Terre's lagoon yielded in culture glycerolipids [105a],



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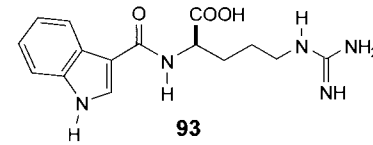

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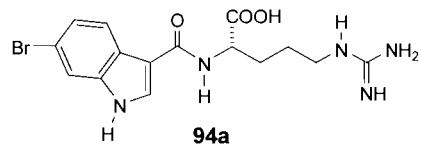
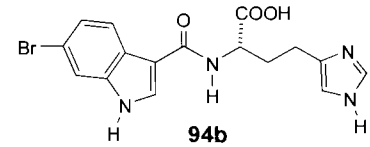
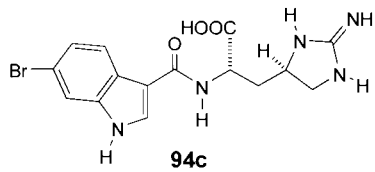


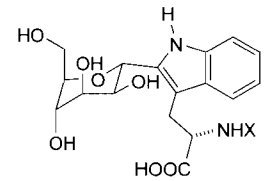
94a



94b



94c



95a X = H
b X = Me

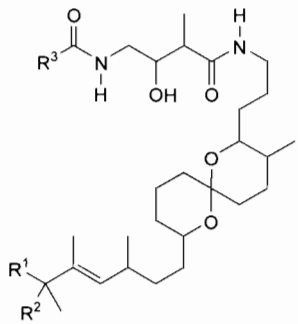
quinoline-2,4-diones and their *N*-oxides, as well as diketopiperazines [61c], quinolones [105b], and chlorinated diphenyl ethers [105c].

During an investigation of the lipid profile of several thraustochytrids from various marine ecosystems, *Schizochytrium mangrovei* from the southwestern New Caledonian lagoon proved most interesting, with an unusual pattern of steroids, dominated by (24*R*)-dehydroporiferasterol [106a]. This contradicts the assumption that cholesterol is always the dominant steroid in these organisms [106b].

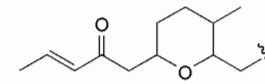
Lignicolous fungi from the New Caledonian lagoon have given a new phenolic tetralone, humicolone (**103**) [107a], and trichothecene sesquiterpenes [107b].

3. Biological Activity and Technological Potential. – Comparing bioactivity and technological potential of natural products on a regional basis is difficult because the results are strongly biased both by the opportunities and the models chosen to evaluate the activity. With these limits in mind, quantitative bioactivity data for products of sponges and other invertebrates from New Caledonia are summarized in the *Table* (Appendix), second column, while comparative data appear in the third column for the same or related products from other ecosystems. Biologically inactive products in the second column may be rationalized either by synergism in raw extracts, resulting in high enough bioactivity for study, or by loss of activity during or after the isolation process due to chemical degradation, which may have occurred before bioassays could be carried out.

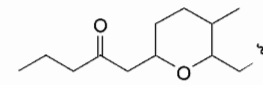
Historical notes help place the pharmacological approach to New Caledonian marine natural products in a global perspective. Initially, from 1977 to 1982, programs of marine pharmacology at *ORSTOM* in Nouméa were carried out in collaborations



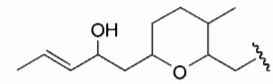
96a R^1 = OH, R^2 = H, R^3 =



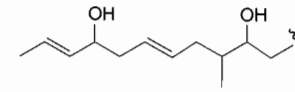
96b R^1 = OH, R^2 = H, R^3 =

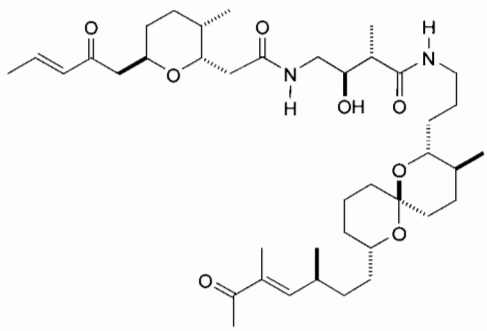


96d R^1 = OH, R^2 = H, R^3 =

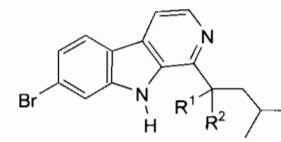


96e R^1 = OH, R^2 = H, R^3 =

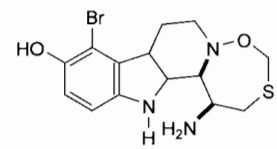




96c



97a R^1 = H, R^2 = NH_2
b R^1,R^2 = O



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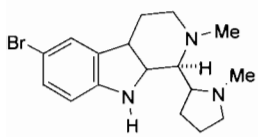

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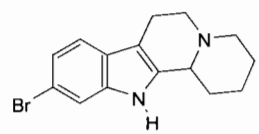
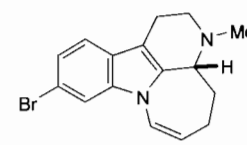
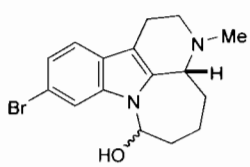


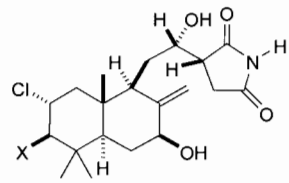
100a



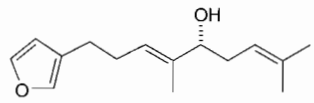
100b



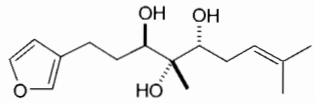
100c α-OH
d β-OH



101a X = Cl
b X = H



102a



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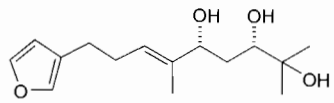
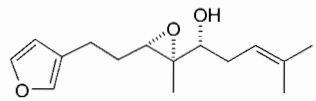
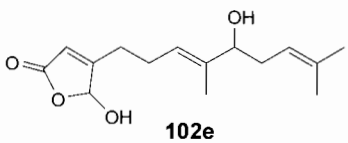


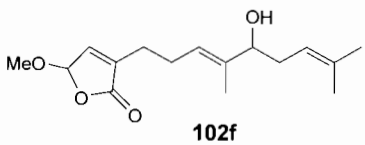
102c



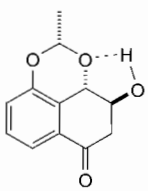
102d



102e



102f



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with both the *CNRS*[1]) and the pharmaceutical company *Rhône-Poulenc*, which was in charge of bioassays on targets for proliferative, cardiovascular, and CNS disorders. The most-significant result was the discovery of girolline (**35c**), a cytotoxic alkaloid from the halichondrid sponge *Cymbastela cantharella* that reached an advanced stage of *in vivo* experimentation against leukemias and solid tumors and, therefore, also triggered synthetic interest [43]. Girolline, an inhibitor of protein synthesis, failed as a drug candidate because of severe hypotensive action [42b,c].

This was a pioneering period for marine pharmacology worldwide, based mainly on bioassays of cell lines, microorganisms, whole-body animals, and isolated organs, following the trends of terrestrial natural products and synthetic products. *Roche Research Institution*, based at Dee Why in northeastern Australia, headed by *R. J. Wells* as a chemist and *J. T. Baker* as a pharmacologist, dominated the industrial side. Although now closed, it has remained a unique example of autonomous research, from marine specimen collection to molecular-structure elucidation, and biological evaluation of the products, with focus on antiproliferative, cardiostimulant, anti-inflammatory, anti-hypertensive, and neuroactive small-molecule agents [108]. In parallel, *Smith-Kline Beecham Pharmaceuticals*, based in Pennsylvania, introduced novel receptor assays, with macrophage scavenger receptors as targets for anti-atherosclerotic agents from gorgonacean corals of the Caribbean [109].

University research, during this period, was dominated by two centers in the U.S.A. The University of Arizona team, headed by *G. R. Pettit*, presented *in vivo* antitumor

substances, called dolastatins, which are peptides from the sea hare *Dolabella auricularia* from the western tropical Indian Ocean [110a] (later also found in Japan [110b]) and the bryostatins, macrolides from the Caribbean bryozoan *Bugula neritina* [111]. The University of Illinois team, headed by *K. L. Rinehart*, announced the first examples of didemnins, which are antiviral and cytotoxic cyclic depsipeptides from colonial ascidians of the Caribbean [112]. In this class, dehydrodidemnin B (= aplidine; **50**), is still at the forefront of oncological pharmaceutical research [53d].

In 1983, *Rhône-Poulenc* lost confidence in natural products as a source of drugs. It only continued with taxane diterpenes and turned to combinatorial chemistry. Therefore, in a new program called *SMIB* (see above), started at *ORSTOM* in conjunction with the *CNRS*, one of the present authors, *D. L.*, initiated in Nouméa a line of simple and rapid bioassays on raw and enriched extracts, including cytotoxicity on epidermal KB cells, disk tests on bacteria and yeasts, and general toxicity assays on *Artemia salina*. This overcame previous problems from bioassays carried out at remote laboratories, probably often carried out on material that had degraded during shipping. Natural-product chemists and pharmacologists from European non-profit institutions were also attracted to this program. This allowed extension of the bioassays to a broader panel of human cancer cell lines, including P388, L1210, HT29, and the leading cause of cancer mortality, non-small cell lung cancer (NSCLC). Viruses were also added, like Human Immunodeficiency Virus 1 (HIV-1), Human herpes virus (*Herpes simplex*, HSV), and Vesicular Stomatitis Virus (VSV). Moreover, following trends in marine pharmacology [113], mechanism-based bioassays were also set up, with special interest in cellular receptors, such as Neuropeptide Y (NPY), Phospholipase A2 (PLA_2), Serotonin (Ser), Somatotropin Release Inhibiting Factor (SRIF), Tyrosine Protein Kinase (TPK), Vasointestinal Peptide (VIP), HIV-Integrase (HIV-int), and Inositol 1,4,5-triphosphate (IP_3).

Cytotoxicity accounted for most of the positive assays from New Caledonian marine invertebrates. Cytotoxic to normal and tumor cells, bistramide A (**96a**), a lipopeptide from the ascidian *Lissoclinum bistratum*, was shown to induce a blockade in the G1 phase, while causing polyploidy suggestive of inaptitude for cytokinesis [99f]. This metabolite is highly toxic, with a rapid CNS effect, leading to paresthesia and loss of muscle tone. It also affects the twitch tension in rat atrial heart muscle [99i], blocking the Na channel and affecting the Ca channels [99h]. A similar blocking action at the G1 phase was also noticed for dichlorolissoclimide (**101a**) and chlorolissoclimide (**101b**), which are labdane diterpenes isolated from *Lissoclinum voeltzkowi* [103d]. Lituarines A–C (**73a**–**73c**), which are macrolides isolated from a pennatulacean coral, *Lituaria australasiae*, proved cytotoxic at the ppb level [82]. At the same dosage level, a family of macrolides from deeper-water lithistid sponges, sphinxolides **14a**–**14i**, proved cytotoxic toward several human cancer cell lines, **14b** being the most active, causing depolymerization of microfilaments, similar to the cyanobacterial macrolides scytophycins [17f] and tolytoxin [17g], which they structurally resemble. Cyclic depsidecapeptides, called callipeltins A–C (**49a**–**49c**), isolated from a shallow-water lithistid sponge, *Callipelta* sp., proved cytotoxic toward various human carcinoma cells *in vitro*. From the observation of an activity higher than **49c** for both **49a** and **49b**, the macrocycle was suggested to play a key role in determining activity [53b]. The antiviral activity of callipeltin A (**49a**) was also demonstrated on CEM4 lymphocytic cell lines

infected with HIV-1 (with activity comparable to AZT, $CD_{50} = 13.3$ μg/ml and a $ED_{50} = 0.008$ μg/ml [53a]). Callipeltosides (**51a–51c**), isolated from the same sponge, showed a moderate cytotoxic activity, with **51a** causing a dependent G1 blockage [54a]. Thorectolide monoacetate (**44b**), isolated from a dictyoceratid sponge, *Hyrtios* sp., proved to be as strongly cytotoxic as manoalide (**45**), and much more than thorectolide (**44a**), against KB cells [50a]. Agelastatin A (**25a**), isolated from an agelasid sponge, *Agelas dendromorpha*, showed insecticidal properties [32d], and, most unusually and importantly, selective inhibition of glycogen synthase kinase-3β [32e,g], while still notably cytotoxic toward KB cells [32a]. Three functional groups, C(8a)–OH, N(5)–H, and N(6)–H, and the natural C/D ring-fusion configuration, as in **25a**, are required for displaying significant activity against leukemia and epithelial tumor cell lines [32c]. It should be noticed that oroidin-related C_{11} and C_{10} alkaloids typically show biological activities, and their relatively simple structures should permit efficient production by chemical synthesis. A recent notable addition is ageladine A, an oroidin-related C_{10} fluorescent alkaloid with anti-angiogenic matrixmetalloproteinase inhibition properties, isolated from the agelasid sponge *Agelas nakamurai* from southern Japanese waters [32l]. Leucascandrolide A (**64a**), from a New Caledonian calcareous sponge, proved to be strongly cytotoxic and fungi-toxic [68b]. Separation of the macrolide ring from the oxazole side chain showed that the first is related to the cytotoxic activity and the latter to the antifungal activity, albeit reduced to fungi-static [68b]. Total synthesis has overcome the problem of availability of **64a**, which has become elusive in nature [68c], while also promising access to a variety of analogues [70a]. This should allow a complete pharmacological profile of this metabolite. Unique 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium alkaloids, called phloeodictynes, isolated from both deep-water and shallow-water haplosclerid New Caledonian sponges of the genus *Phloeodictyon* (= *Oceanapia*), proved to be moderately cytotoxic toward KB cell lines but exhibited noticeable antibacterial activity against *Gram*-positive and *Gram*-negative bacteria *in vitro* [36a]. Cytotoxicity toward KB cell lines was also ascertained for humicolone (**103**), a fungal phenolic tetralone [107a]. A wealth of stereogenic centers in this simple structure should stimulate development of libraries of synthetic analogues, which, for the same reasons, also holds true for girolline (**35c**). This promising new approach to combinatorial chemistry, pivoting on natural products [114], awaits applications to New Caledonian products.

A special case is represented by nortopsentin D (**26a**). Although many bis-indole alkaloids proved cytotoxic toward cancer cell lines [33d,e], as well as showing antifungal [33c] and antibacterial activity [33e], **26a** proved inactive in the KB assay [33a]. However, the sponge taxonomy and the unique feature of an imidazole appendage at the central nucleus of **26a**, stimulated the assaying of semisynthetic analogues. This was rewarded by finding high cytotoxicity for the permethylated derivative **26b**, possibly reflecting an augmented permeability of cell walls [33a].

Less powerful cytotoxic activity was detected for other New Caledonian metabolites, such as eudistomin-type β-carboline alkaloids called eudistalbins A and B (**97a** and **97b**), isolated from an ascidian of the genus *Eudistoma* [100a], new pentacyclic guanidine alkaloids, fromiamycalin (**81**) and celeromycalin (**82b**), isolated from a starfish [92a], γ-pyrone polypropionates, onchitriols I (**79c**) [89b] and II (**79b**) [88][89b], from a pulmonate mollusk, as well as a mixture of sterone acetals **74** from a

gorgonacean coral [83a]. Sponges yielded petrosaspongiolides A (**39a**), B (**39b**) [47a,b], and C–L (**39d–39l**) [47b], aurorals A–D (**33a–33d**) [39a], dipuupehedione (**47b**), a new dimer of **47a**, albeit less active than the latter [51a], and xestospongin-type alkaloids **60a–60c** [64a]. Marginal cytotoxicity for aztèquinols A (**59a**) and B (**59b**) does not account for the high cytotoxicity determined for the raw extract of the sponge *Petrosia* sp. [63].

Antibiotic assays have guided the isolation of new substances from New Caledonian marine invertebrates. Besides the phloeodictynes, as mentioned above, these include an antibacterial β-carboline alkaloid, woodinine (**99**), from an ascidian [101a], and antifungal peptides, microsclerodermin A (**15a**) and B (**15b**) [22a], and a depsipeptide, neosiphoniamolide A (**11**) [13], from lithistid sponges. A well-known merosesquiterpene from sponges, puupehenone (**47a**), was also determined to be antimicrobial [51a].

Concerning antivirals, besides anti-HIV-1 callipeltin A (**49a**) from sponges, as described above, molluscan onchitriols I (**79c**) [89b] and II (**79b**) proved active toward HSV-1 and VSV [88].

Receptor activity was determined for several products of New Caledonia sponges. Thus, xestospongins **61a–61c** proved to be potent membrane-permeable inhibitors of IP_3-mediated Ca^{2+} release from endoplasmic reticulum stores [64b]. Because the phosphoinositide signaling cascade plays a prominent role in neuronal signaling, xestospongins may become a new pharmacological tool for studying IP_3-dependant signal transduction in living cells. Petrosaspongiolides A (**39a**), B (**39b**), and C–L (**39d–39l**), as PLA_2 inhibitors, irreversibly block these enzymes with IC_{50} values in the micromolar range [47c]. Thorectolide (**44a**), as a HIV-int and HIV-1 nucleocapside inhibitor, and its monoacetate derivative (**44b**), as a cobra venom PLA2 inhibitor, displayed activity in the range of manoalide (**45**) [50a]. Ageliferin (**23a**) and sceptrin (**24**) behave as SRIF and VIP inhibitors [31a]. Eurypongiols A1 (**37a**) and A2 (**37b**), inhibit the release of histamine from rat mastocysts [46a] and, therefore, may have anti-inflammatory properties. Penta- (**20a**), hexa- (**20b**), and heptaprenylhydroquinone 4-sulfate (**20c**) exert TPK, HIV-int, and NPY inhibition [29a], and gelliusines **28a–28f** Ser agonism and SRIF and NPY inhibition [35a,b]. In addition, a gorgonacean protein, iela melst, showed elastase inhibition [84], while gorgonacean indoloquinolizidine alkaloids, called villogorgins A and B (**75** and **76**), showed acetylcholine antagonism [85a].

CNS Activity was also exhibited by α-CnIA conotoxin from the New Caledonian mollusk *Conus consors*. This conotoxin blocks synaptic potentials in frog and mice [87a], while another conotoxin, CcTx, alters synaptic efficacy and neuromuscular transmission [87b]. Limited availability of α-CnIA from nature was overcome by total synthesis, allowing these biological assays.

According to an administrative reform, the natural product unit of *ORSTOM* was then integrated into a larger group aimed at the study of vectorial diseases. In association with the *Institut Pasteur de Nouvelle-Calédonie*, dengue virus, which constitutes a serious health problem in the tropics [96c], was added to the antiviral tests. The most promising substances discovered so far in this line are phenanthroperylenequinone pigments from a 'living fossil' crinoid, gymnochromes A (**86a**), B (**86b**), C (**87**), D (**88**), and isogymnochrome D (**89**) [96]. The side chain reinforces the photo-activity of the polycyclic nucleus of semisynthetic, brominated hypericin [96b].

In spite of a high annual death rate of two million people, the search for drugs against paludism is neglected by the pharmaceutical industry because of poor economic prospects for revenues, and, due to lack of funding, it has gained little popularity in academia as well. Assays on enzymes specific to *Plasmodium falciparum*, the deadlies malaria parasite, and the search for small molecules that play a role in its development, were added to the research lines at the IRD. These assays have been miniaturized and robotized in the search for new antimalarial drugs. Positive results have been obtained with 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium alkaloids, phloeodictynes, from an haplosclerid sponge [36d], and epidioxy norditerpenes from the poecilosclerid sponge *Diacarnus levii* [57b], active against chloroquine-resistant *P. falciparum*. Methyl 2-epinuapapuanoate (**55b**) is an especially promising lead, being scarcely cytotoxic while, at the same time, being particularly active against the malaria parasite [57b]. Bistramides D and K, lipopeptides derived from an ascidian, also proved to reduce this parasitism, albeit at dosages close to their LD_{50} [99l]. These results should stimulate the development and screening of synthetic libraries of phloeodictynes and epidioxy norditerpenes.

It is true that natural-product diversity from deep-water invertebrates has revealed scarce structural peculiarity thus far [2a]. Nonetheless, regarding New Caledonia, products from deep-sea lithistid sponges showed powerful bioactivity, as noticed for a free porphyrin, corallistin A (**6**) [12a], macrolides, such as superstolide A (**13a**) [16a] and B (**13b**) [16b], and a cyclic depsipeptide, neosiphoniamolide A (**11**) [13]. The same conclusion holds for most of the unusual products isolated from deep-water Caribbean lithistids, such as discodermindole [24a], polydiscamide A [24b,c], and discobahamins [24d], presented above in *Sect. 2*. However, this may not be an accurate representation of nature, because, in both areas, extracts were selected on the basis of pharmacological activity. Before drawing a definitive conclusion, unbiased sampling and chemical examination of deep-water organisms from both areas should be carried out, shedding light on inter- and intraspecific competition in deep *vs.* shallow waters. Although of high ecological interest, a sponsor for such a costly enterprise is not on the horizon at this time.

To date, the technological potential of natural products from New Caledonia has scarcely been exploited. Quinoline-2,4-diones, isolated from marine bacteria [61c], and a tyrosine metabolite, dibromoverongiaquinol (**58e**), from two verongid sponges, *Verongia* sp. [61a] and *Suberea creba* [61c], proved to be useful antibacterial agents for mariculture. Total synthesis of **58e** [61b] (*Sect. 2*) has allowed extensive tests to this regard [61c]. A xenicane diterpene (**68c**) showed antifouling properties [74]. In addition, a thermochromic system was derived from a poecilosclerid sponge, *Zyzza massalis*. As shown in the *Scheme*, an indole alkaloid, zyzzin (**31a**), from this sponge, was observed to undergo S/O exchange in the presence of H_2O, giving a yellow-colored derivative, **31b**, which adds hydroxylic solvents ROH at C(4)=N, affording colorless products, such as **31c** and **31d**. This addition reaction is thermally reversible, establishing the first thermochromic system of marine origin [37a].

Human intoxication from marine organisms is of much concern. Trichothecene sesquiterpenes, isolated from a New Caledonian marine-derived fungus (*Sect. 2*, last sentence), represent the first powerful toxins ever isolated from marine-derived fungi [107b]. Other such toxins have more recently been found in a fungus from Micronesian waters [107c]. Also, before the tropical green seaweed *Caulerpa taxifolia* (VAHL) J.

AGARDH came in the limelight as a species invading the Mediterranean with toxic non-mevalonic [115a] terpenoids, toxicity was ruled out for its caulerpin and caulerpicin[7]) [115b]. It was also shown that the same toxic sesquiterpenoids are present both in New Caledonian and Mediterranean strains of this alga [115d]. This signifies that in migrating to colder seas, the seaweed has conserved this trait. Once again [2a], this demonstrates how coding for secondary metabolites may be deeply written in the genome.

This account has shown that the pharmacological and technological approach to natural products varies according to the research groups, the industrial partners, and the opportunities of funding, which makes any comparison on a regional basis difficult. Also, during the nearly three decades since the inception of these studies, research in marine pharmacology has significantly evolved, often toward more costly projects, both in regard to providing organisms, in particular from deep waters, and means for molecular structure elucidation and bioassay. All this exerts a profound influence on projects in different geographical areas. An example of advancement in bioassay is the new industrial approach to multiple enzymes in a high-throughput search for new antibiotics [116], which makes previous step-by-step methods obsolete.

It is true, however, that, without restriction for funding, fractionation of extracts currently benefits from high-performance chromatography coupled to both a soft-ionization mass spectrometer and a NMR spectrometer, allowing quick examination of small amounts of products, even of high molecular weight and low volatility and stability. Many more products present in nature in trace amounts may thus be made available, although, at this advanced stage of biodiversity examination, new products are mostly expected on known structural themes [2a]. This may not detract pharmacological interest, however, as the different functional groups may account for novel bioactivity of metabolites of a given class, which poses soft-ionization-mass-spectrometry-guided [36d] extraction procedures from nature in competition with establishing libraries from combinatorial chemistry based on natural products [114]. Under these conditions, biological assays, that incorporate advances in robotics, miniaturization, and molecular biology, are no longer a limiting factor. Many new biological targets are offered by the human genome sequence and gene functions. Banks of raw extracts from marine organisms could be made available to the pharmaceutical industry from research organizations that have access to biodiversity, once problems of sharing revenues are solved under the auspices of the Rio de Janeiro convention.

It is under these prospects that the *IRD* (currently associated to the Université Paul Sabatier, Toulouse) and the pharmaceutical company *Pierre Fabre* have recently joined their efforts in the search for new agents against cancer, cardiovascular and neurological dysfunctions, and paludism. Hopefully, this synergism of expertise and funding will aid discovery of treasures still hidden in New Caledonian lagoons and sea mountains, bringing therapeutic advances, if not remedies, for diseases that have no cures as of yet.

Appendix. – For convenience, a summary of metabolites from New Caledonia invertebrates, along with comparisons with natural products from other regions, is given in the *Table*.

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[7]) The name caulerpicin is used here for historical reasons, although it does not refer to any single defined compound. As an isolate from *Caulerpa racemosa* from the Philippines, it was determined as a mixture of ceramides [115c].

Table. *Metabolites from Invertebrates from New Caledonia (NC), and their Bioactivities: Comparison with Organisms from Other Ecosystems*

Taxon[a])/Region[b])	Metabolites from NC (bioactivity[c]))/biogenetic class	Relationships to products from the same nominal species or other species, from other ecosystems (shallow waters, unless otherwise specified), bioactivity, and total synthesis (**TS**)
Porifera (Demospongiae)		
Agelasida, Agelasidae, *Agelas dendromorpha* Lévi/**260 m**	(−)-Agelastatin A (**25a**) (ct KB 0.075, L1210 0.033) [32a] and B (**25b**) [32b]; GSK-3β selective inhibitor [32e]/unusual C_{11} alkaloids	**25a** and agelastatins C and D (**25c** and **25d**) from a W Australian halichondrid sponge, *Cymbastela* sp. (**25a** and **25c** toxic in brine shrimp assay, and **25a** also insecticidal [32d]). **TS 25a** [32f–i].
Agelasida, Agelasidae, *Agelas novaecaledoniae* Lévi & Lévi, 1983/**260 m**	Ageliferin (**23a**) and sceptrin (**24**) (SRIF active 2.2 and 0.27 μM, resp., VIP active 19.2 and 19.8 μM, resp.) [31a] /dimeric C_{11} oroidin-related alkaloids	**23a–23c** (ab, av, antifouling, and active in biochemical prophage induction assay) from Okinawan *Agelas* sp., Caribbean *Agelas conifera* [31b], and Micronesian *Astrosclera willeyana* [31c]; **24** (antimicrobial) from Caribbean *Agelas sceptrum* [31d] and *Agelas conifera* [31b].
Astrophorida, Ancorinidae, *Rhabdastrella globostellata* (Carter, 1883)/E and W lagoons	Auroral 1–4 (**33a–33d**, resp., ct KB 0.8–8) [39a]/unusual (C(3)-α-OH) truncated isomalabaricane triterpenes	Structural analogy with jaspiferals A–G from Okinawan *Jaspis stellifera*, which, therefore, is probably to be reassigned as *R. globostellata*) (ct L1210 0.5–4.3 and KB 1.8–>10; G also af and ab) [39b].
Astrophorida, Ancorinidae, *Stelletta* sp./**700 m**	Stigmastane sterones **17a–17c** and sterols **17d/17e** [26]	Steroid class typical of terrestrial plants.
Astrophorida, Geodiidae, *Erylus* sp./**500 m**	Eryloside C (**19a**) and D (**19b**)/triterpene oligoglycosides [28a]	Structural analogy with products from other *Erylus* sp. (see text).
Astrophorida, Ancorinidae, *Jaspis carteri* (Ridley, 1884)/E lagoon	Bengamide A (**34a**) and B (**34b**), and G–K (**34c–34g**) (inactive on Ca)/amino acid derivatives [40a]	**34a** and **34b** (anthelmintic and ct) from Fijian *Jaspis* sp. [40b]; bengamides Y and Z and bengazole Z (ct) from NW Australian *Japsis* sp. [40d].
Dendroceratida, Dysideidae, *Dysidea fusca* Ridley/E lagoon	Drimane sesquiterpenes [45]	Sesquiterpene class of widespread occurrence, particularly in sponges of this family.
Dendroceratida, Dysideidae, *Euryspongia* sp./S lagoon	Euryspongiols A1 (**37a**) and A2 (**37b**) (inhibitors of release of histamine from rat mastocysts) and other minor analogues/polyhydroxylated 9,11-secosterols [46a]	Related to products of S Australian *Euryspongia arenaria* Bergquist, 1961 [46b]; similar bioactivity for xestobergsterol A (**38a**) and B (**38b**), polyhydroxylated *cis*-C/D-ring-fused steroids from Okinawan haploscerid sponge *Xestospongia bergquistia* Fromont [46c].
Dictyoceratida, Irciniidae, *Ircinia* sp./**450 m**	Penta- (**20a**), hexa- (**20b**), and heptaprenylhydroquinone 4-sulfate (**20c**) (inhibitors of NPY, TPK, and HIV-int) [29a]	Related chromenol sulfates from SE Australian deep-water dictyoceratid sponge *Sarcotragus spinulosus* [29b]; prenylhydroquinone sulfates from Mediterranean *Ircinia spinosula* Schulze [29c] and NE Pacific *Dysidea* sp. [29d].

Dictyoceratida, Thorectidae, *Fasciospongia* sp./Loyalty Island	Fasciospongides A – C (**46a – c**, resp.)/manoalide-like sesterterpenes [50c]	See *Hyrtios* sp. below
Dictyoceratida, Thorectidae, *Fasciospongia* sp./SW lagoon	Linear diterpene dihydric phenol **48** [52]	Phenolic terpenes are widely distributed in marine organisms.
Dictyoceratida, Thorectidae, *Hyrtios erecta* (KELLER, 1889)/whole lagoon	12-Epiheteronemin (**43a**) and known heteronemin (**43b**) [49a]/scalarane sesterterpenes	**43b** from *Hyrtios erecta* from Japan [49b], NE Australia [49c], Red Sea (ct L1210 4.0, KB 1.0 [49b], and inhibitor of *Mycobacterium tuberculosis MIC* 6.25, IC_{50} 1.3 [49d]); 12-epiheteronemin acetate (**43c**) from Tongan *H. erecta* [49e]; β-carboline alkaloids from Red Sea *H. erecta* [49f].
Dictyoceratida, Thorectidae, *Hyrtios* sp./SW Walpole Island	Thorectolide (**44a**) (ct KB 5.3; av HIV-1 nucleocapside and HIV-integrase inhibitor 10 and 20, resp.) and monoacetate **44b** (ct K: 0.3; PLA_2 inhibitor 2 μM/manoalide-like sesterterpenes [50a]	Manoalide (**45**) (ct KB 0.3; PLA_2 inhibitor: 1.7 μM [50b]) and related sesterterpenes from dictyoceratids *Luffariella* sp. from Micronesia, NE Australia, and Okinawa, *Thorectandra excavatus* from N Australia, and *Hyrtios erecta* from Japan.
Dictyoceratida, Thorectidae, *Hyrtios* sp./E lagoon	Puupehenone (**47a**) (ct KB 0.8; af on CT and ab, Sa 12/0.05); dipuupehedione (**47b**) (ct KB 3; no ab Ca and Sa) [51a]/merosesquiterpenes	**47a** (ct human lung, colon, and mammary cancer cell lines [51b]; inhibitor of *Mycobacterium tuberculosis MIC* 12.5, IC_{50} 2.0 [49d]) from Hawaiian dictyoceratid and verongid sponges and haplosclerid sponges of deep Caribbean waters, and a colorless dimer from Tahitian *Hyrtios eubamma* [51a].
Dictyoceratida, Thorectidae, *Petrosaspongia nigra* (BERGQUIST, 1995)/S lagoon	Petrosaspongiolides A (**39a**), B (**39b**) [47a,b], C – L (**39c – 39l**) [47b] (ct NSCLC-N6 0.5), M – N (**39m** and **39n**) and P – R (**39p – 39r**) [47c] (PLA_2 inhibitors)/cheilantane-type sester- and norsesterterpenes	Related to suvanine (**40**) (ichthyotoxic and inhibitor of sea urchin egg cell division [48a]) from Micronesian dictyoceratid *Coscinoderma* sp. [48b], inorolide C (**41**) (ct L1210 0.2, KB 2.8) from Japanese nudibranch *Chromodoris inornata* [48c], and luffolide (**42**) (anti-inflammatory) from Micronesian dictyoceratid *Luffariella* sp. [47a].
Halichondrida, Axinellidae, *Cymbastela cantharella* (LÉVI, 1983)/S lagoon	Odiline (**35a**), dibromocantharelline (**35b**), dibromophakellin [42a]/C_{11} alkaloids; aldisin, 2-bromoaldisin [42a], girolline (**35c**) [42b – d]/degraded C_{11} alkaloids (**35c** ct P388 0.01; antitumor) [42d]; hydroxymethyl-3β-nor-A cholestanes [41]; pyraxinine (**36**) (no inhibition of macrophagic NO synthase) [44]	Odiline (**35a**) (=stevensine) from unidentified Micronesian sponge [42e]; dibromophakellin from other halichondrid and agelasid sponges [42f]; aldisin and 2-bromoaldisin from Micronesian halichondrids [42g]. **TS** racemic girolline in three steps, 10% yield, from commercially available *N*-(hydroxymethyl)phtalimide [43a], while natural (+)-girolline was obtained only in low yield [43b].
Halichondrida, Axinellidae, *Dragmacidon* sp./**300 m**	Nortopsentin D (**26a**); permethylated analogue **26b** (ct KB 0.014 [33a])/bis-indole alkaloids	For bis-indole alkaloid distribution in sponges, see text.
Halichondrida, Halichondriidae, *Stylotella* sp./**250 m**	Stylotelline (**27**)/eudesmane sesquiterpene isocyanide [34a]	Eudesmane isonitriles are known from other halichondrid sponges, such as Caribbean *Axinyssa ambrosia* [34b].

Table (cont.)

Taxon[a])/Region[b])	Metabolites from NC (bioactivity[c]))/biogenetic class	Relationships to products from the same nominal species or other species, from other ecosystems (shallow waters, unless otherwise specified), bioactivity, and total synthesis (**TS**)
Haplosclerida, Chalinidae, *Orina* sp./N Grand Passage, **300 m**	Gelliusine A (**28a**), B (**28b**) [35a], C (**28c**), D–F (**28d**–**28f**) [35b]/racemic tris (A–C) and bis-indole alkaloids (D–F) (Ser agonist 10–100 μM; SRIF and NPY active 5)	Antibiotic trisindoline (**29**) from a bacterium, *Vibrio* sp., from an Okinawan dictyoceratid sponge, *Hyrtios altum* [35c]; bis-indoles are common in green and red seaweeds, sponges, hemichordates, and ascidians.
Haplosclerida, Petrosiidae, *Petrosia* sp./ Norfolk Ridge	Aztèquynols A (**59a**) and B (**59b**) (KB: > 10) [63]/ C-branched polyacetylenes	Unbranched polyacetylenes are common in demosponges, particularly in Haplosclerida, rarely in Dictyoceratida, Halichondrida, and Lithistida.
Haplosclerida, Petrosiidae, *Xestospongia exigua* (KIRKPATRICK, 1900)/S lagoon	Demethylxestospongin B (**60a**), xestospongin B (**60b**) and D (**60c**) [64a] (ct KB 2–2.5, L1210 0.2–2; IP_3 active [64b]) and araguspongine F (**60d**) [64a]/bis-1-oxaquinolizidine alkaloids; xestoamine [64a]/β-carboline alkaloid	Related, vasodilative aragupetrosine A (**61**) from Okinawan *Xestospongia* sp. [64c], and vasodilative and ichthyotoxic analogues from *Xestospongia* spp. [64d].
Haplosclerida, Phloeodictyidae, *Oceanapia fistulosa* (BOWERBANK, 1873)/E lagoon	Phloeodictynes (antimalarial)/1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium alkaloids [36d]	Similar production by *Phloeodictyon* (= *Oceanapia*) sp. [36a,b] (see below).
Haplosclerida, Phloeodictyidae, *Oceanapia* cf. *tenuis* DESQUEYROUX-FAUNDEZ, 1987/S lagoon	Oceanapins A–F (**62a**–**62f**) [65]/ceramides with C-branching on both chains	Unbranched, or single-chain C-branched, ceramides are common in marine organisms.
Haplosclerida, Phloeodictyidae, *Phloeodictyon* (= *Oceanapia*) sp./**235 m**	Phloeodictynes in three groups (see text) (ct KB 1.5–11.2; ab (*MIC*) Sf 5– > 15, Sa: 1–3, Ec 1–30, Pa 10– > 30 [36a,b])	Similar production by *Oceanapia fistulosa* (see above). **TS 30h** [36d].
Haplosclerida, Chalinidae, *Cladocroce incurvata* LÉVI, C. & LÉVI, P./**500 m** Lithistida, Neopeltidae. *Callipelta* sp./E lagoon	Cladocrocin A (**21a**)/polypropionate; cladocrocic acid (**22**)/eicosanoid [30a] Callipeltin A (**49a**) [53c] (ct P388 < 3.3, NSCLC-N6 < 1.1; av HIV-1 0.01; af Ca: 30/100 [53a,c]); callipeltin B (**49b**) (ct P388 < 3.3, NSCLC-N6 1.3) [53b]; callipeltin C (**49c**) (ct NSCLC-N6 53.5; af Ca: 9/100 [53b,c])/cyclic depsidecapeptides; callipeltins D and E (**49d** and **49e**)/acyclic forms [53c]; callipeltosides A (**51a**) [54a], and B and C (**51b** and **51c**) [54b] (ct P388 15.3, NSCLC-N6 11.3-30)/ glycosidic macrolides	Structural relationships of **21a** to other sponge products and **22** to red seaweeds and invertebrate products (see text). Compound **49a** related to aplidine (**50**) from Mediterranean ascidian *Aplidium albicans* (non-cardiotoxic antitumor) [53d]; **49a**–**49c** also from other sponges (see text); **51a** related to polycavernoside A (**52**) (toxic on mice at 0.2 mg/kg i.p.) from Micronesian red seaweed *Polycavernosa tsudai* [54c], auriside B (**53**) from the opisthobranch *Dolabella auricularia* from Japan (ct HeLa S_3 1.2) [54d], and lyngbouilloside (**54**) from the cyanobacterium *Lyngbya bouillonii* from Papua New Guinea [54e]. **TS 49a** [53f,g] and **51a** [54f–h], based on aldol technology.

Lithistida, Corallistidae, *Corallistes fulvodesmus* LÉVI, C. & LÉVI, P., 1983/**500 m**	Corallistine (**1**) [9]/bis-imidazole alkaloid; 1-methylpteridine-2,4-dione (**4**) [9]/pteridine	Corallistine (**1**) is the sole representative of the class.
Lithistida, Corallistidae, *Corallistes undulatus* LÉVI, C. & LÉVI, P., 1983/**510 m**	(1′*R*,2′*S*)-6-(1′,2′-Dihydroxypropyl)-1-methylpteridine-2,4-dione (**5**) [11]/pteridine; known serotonin [11]/indole alkaloid	Serotonin (hormone in land animals) from Mediterranean gorgonacean *Paramuricea chamaeleon*, pteridines from diatoms, the Bermudan calcareous sponge *Leucetta microraphis*, and the Japanese polychaete *Odontosyllis undecimonta* [11].
Lithistida, Corallistidae, *Corallistes* sp./**350 m**	Corallistins A–E (**6**–**10**) [12] (**6** ct KB 10; inefficient *in vivo* in the dark [12a]/free porphyrins	Free porphyrins detected in meso- and bathpelagic NE Atlantic schyphozoans and hydrozoans [20]. **TS 6** [15a] and **7**–**10** [15b] along *a,c*-biladiene routes.
Lithistida, Azoricidae, *Jereicopsis graphidiophora* LÉVI, C. & LÉVI, P./N Grand Passage, **225 m**	Jereisterols A and B (**16a** and **16b**) [23a]/9,11-seco-3β-*O*-methyl-sterols and 15 ring-intact analogues [23b]	3β-OH Sterol analogues are widespread in marine organisms.
Lithistida, Scleritodermidae, *Microscleroderma* sp./**300 m**	Microsclerodermins A and B (**15a** and **15b**) (af Ca 2.5 μg/disk [22a]; ct [22e]/cyclic hexapeptides presumably of bacterial origin [22d]	Analogues (C–E) from Philippine *Theonella* sp. and *Microscleroderma* sp. (A and B af Ca 2.5, C 5, E 10, D 100 μg/disk [22b]); F–I from Micronesian deep-sea *Microscleroderma* sp. (F af Ca 1.5, G 3.0, H 12.0, I 25 μg/disk; ct HCT-116 H 1.0, I 1.1, F 1.8, G 2.4 [22c]).
Lithistida, Phymatellidae, *Neosiphonia superstes* SOLLAS/**500 m**	Sphinxolide (**14a**) [17a,b][18a], sphinxolides B–D (**14b**–**14d**) [17a,b], E–G (**14e**–**14g**) [17c] (ct KB $3\cdot10^{-5}$–$4\cdot10^{-2}$, P388 $3\cdot10^{-3}$–$4\cdot10^{-2}$, NSCLC-N6 $1.6\cdot10^{-2}$–$6\cdot10^{-2}$, HT29 $2.4\cdot10^{-3}$–10^{-1}; superstolide A (**13a**) [16a] and B (**13b**) [16b] (KB $5\cdot10^{-3}$–$2\cdot10^{-2}$, P388 $3\cdot10^{-3}$, NSCLC-N6 $4\cdot10^{-2}$; HT29 $4\cdot10^{-2}$)/macrolides; neosiphoniamolide A (11) (af IC_{90} Po and Hg 5)[13]/cyclic depsipeptide	Sphinxolide (**14a**) and sphinxolide D (**14d**) from a Hawaiian nudibranch [18]; neosiphoniamolide A is a valine analogue of geodiamolide D (**12**) (ct L1210 $3.9\cdot10^{-2}$) from a Papua New Guinean halichondrid sponge, *Pseudaxinyssa* sp. [14].
Lithistida, Phymatellidae, *Reidispongia coerulea* LÉVI, C. & LÉVI, P./**505 m**	Reidispongiolides A and B (**14h** and **14i**) [17d] and C (**14j**) [17c] (ct KB 0.1–0.06, P38: 0.16–0.06, NSCLC-N6 0.07–0.05, HT29 0.04)/sphinxolide-type macrolides	Class also known from the lithistid sponge *Neosiphonia superstes* and a Hawaiian nudibranch (see above).
Lithistida, Pleromidae, *Pleroma menoui* LÉVI, C. & LÉVI, P., 1983/**500 m**	Ethyl 6-bromoindole-3-carboxylate (**2**) and 6-bromo-3-(hydroxyacetyl)-1*H*-indole (**3**)/indole alkaloids [10]	6-Bromoindole alkaloids are widely distributed in marine organisms.
Poecilosclerida, Acarnidae, *Zyzza massalis* (DENDY)/**235 m**	Zyzzin (**31a**) [37a] (the origin of a thermochromic system; see *Fig.*)/indole alkaloid	Zyzzin (**31a**) is structurally related to other ascidian products (see *Sect. 2*).
Poecilosclerida, Microcionidae, *Echinochalina bargibanti* HOOPER & LÉVI, 1993/NE and SW lagoon	Low-polarity poly-arsenic metabolite [56]	Poly-arsenic compounds are known only from chemical synthesis.

Table (cont.)

Taxon[a])/Region[b])	Metabolites from NC (bioactivity[c]))/biogenetic class	Relationships to products from the same nominal species or other species, from other ecosystems (shallow waters, unless otherwise specified), bioactivity, and total synthesis (**TS**)
Poecilosclerida, Microcionidae, *Echinochalina mollis* LÉVI/S lagoon	Hydroxyeicosa- and -docosatetra- and -pentaenoic acids [55a]	Hydroxylated polyunsaturated fatty acids, other than as hatching pheromones of barnacles [55b], are known from starfish [55a] and deep-sea pre-Antarctic antipatharian [55c] and scleractinian corals [55d].
Poecilosclerida, Myxillidae, *Stelodoryx chlorophylla* LÉVI/**540 m**	C_{27}–C_{29} Δ^5-Mono- and di-unsaturated sterols **18a–d** [27a]	Related to 24-keto-Δ^5 sterols from haplosclerid sponge *Haliclona chilensis* [27b].
Poecilosclerida, Podospongiidae, *Diacarnus levii* KELLY-BORGES & VACELET, 1996/SW outer reef	Methyl diacarnoate (**55a**), methyl 2-epinuapapuanoate (**55b**) (antimalarial) [57b], methyl 2-epimukubilin benzyl ester (**55c**) (ct KB 1) [57a], methyl prenyldiacarnoate A (**55d**) (ct KB 3.3) [57a], methyl 2-epiprenyldiacarnoate A (**55e**) [57a]/epidioxy norditerpenes and norsesterterpenes	Stereoisomers from Tongan *Diacarnus* cf. *spinulosum* and Red Sea halichondrid sponge *Prianos* sp. [57a,b].
Spirophorida, Tetillidae, *Cinachyrella* aff. *schulzei* KELLER, 1891/S lagoon	23,24ξ-Dimethylcholestanes [59a] as well as fatty acids [59b] and isoprenic fatty acids [59c] of phospholipids	Isoprenoids also from Senegalese *Cinachyrella alloclada* and *Cinachyrella kükenthali* [59c]; Caribbean *Cinachyrella schulzei* gave phosphatidylethanolamines and phosphatidylserines incorporating brominated fatty acids [59d].
Verongida, Aplysinellidae, *Suberea creba* BERGQUIST, 1995/E lagoon	Quinol **58e** [61c]	Common in verongids. **TS 58e** *via* anodic oxidation of halogenophenolic precursors [61b]
Verongida, Aplysinidae, *Verongia* sp./S Barrier reef	Hemifistularin 3 (**58a**), 19-deoxyfistularin 3 (**58b**), 19-deoxy-11-oxofistularin 3 (**58c**), 11-oxofistularin 3 (**58d**), and quinol **58e** [61a]	Bromotyrosine metabolites are typical of the Verongida.
Verongida, Pseudoceratinidae, *Pseudoceratina verrucosa* BERGQUIST, 1995/Chesterfield	Pseudoceratinines A–C (**57a–57c**) and other known bromotyrosine metabolites [60]	Bromotyrosine metabolites are typical of the Verongida.
Porifera (Calcarea)		
Clathrinida, Leucettidae, *Leucetta* sp./N lagoon	Naamidine-type guanidinium alkaloids **63a–63g** and Zn^{II} complexes **63h–63j** [66h]	**63a** from Fijian (ct HT29 and EGF inhibitor [66c]) and Red Sea *Leucetta* sp. [66f]; Zn^{II} complexes of isonaamidines from Micronesian [66b] and Papua New Guinean *Leucetta* sp. [66d].
Leucosoleniida, Jenkinidae, *Leucascandra caveolata* BOROJEVIC & KLAUTAU, 1998/E lagoon	Leucascandrolide A (**64a**) (ct KB 0.05, P388 0.25; af Ca 26/40) [68b] and leucascandrolide B (**64b**) [68c]/macrolides	Compound **64a** is structurally related to aplysiatoxin (**64c**). **TS** has overcome shortage of **64a** from nature (see text).

Cnidaria (octocorallia)		
Alcyonacea, Xeniidae, *Xenia garciae* Bourne/E lagoon	7-*epi*-11,19-Desoxyhavannahine (**68c**) [74] (antifouling)/xenicane diterpene	Xenicin (**66**) was first isolated from NE Australian *Xenia elongata* Dana, 1846 [75].
Alcyonacea, Xeniidae, *Xenia membranacea* Schenk/S lagoon	Xenicin-type **68a** [76a], **68b–68d** [76b,c], and xeniolide-type diterpenes [76c]	Xeniolide A (**67**) from Red Sea *Xenia macrospiculata* [77a] and Okinawan *Xenia* sp. [77b]; related diterpenes are common in alcyonaceans and brown seaweeds, less in gorgonaceans.
Pennatulacea, Pteroeididae, *Pteroeides laboutei* Hondt, 1984/E lagoon	Pteroeidin (**69a**), ichthyotoxic derivative **69b** (DL_{100} 50), and labouteine (**69c**)/briarane diterpenes [80a]	Briaranes are common in pennatualaceans, gorgonaceans, and nudibranchs; rare in alcyonaceans and stoloniferans; **69a–69c** resemble both briarein A (**70**), from Caribbean gorgonacean *Briareum asbestinum* [80b], and stylatulide (**71**), from Californian pennatulacean *Stylatula* sp. [80c]. See comments about *P. laboutei* above.
Pennatulacea, Veretillidae, *Cavernulina grandiflora* Hondt, 1984/E lagoon	Cavernulin (**72a**), derivative **72b**, and cavernulinin (**72c**) [81]/briarane diterpenes	
Pennatulacea, Veretillidae, *Lituaria australasiae* (Gray, 1970)/SW lagoon	Lituarines A–C (**73a–73c**) (ct KB $3.7-5\cdot10^{-3}$, $1-2\cdot10^{-3}$, $5-6\cdot10^{-3}$, resp.)/polyether macrolides [82]	Unique examples of macrolides from pennatulacean corals.
Gorgonacea, Calcaxonia, Ellisellidae, *Ctenocella* sp./SW lagoon	Mixture of sterone acetals **74** [83a]	Related to pectinoacetals A–C from W Australian *Ctenocella pectinata* [83b].
Gorgonacea, Scleraxonia, *Melithaea caledonica* Grasshoff 1999/S lagoon	Iela melst (inhibitor of amidolysis of Suc(Ala)3p-NA by porcine pancreatic elastase) [84]/protein	It bears 65% sequence homology for the first 20 residues with iela anesu from an actinian, *Anemonia sulcata* [84].
Gorgonacea, Holaxonia, Plexauridae, *Villogorgia nozzolea* Grasshoff 1996/SW barrier reef	Villogorgins A (**75**) and B (**76**) (acetylcholine antagonism [85a])/indoloquinolizidine alkaloids; caffeine-xanthine type alkaloid [85a]	Caffeine (on land from coffee beans and maté), from a Marmaran gorgonian, *Paramuricea chamaeleon* [85b]; other xanthine alkaloids from NE Pacific bryozoan *Phidolopora pacifica* [85c].
Cnidaria (Hexacorallia)		
Scleractinia, Caryophylliidae, *Deltocyathus magnificus* Moseley, 1876/Loyalty Island, **461 m**	Typical and unusual cholanic acid type sterones **77a–77h** [21]	Typical cholanic acid type sterones from mammalian and fish bile, as well as marine invertebrates (see text).
Mollusca		
Prosobranchia, Conidae, *Conus consors*/ Chesterfield	α-CnIA, α-CnIB [87a], and CcTx [87b] (synaptic [87a] and neuromuscular active [87b])/peptides	α-CnIA and α-CnIB resemble α-MI from *Conus magus*, while CcTX has 66% homology with κA-conotoxin from *Conus striatus* [87b], in a group where α-conotoxin MII has been proposed as both CNS [87c] and cardiovascular active agents [87d]. **TS** α-CnIA [87a].
Pulmonata, Onchidiidae, *Onchidium* sp./ Chesterfield	Onchitriols I (**79c**) [89b] and II (**79b**) (ct P388, A-549, and HT29 10 and 20 resp.; av HSV-1 and VSV 20) [88]/polypropionates; onchidin (**80a**) (ct P388 8 [90a]) and onchidin B (**80b**) (ct KB 8 [90b])/cyclic depsipeptide	Polypropionates are common in opisthobranch mollusks; depsipeptides are rarer. **TS** Onchitriol II (**79b**) and proposed [88] onchitriol I (**79a**) [89a], which was revised as **79c** [89b], along a multistep path from optically active triketides.

Table (cont.)

Taxon[a])/Region[b])	Metabolites from NC (bioactivity[c]))/biogenetic class	Relationships to products from the same nominal species or other species, from other ecosystems (shallow waters, unless otherwise specified), bioactivity, and total synthesis (**TS**)
Echinodermata[d])		
Asteroidea, Asterinidae, *Tremaster novaecaledoniae* JANGOUX, 1982/**530 m**	Tremasterols A–C (**84a–84c**)/polyhydroxylated steroids [94b]	New type of polyhydroxylated steroids.
Asteroidea, Ophiadiasteridae, *Fromia monilis* PERRIER, 1875/S lagoon	Fromiamycalin (**81**) and crambescidin 800 (**82a**) (ct CEM 4 0.11) [82a]/guanidine alkaloids	Compound **82a** from Mediterranean poecilosclerid sponge *Crambe crambe* (ct L1210 0.1; av HSV-1 1.25 μg/well) [82b] is a structural analogue.
Asteroidea, Oreasteridae, *Celerina heffernani* LIVINGSTONE, 1931/S lagoon	Celeromycalin (**82b**), ptilomycalin A (**82c**), and **82a** (ct CEM 4 0.32, 0.11, and 0.11, resp.) [92a]/guanidine alkaloids	These alkaloids may derive from a sponge diet (see text).
Asteroidea, Oreasteridae, *Protoreaster nodosus* LINNÉ, 1758/SE lagoon	Nodososide (**83**) [94a]/steroidal glycoside	New type steroidal glycoside [94a].
Asteroidea, Porcellanasteridae, *Styracaster caroli* LUDWIG/Loyalty Island, **2000 m**	Carolisterols A–C (**85a–85c**)/polyhydroxylated cholanic acid type sterols [86c]	See *Deltocyathus magnificus* above.
Crinoidea, Hemicrinidae, *Gymnochrinus richeri* BOURSEAU, AMEGIANE-COMINARDI & ROUX, 1987/**520 m**	Gymnochromes A (**86a**), B (**86b**), C (**87**), D (**88**), and isogymnochrome D (**89**) [96a] (av dengue [96b])/phenanthroperylene-quinone pigments	Non-brominated analogues from terrestrial plants and fossil crinoids [72].
Ascidiacea Aplousobranchia		
Didemnidae, *Didemnum rodriguesi* ROCHA & MONNIOT 1993/SW lagoon	Caledonin (**90**)/lipopeptide [97a]: minalemines A–F (**91a–f**)/sulfamic acid bearing peptide guanidine derivatives [97b]	Compounds **91a–f** are structurally related to non-sulfated guanidine peptides of ascidians.
Didemnidae, *Leptoclinides dubius* SLUITER, 1909/Canal Woodin; Polyclinidae, *Pharyngodictyon cauliflos*/**500 m**	Modified dipeptides **92**, **93**, and **94a–94c** [98a] and glycosylated tryptophan (**95a**) [98b]	*N*-α-Methyl derivative **95b** from *Ritterella rete* (see below).
Didemnidae, *Lissoclinum bistratum* SLUITER/S lagoon	Bistramide A (**96**) [99a] (ct MRC5CV1 and T24) [99a], B–D (**96b–96d**), K (**96e**) [99d,e] (ct KB 0.53–>10, P388 0.02–0.57, NSCLC-N6 0.03–3.43, HT29 0.32–5.6 [99f]; immunomodulating at 0.1–1 ppm [99g]/lipopeptides	Bistramide A (**96a**) (= bistratene) also from NE Australian *L. bistratum* and Fijian *Lissoclinum* sp. (ct HCT116 and L1210 0.1) [99a]. **TS** and chiroptical studies served to assign the absolute configuration of **96c** [99m] (see text).
Didemnidae, *Lissoclinum voeltzkowi* MICHAELSON/SW lagoon	Dichloro- (**101a**) [103a–c] and chlorolissoclimide (**101b**) [103b,c] (ct KB $14-52\cdot10^{-3}$, P388 $1-1.7\cdot10^{-3}$, P388r $300-200\cdot10^{-3}$, NSCLC-N6 $9-10\cdot10^{-3}$) [103c]/labdane diterpenes	Uncommon in ascidians, marine labdane diterpenes are common in red seaweeds of the genus *Laurencia* [2a].

Polycitoridae, *Eudistoma album* F. MONNIOT/SW lagoon	Eudistalbins A and B (**97a** and **b**) (A ct KB 3.2.) and eudistomin E (**98**)/β-carboline alkaloids [100a]	Eudistomins are common in ascidians of this genus; antiviral **98** from Caribbean *Eudistoma olivaceum* [100b].
Polycitoridae, *Eudistoma fragum* F. MONNIOT/Canal Woodin	(−)-Woodinine (**99**) (ab Sa 16/100, Ec 8/100)/β-carboline alkaloid [101a]	β-Carbolines are common in marine invertebrates. **TS 99** from tryptamine along *Pictet–Spengler* reaction with L-(Boc)prolinal [101b].
Polyclinidae, *Pseudodistoma arborescens* MILLAR/NE barrier reef	Arborescidins A–D (**100a–100d**) (D ct KB 3)/β-carboline alkaloids [102]	Compounds **100a–100d** are structurally related to akagerine from a terrestrial plant, *Strychnos usambarensis* [102a]. **TS** Racemic **100a–100c** from 6-bromo-(*N*-methyl)tryptamine [102c].
Polyclinidae, *Ritterella rete* MONNIOT C. & MONNIOT F., 1991/**300 m**	Furanosesquiterpenes **102a** (ct KB 1), **102b–102f** [104]; **95b** derivative of **95a** [98b]	Compound **95a** from *Leptoclinides dubius* (see above) [98b].

[a]) From Porifera to Tunicata, at class, order, family, genus, and species levels, according to literature [3], [5], [7], and [79]. [b]) Unless otherwise stated, shallow-water regions are relative to the main island. For deep-water organisms (> 80 m) the depth is given, in boldface figures, for the Norfolk Ridge area, in the south of the main island (*Fig.*), unless otherwise stated. [c]) Definitions of abbreviations and units used for bioactivity: **Antibacterial** (ab) [Ec (*Escherichia coli*), Pa (*Pseudomonas aeruginosa*), Sa (*Staphylococcus aureus*), Sf (*Streptococcus fecalis*), and Va (*Vibrio anguillarum*)]. **Antifungal** (af) [Ca (*Candida albicans*), Hg (*Helminthosporium graminearum*), Ht (*Helminthosporium tursicum*), Pi (*Penicillium italicum*), Pp (*Phytophtora parasitica*), and Po (*Piricularia oryzae*)], given as inhibition diameter in mm/mg compound per disk). **Antiviral** (av): HIV (Human immunodeficiency virus; AIDS virus), HSV-1 (Human herpes virus; *Herpes simplex*), VSV (Vesicular stomatitis virus) (IC_{50} in μg/ml). **Cytotoxic** (ct) on cell lines: A-549 (human lung cancer), CEM-4 (lymphocytic cells), KB (human nasopharyngeal carcinoma), HCT-116 (human colon carcinoma), HT29 (human Caucasian colon adenocarcinoma), L1210 (murine leukemia), NSCLC-N6 (human bronchopulmonary non-small-cell lung carcinoma), P388 and P388r (doxorubicin-resistant leukemia) (IC_{50} in μg/ml). **Receptors**: Epidermal growth factor receptor (EGF), Glycogen synthase kinase-3β (GSK-3β), neuropeptide Y (NPY), phospholipase A2 (PLA_2), serotonin (Ser), somatotropin release inhibiting factor (SRIF), tyrosine protein kinase (TPK), vasointestinal peptide (VIP), HIV-integrase (HIV-int), and inositol 1,4,5-triphosphate (IP_3). [d]) The echinoderm list is restricted to species characterized by unusual metabolites; for a complete account, see [93].

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