



A Minireview on Biodiscovery in Antarctic Marine Benthic Invertebrates

Conxita Avila^{1*} and Carlos Angulo-Preckler^{1,2}

¹ Department of Evolutionary Biology, Ecology, and Environmental Sciences, Biodiversity Research Institute (IRBIO), Faculty of Biology, University of Barcelona, Barcelona, Spain, ² Norwegian College of Fishery Science, UiT The Arctic University of Norway, Tromsø, Norway

OPEN ACCESS

Edited by:

Ana Rotter,
National Institute of Biology (NIB),
Slovenia

Reviewed by:

Angelina Lo Giudice,
Institute of Polar Sciences (CNR), Italy
Carmen Rizzo,
Stazione Zoologica Anton Dohrn
Napoli, Italy

*Correspondence:

Conxita Avila
conxita.avila@ub.edu

Specialty section:

This article was submitted to
Marine Biotechnology,
a section of the journal
Frontiers in Marine Science

Received: 26 March 2021

Accepted: 29 June 2021

Published: 21 July 2021

Citation:

Avila C and Angulo-Preckler C
(2021) A Minireview on Biodiscovery
in Antarctic Marine Benthic
Invertebrates.
Front. Mar. Sci. 8:686477.
doi: 10.3389/fmars.2021.686477

Antarctic marine benthic invertebrates are an underexplored source of natural products for biodiscovery. Bioactive marine natural products from Antarctica are reviewed here for their potential use as drugs, considering the main examples in Porifera (15 species), Cnidaria (eight species), Mollusca (one species), Bryozoa (one species), Nemertea (one species), Echinodermata (six species), and Tunicata (five species). A wide variety of bioactivities are reported here, from antitumoral to antimicrobial activities, as well as against neurodegenerative diseases and others. If we aim to use their chemodiversity for human benefits we must maintain the biodiversity, solving the supply problem, speeding up the process, and decreasing research costs to fully exploit the benefits of biodiscovery in Antarctic Marine Natural Products in a near future in a sustainable way.

Keywords: bioactive natural products, Porifera, Cnidaria, Mollusca, Bryozoa, Nemertea, Echinodermata, Tunicata

INTRODUCTION

Humans have used nature for obtaining food and bioactive compounds to treat diseases or as poisons for centuries. A paradigmatic example are medicinal plants. Indeed, nature has provided humankind with a wide array of bioactive compounds potentially useful as drugs against deadly diseases or as lead structures for novel synthetic drugs (Newman and Cragg, 2016). Currently, the combination of preserving biodiversity while bioprospecting natural products (chemodiversity) for human uses is a global challenge. Marine habitats comprise 71% of our planet including tropical to polar waters, and shallow to abyssal depths. This huge environment is inhabited by many different organisms adapted to the diverse physico-chemical conditions found in there. Marine ecosystems include many unique habitats hosting species and chemicals still vastly unknown (including novel compounds' classes and chemical skeletons), as well as unique phyla that never evolved to colonize land. The variety of chemicals found in these organisms constitutes what we call chemodiversity. These marine natural products (MNPs) are likely the result of evolutionary pressures, such as predation or competition (Avila et al., 2008), and have been shaped into structurally diverse compounds with specific biological and ecological activities rarely found in terrestrial organisms (Höller et al., 2000; Carroll et al., 2020). Chances of finding new drug candidates or relevant bioactive compounds in the ocean are especially high. However, marine sources are much less explored than terrestrial organisms and only 1% of recorded marine species have had their chemical composition analyzed, even if ca. 10% of the 145,000 natural substances described to date come from marine organisms (Núñez-Pons and Avila, 2015). Therefore, the discovery potentialities of novel MNPs and their putative applications remain wide open. Currently, more than 35,000

MNPs are known from macro- and microorganisms (MarinLit database¹), some of them being in advanced clinical development as anticancer drugs, and many more being tested for the treatment of pain, neurodegenerative disorders, tuberculosis, AIDS, malaria, and many other diseases, as well as for their use in cosmetics, nutraceuticals and food industries (Kim and Wijesekara, 2010; Suarez-Jimenez et al., 2012; Fan et al., 2014; Martins et al., 2014; Tripathi et al., 2014).

Research on MNPs is based on multidisciplinary collaboration between scientists from different fields, such as chemical ecology, chemistry, biosynthesis, pharmacology, molecular biology, genomics, metabolomics, and others. Furthermore, the new techniques and methodologies used in the isolation and chemical characterization of compounds are rapidly improving the biodiscovery path. Over the years, bioactive MNPs from different oceans have found many pharmaceutical applications, as said above, ranging from antitumoral to antimicrobials. Some drug examples include the nucleosides isolated in the 1950s from a Caribbean sponge, later used as scaffolds for commercial antiviral drugs [Ara-A (Acyclovir[®]) or Ara-C], the analgesic ω -conotoxin analog ziconotide (Prialt[®]) from a *Conus* mollusc used for chronic pain, ecteinascidin 743 (Yondelis[®]) from a tunicate for cancer chemotherapy (sarcoma), and eribulin mesylate (Halaven[®]), a derivative of halichondrin B from the cold-water sponge *Halichondria okadai* as an anticancer drug (Gerwick and Moore, 2012; Jaspars et al., 2016; Giordano et al., 2018). Many MNPs are commonly used in food industry as stabilizers and food additives, like the carrageenans from red seaweeds (Carragelose[®]), also employed in antiviral sprays, or carotenoids, used as food colorants, additives, and nutraceuticals (Jaspars et al., 2016). The use of new enzymes is also of great interest for many industrial processes, like the proteases, amylases, cellulases, carboxymethylcellulases, xylanases, . . ., for their use in the production of pharmaceuticals, foods, beverages, confectionery, paper, textile and leather processing, and waste-water treatment (Jaspars et al., 2016; Giordano et al., 2018). Cosmetics, on the other hand, include MNPs used as sun protectors, face, skin, and hair care products, such as Abyssine[®], Depollutine[®], Grevilline[®], RefirMAR[®], Resilience[®], SeaCode[®], XCELL-30[®], and others (Martins et al., 2014; Reen et al., 2015). In fact, the cosmetic industry, like Elemis (The Steiner Group, London, United Kingdom), La Prairie (Beiersdorf, Montreux, Switzerland), Crème de la Mer (Estée Lauder, New York, NY, United States), Blue Therapy (Biotherm, Tours, France), is constantly innovating using marine-derived bioactive compounds (Martins et al., 2014).

Antarctic waters harbor about 4% approximately of the currently known marine invertebrate species, while a huge amount of species are considered to be still unknown (Arrieta et al., 2010; Griffiths, 2010; Ronowicz et al., 2019). The environmental conditions there are extreme, with cold, constant temperatures and a seasonal light regime, with many species being endemic to these habitats, representing a huge, still unexplored biodiversity. The South Ocean therefore holds a huge potential for MNPs biodiscovery, based on both their

untapped bio- and chemodiversity. In part, the scarce current knowledge on the topic is due to the well-known difficulties in sampling and studying Antarctic organisms (Avila et al., 2008). Nevertheless, Antarctic bioprospecting is being developed currently by different groups using different methods and strategies (e.g., Avila, 2016a,b; Soldatou and Baker, 2017) although the topic has not been reported sufficiently in the general literature (e.g., Thomas et al., 2008). Some of the MNPs found so far in Antarctica are potentially useful for humans, as precursors of active molecules to design new drugs with a pharmacologic potential, as antimicrobials, or as antifouling, or have been tested within extracts but are not identified yet (e.g., Moles et al., 2014; Angulo-Preckler et al., 2017; Sacristán-Soriano et al., 2017). We review here the current status of biodiscovery in Antarctic marine benthic invertebrates.

THE CONCEPT OF BIOPROSPECTING

“Bioprospecting” (or biodiversity prospecting) is the exploitation of natural richness by searching for unknown or not studied organisms holding singular small molecules, macromolecules, and biochemical and genetic heritage, which may possess biological activities (Eisner, 1990; Jabour-Green and Nicol, 2003). These biological activities may be further developed into commercially valuable products for the agriculture (Beattie et al., 2011; Pandey and Yarzabal, 2019), aquaculture (Mazarrasa et al., 2014; Pascoal et al., 2020), bioremediation (Abida et al., 2013; Mazarrasa et al., 2014), cosmetic (Upadhyay et al., 2016; Gupta et al., 2019), nanotechnology (Mazarrasa et al., 2014; Cushnie et al., 2020), and/or pharmaceutical markets (Newman and Cragg, 2016; Pandey and Yarzabal, 2019). Usually biodiscovery starts with the collection of biological samples, targeting a reduced amount of biomass, followed by a bioactivity screening in order to select and further purify and identify the bioactive molecules, as well as to further synthesize them, when possible. The next steps include the *in vitro*, *in vivo*, and clinical assays, and the eventual progress to the market according to the pertinent regulatory issues. In the pharmaceutical industry, for example, almost one third of all small-molecule drugs approved by the U.S. Food and Drug Administration (FDA) between 1981 and 2014 were either NPs or compounds directly derived from natural products (Newman and Cragg, 2016).

When bioprospecting marine benthic invertebrates, we look for bioactive NPs. NPs are a small organic secondary metabolites (<3000 Da) synthesized by all organisms in response to different external stimuli. Because MNPs are produced under unique environmental conditions in the oceans, they are characterized by uncommon functional groups (isonitrile, dichloramine, isocyanate, and halogenated functional groups, among others) and peculiar structures, often with no analogs in terrestrial NPs (Imhoff et al., 2011; Rocha-Martin et al., 2014). NPs present many advantages over non-natural compounds, like a huge chemical diversity, biochemical specificity, binding efficiency and a strong ability to interact with biological targets. Therefore, NPs are considered more suitable for biological applications (such as anti-tumor, anti-proliferative, antibiotic,

¹<http://pubs.rsc.org/marinlit/>

anti-infective, antifungal, antiviral, antiparasitic, antihelminthic, photoprotective) and potentially relevant lead structures (Kayser et al., 2003; Nishimura et al., 2010; Waters et al., 2010; Mayer et al., 2010, 2013; Martins et al., 2014; Buenz et al., 2018). In fact, NPs account for most of the clinically approved drugs (Newman and Cragg, 2012; Patridge et al., 2016) and were mainly described from bacteria, fungi, and plants, while marine organisms were investigated only in recent decades (Bérdy, 2012; Gerwick and Fenner, 2013). Currently, the number of MNPs described has risen to more than 35000 (MarinLit database²). Among them, a part of the examples cited above, ca. 30 MNPs are in clinical trials, with more than 20 being classified as anticancer, and a few more for schizophrenia and Alzheimer's diseases, as well as for chronic pain treatment³ and therefore, the number of MNPs is expected to increase soon (Jaspars et al., 2016). Regarding Antarctic organisms, the bioactivity levels of MNPs have been reported to be comparable to those recorded in temperate marine environments, although only about 3% of the discovered MNPs originate from the polar regions (Lebar et al., 2007; Avila et al., 2008; Leal et al., 2012; Soldatou and Baker, 2017), and thus, more data are needed to draw general conclusions. According to the biodiversity data, a hidden treasure of bioactive MNPs is still waiting to be discovered in Antarctica, and considering the peculiar characteristics of the organisms living there, expectations are high.

PORIFERA

Sponges comprise some of the most abundant macroinvertebrates of Antarctic benthic communities, serving both as substrates for colonizing epibionts and endobionts, and as food sources for predators (McClintock et al., 2005). Antarctic sponges are a valuable source of biologically active compounds with drug potential, accounting for almost half of the pharmacologically active compounds of marine origin (Hu et al., 2011; Leal et al., 2012). Several Antarctic sponge species possess extracts with a wide range of bioactivities, such as cytotoxicity, hemolytic activity, antialgal activity, α -amylase activity, cholinesterase activities, antibacterial activity, and antifungal activity (Turk et al., 2013) (Table 1). One of the most prominent is the genus *Latrunculia*, showing hemolysis, inhibition of acetylcholinesterase, cytotoxicity toward normal and transformed cells, and growth inhibition of laboratory, commensal, and clinically and ecologically relevant bacteria (Turk et al., 2013). The brominated pyrroloiminoquinone alkaloids isolated from methanol extracts of two specimens of *Latrunculia* sp. demonstrated for the first time to be reversible competitive inhibitors of cholinesterases, with K_i for electric eel acetylcholinesterase of 1.6–15.0 μ M, for recombinant human acetylcholinesterase of 22.8–98.0 μ M, and for horse serum butyrylcholinesterase of 5.0–76.0 μ M. The most active compound, discorhabdin G (Figure 1), had no detectable undesirable effects on neuromuscular transmission and skeletal

muscle function (Botić et al., 2017). The pigment epinardin C (Figure 1), proved strongly active, albeit with poor resistant index against L1210 and doxorubicin-resistant L1210/DX murine lymphocytic leukemia cells *in vitro* (D'Ambrosio et al., 1996). Epinardin C was isolated from an undetermined demosponge and it differs from members of the discorhabdin/prianosin family in having an allylic alcohol functionality in place of the enone system, being compatible with the genus *Latrunculia*. Similarly, the extracts of *L. biformis* showed potent *in vitro* anticancer activity (Li et al., 2020b), with two discorhabdin-type alkaloids, tridiscorhabdin (Figure 1) and didiscorhabdin isolated from it. Only tridiscorhabdin exhibited strong cytotoxic activity against the human colon cancer cell line HCT-116 (IC_{50} value 0.31 μ M) (Li et al., 2020b). Further, (-)-(1R,2R,6R,8S,6'S)-discorhabdin B dimer and (-)-(1S,2R,6R,8S,6'S)-discorhabdin B dimer showed significant *in vitro* anticancer activity against the same cell line (HCT-116), with IC_{50} values of 0.16 and 2.01 μ M, respectively (Li et al., 2020a). Compared to monomeric discorhabdins, dimeric discorhabdins are very rare in nature. Moreover, a molecular networking approach combined with a bioactivity-guided isolation led to the targeted isolation of the pyrroloiminoquinone, tsitsikammamine A (Figure 1) and its analog 16,17-dehydrotsitsikammamine A (Li et al., 2018). Both tsitsikammamines and discorhabdins show potent anticancer activities *in vitro* and further potential anticancer activity was assessed with a virtual approach by molecular modeling for the tsitsikammamines (Li et al., 2018). *L. biformis* is an excellent source of chemically diverse discorhabdin alkaloids. (-)-discorhabdin L (Figure 1), (-)-1-acetyl-discorhabdin L, and (+)-1-octacosatrienoyl-discorhabdin L, showed promising anticancer activity with IC_{50} values of 0.94, 2.71, and 34.0 μ M, respectively (Li et al., 2019). These compounds were docked to the active sites of two anticancer targets, topoisomerase I-II and indoleamine 2,3-dioxygenase (IDO1), revealing the binding potential of discorhabdins to these proteins (Li et al., 2019). Furthermore, *Latrunculia* sp. yielded a new antibacterial pyrroloiminoquinone, discorhabdin R (Figure 1) with antibacterial activity against Gram + (*Staphylococcus aureus*, *Micrococcus luteus*) and Gram - (*Serratia marcescens*, *Escherichia coli*) bacteria (Ford and Capon, 2000).

Membranolides C and D (Figure 1) from the sponge *Dendrilla membranosa* possess carboxylic acid functional groups and display Gram - antibiotic and antifungal activities (Ankisetty et al., 2004). The 9,11-dihydrogracilin A (DHG) and membranolide (Figure 1) from *D. membranosa* both inhibited the growth of *Bacillus subtilis* at 100 μ g/disk and membranolide was also mildly active against *S. aureus* (Molinski and Faulkner, 1987). DHG induced apoptosis in human peripheral blood mononuclear cells (PBMC) (Ciaglia et al., 2017). In addition, DHG possesses promising anti-inflammatory properties both *in vitro* and *in vivo*. These effects are accompanied by DHG down-regulation of NF- κ B, STAT, and ERK phosphorylation at further stages (Ciaglia et al., 2017). The antimicrobial activity of the extracts of this sponge against *S. aureus*, *Vibrio anguillarum*, and *Beneckeia harveyi* (100 μ g/disk), was due to 4,5,8-trihydroxyquinoline-2-carboxylic acid (Molinski and Faulkner, 1988). Darwinolide A

²<http://pubs.rsc.org/marinlit>

³<https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline.xml>

TABLE 1 | Brief summary of bioactive natural products from Antarctic marine benthic invertebrates.

Phylum (spp #)	Order/Class	Species	Compound	Activity	Locality	References
Porifera (15)	Demospongiae	<i>Crella</i> sp.	Norselic acid A–E	Antibiotic activity against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), methicillin-sensitive <i>S. aureus</i> (MSSA), vancomycin-resistant <i>Enterococcus faecium</i> (VRE), and <i>Candida albicans</i> . Active against <i>Leishmania</i> parasite	Anvers Island	Ma et al. (2009)
	Demospongiae	<i>Dendrilla antarctica</i>	Tetrahydroaplysulphurin-1, Membranoids B, D, G	Inhibitors of <i>Leishmania</i> parasite	Anvers Island	Shilling et al. (2020)
	Demospongiae	<i>Dendrilla antarctica</i>	Aplysulphurin, Membranolide, Dendrillins B–D	Bioactive against <i>Leishmania donovani</i> , <i>Plasmodium falciparum</i> , and methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Anvers Island	Bory et al. (2020)
	Demospongiae	<i>Dendrilla membranosa</i>	Darwinolide	Inhibits methicillin-resistant <i>Staphylococcus aureus</i> biofilm	Anvers Island	von Salm et al. (2016)
	Demospongiae	<i>Dendrilla membranosa</i>	Dihydrogracilin A (DHG)	Immuno-modulatory and anti-inflammatory	N.A.	Ciaglia et al. (2017)
	Demospongiae	<i>Dendrilla membranosa</i>	9,11-dihydrogracilin A, Membranolide	Inhibits the growth of <i>Bacillus subtilis</i> and <i>Staphylococcus aureus</i>	McMurdo Sound	Molinski and Faulkner (1987)
	Demospongiae	<i>Dendrilla membranosa</i>	4,5,8-trihydroxyquinolirihydroxylic acid	Antimicrobial to <i>Staphylococcus aureus</i> , <i>Vibrio anguillarum</i> , <i>Beneckea harveyi</i> (B-392)	N.A.	Molinski and Faulkner (1988)
	Demospongiae	<i>Inflatella coelosphaeroides</i>	Friomaramide	Inhibits <i>Plasmodium falciparum</i> liver-stage development	Antarctic waters	Knestrick et al. (2019)
	Demospongiae	<i>Isodictya antarctica</i>	Ceramide, Erebusinonamine	Antimicrobial to <i>Staphylococcus aureus</i> , methicillin-resistant <i>S. aureus</i> (MRSA), <i>Escherichia faecium</i> , and <i>Candida albicans</i>	Palmer station	Park (2004)
	Demospongiae	<i>Isodictya erinacea</i>	Erebusinone, Erinacin	Cytotoxic against mouse lymphoblastoid cell line (L5178Y). Antimicrobial to <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , and <i>S. epidermidis</i>	McMurdo Sound	Moon et al. (2000, 1998)
	Demospongiae	<i>Kirkpatrickia variolosa</i>	3,4',5-triacetoxystilbene	Inhibits protein tyrosine kinase (PTK) and protein kinase C (PKC)	McMurdo Sound	Jayatilake et al. (1995)
	Demospongiae	<i>Kirkpatrickia variolosa</i>	Variolin A	Cytotoxic against the P388 leukemia cell line	McMurdo Sound	Trimurtulu et al. (1994)
	Demospongiae	<i>Kirkpatrickia variolosa</i>	Variolin B, N(3')Methyl tetrahydrovariolin B	Inhibits <i>Saccharomyces cerevisiae</i> growth. Active against HCT 116 cell line and P388 leukemia	McMurdo Sound	Perry et al. (1994)
	Demospongiae	<i>Latrunculia apicalis</i>	discorhabdin C,G	Antibiotic against Gram + and Gram - bacteria	McMurdo Sound	Yang et al. (1995)
	Demospongiae	<i>Latrunculia biformis</i>	Tridiscorhabdin, Didiscorhabdins	Strong cytotoxic activity against human colon cancer cell line HCT-116	Weddell Sea	Li et al., 2020a,b
	Demospongiae	<i>Latrunculia biformis</i>	Tsitsikammamines, Discorhabdins	Anticancer activity against six human cancer cell lines	Weddell Sea	Li et al. (2018, 2019)
	Demospongiae	<i>Latrunculia</i> sp.	Discorhabdin R	Antibacterial activity	Prydz Bay	Ford and Capon (2000)
	Demospongiae	<i>Latrunculia</i> spp.	Discorhabdins B, L, G, and 3-dihydro-7,8-dehydrodiscorhabdin C	Cholinesterase inhibitors (AD)	Antarctic Peninsula	Botić et al. (2017)
	Demospongiae	<i>Phorbas areolatus</i>	Isosuberitenone B, 19-episuberitenone B, Isoxaspirosuberitenone, Suberitenone A–B, Oxaspirosuberitenone	Cytotoxicity against lung (A549), breast (MCF-7), colon (HT29), and liver (HepG2) tumor cell lines. Antimicrobial activity against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	South Shetland Islands	Solanki et al. (2018)

(Continued)

TABLE 1 | Continued

Phylum (spp #)	Order/Class	Species	Compound	Activity	Locality	References
	Demospongiae	<i>Suberites</i> sp.	Suberitenone B	Inhibits the cholesteryl ester transfer protein (CETP)	King George Island	Shin et al. (1995)
	Demospongiae	Undetermined deep-water green demosponges	Epinaridins A–D	Epinaridin C cytotoxic toward doxorubicin-resistant L1210/DX tumoural cells <i>in vitro</i>	Crozet Islands	D'Ambrosio et al. (1996)
	Unidentified	Unidentified	Non-nitrogenous eudesmane	Antibiotic activity against <i>Staphylococcus aureus</i>	Prydz Bay	Urban et al. (1995)
	Calcarea	<i>Leucetta leptorhpsi</i>	Rhaphsamine	Cytotoxicity against KB nasopharyngeal cell line	McMurdo Sound	Jayatilake et al. (1997)
Cnidaria (8)	Octocorallia	<i>Acanthogorgia laxa</i>	Azulenoid sesquiterpenes	Antifouling activity	South Shetland Islands	Patiño-Cano et al. (2018)
	Octocorallia	<i>Ainigmaptilon antarcticum</i>	Ainigmaptilones A	Antifouling and antibacterial activity	Eastern Weddell Sea	Iken and Baker (2003)
	Octocorallia	<i>Alcyonium paessleri</i>	Alcyopterisins A–O	Cytotoxic against human tumor cell lines	South Georgia Islands	Palermo et al. (2000)
			Paesslerins A–B	Cytotoxic against human tumor cell lines	South Georgia Islands	Rodríguez-Brasco et al. (2001)
	Octocorallia	<i>Anthomastus bathyproctus</i>	Steroids 2–5	Cytotoxicity against human tumor cell lines	South Shetland Islands	Mellado et al. (2005)
	Octocorallia	<i>Anthoptilum grandiflorum</i>	Bathyptilones A–C	Cytotoxicity toward the neurogenic mammalian cell line Ntera-2	Scotia Arc	Thomas et al. (2019)
	Octocorallia	<i>Dasystenella acanthina</i>	Polyoxygenated steroids	Growth inhibitors of several human tumor cell lines. Cytostatic and cytotoxic on selected tumor cell lines	Eastern Weddell Sea	Mellado et al. (2004)
	Octocorallia	<i>Plumarella delicatissima</i>	Keikipukalides B–E, Pukalide aldehyde, Norditerpenoid ineleganolide	Activity against <i>Leishmania donovani</i>	Falkland Islands	Thomas et al. (2018)
	Octocorallia	Unidentified soft coral	Shagenes A–B	Activity against <i>Leishmania donovani</i>	Scotia Arc	von Salm et al. (2014)
Mollusca (1)	Gastropoda	<i>Doris kerguelenensis</i>	Palmadorins	Inhibits human erythroleukemia	Ross Sea, Antarctic Pen.	Maschek et al. (2012)
Bryozoa (1)	Cheilostomata	<i>Aspidostoma giganteum</i>	Aspidostomide E	Active against the 786-O renal carcinoma cell line	Patagonia (Argentina)	Patiño-Cano et al. (2014)
Nemertea (1)	Heteronemertea	<i>Parborlasiya corrugatus</i>	Parbolysins	Cytotoxic and hemolytic activity	Ross Sea, Antarctic Pen.	Göransson et al. (2019)
Echinodermata (6)	Asteroidea	<i>Acodontaster conspicuus</i>	Polyhydroxylated steroids, Steroidal oligoglycosides	Antimicrobial activity	McMurdo Sound	De Marino et al. (1997b)
	Asteroidea	<i>Diplasterias brucei</i>	Diplasteriosides A–B	Cytotoxic against different human cancer cell lines	Ross Sea	Ivanchina et al. (2011)
	Asteroidea	<i>Henricia</i> sp.	Asterosaponins, Glicosides of polyhydroxysteroids, Polyhydroxylated steroids	Cytotoxic against human broncopulmonary non-small-cell-lung-carcinoma cells (NSCLC-N6)	Tethys Bay	Iorizzi et al. (1996)
	Asteroidea	Unidentified	Asterasterol A–C, Asteriidosides A–L	Cytotoxic against human broncopulmonary non-small-cell-lung-carcinoma cells (NSCLC-N6)	Tethys Bay	De Marino et al. (1997a, 1998)
	Holothuroidea	<i>Stauroucucumis liouvillei</i>	Liouvillosides A–B	Virucidal against herpes simplex virus type 1 (HSV-1)	South Georgia Islands	Maier et al. (2001)
	Ophiuroidea	<i>Ophiosparte gigas</i>	Sulphated polyhydroxysteroids	Cytotoxic activity, cytoprotective against HIV-1	Ross Sea	D'Auria et al. (1993)
Tunicata (5)	Asciacea	<i>Aplidium cyaneum</i>	Aplicyanins A–F	Cytotoxic and antimetabolic activities	Weddell sea	Reyes et al. (2008)
	Asciacea	<i>Aplidium meridianum</i>	Meridianins A–E	Cytotoxicity toward murine tumor cell lines, against Alzheimer disease	South Georgia Islands, Antarctic Pen.	Franco et al. (1998); Llorach-Parés et al. (2017)

(Continued)

TABLE 1 | Continued

Phylum (spp #)	Order/Class	Species	Compound	Activity	Locality	References
	Asciadiacea	<i>Aplidium</i> sp.	Rossinones A–B	Antiinflammatory, antiviral and antiproliferative activities	Ross Sea	Appleton et al. (2009)
	Asciadiacea	<i>Synoicum adareanum</i>	Palmerolides A, C, D–G	V-ATPase inhibitors	Anvers Island	Diyabalanage et al. (2006); Noguez et al. (2011)
			Abeohyosterone, Hyosterones A, C	Cytotoxic	Antarctic Peninsula	Miyata et al. (2007)
	Thaliacea	<i>Salpa thompsoni</i>	Fatty acids and sterols	Hemolytic activity	South Orkney Islands	Mimura et al. (1986)

(Figure 1), a diterpenoid from *Dendrilla antarctica* (previously *D. membranosa*) showed potential as a scaffold for methicillin-resistant *S. aureus* (MRSA) (von Salm et al., 2016). This is a chemically rich sponge, being a prolific source of highly oxidized diterpenoids with moderate antibiotic and antifungal activities against *S. aureus*, *E. coli*, and *Candida albicans* (Molinski and Faulkner, 1987). Bioactivities against infectious disease models including pathogens that cause leishmaniasis, malaria, and MRSA infections were also found (Bory et al., 2020). Four more diterpenes, tetrahydroaplysulphurin-1 (Figure 1), as well as membranoids B (Figure 1), D, and G, displayed low micromolar activity against *Leishmania donovani* with no discernible cytotoxicity against uninfected J774A.1 cells (Shilling et al., 2020).

Friomaramide (Figure 1), a highly modified hexapeptide isolated from the sponge *Inflatella coelosphaeroides* blocks > 90% of *Plasmodium falciparum* liver-stage parasite development at 6.1 μ M (Knestrick et al., 2019). The Antarctic red sponge *Kirkpatrickia variolosa* presents a resveratrol triacetate (3,4',5-triacetoxystilbene) (Jayatilake et al., 1995). Stilbenes exhibit a variety of biological and pharmacological activities including protein tyrosine kinase (PTK) and protein kinase C (PKC) inhibitory effects (Jayatilake et al., 1995), but this compound has not yet been tested. Also in *K. variolosa*, variolins display cytotoxic, antiviral, and antifungal properties (Perry et al., 1994; Trimurtulu et al., 1994). Variolin A (Figure 1) showed weak *in vitro* activity against the P388 cell line (IC_{50} = 3.8 μ g/mL). N(3')-Methyl tetrahydrovariolin B inhibited the growth of *Saccharomyces cerevisiae* (2 mg/mL), showed *in vitro* activity against the HCT 116 cell line (IC_{50} = 0.48 μ g/mL), and modest *in vivo* activity against P388 leukemia (at 10 mg/Kg) (Trimurtulu et al., 1994). Variolin B, with an IC_{50} of 210 ng/mL against P388, was also effective against *Herpes simplex* Type I (Perry et al., 1994). Variolin B is a pyridopyrrolopyrimidine alkaloid with antitumor and antiviral properties.

All of the norselic acids (A–E) from the encrusting, bright red sponge *Crella* sp. display activity against the *Leishmania* parasite at low micromolar concentration. Norselic acid A (Figure 1) displays antibiotic activity against methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), vancomycin-resistant *Enterococcus faecium* (VRE), and *C. albicans*, and it is also active against the *Leishmania* parasite with modest anti-infective properties (Ma et al., 2009).

Suberitenone B (Figure 1) inhibits the cholesteryl ester transfer protein (CETP), which mediates the transfer of cholesteryl ester and triglyceride between high-density lipoproteins and low-density lipoproteins (Shin et al., 1995). CETP inhibition is considered to be a good target for the development of an effective agent for atherosclerotic diseases. Three suberitane derivatives, isosuberitenone B, 19-episuberitenone B, and isoxaspirosuberitenone are found in the sponge *Phorbas areolatus*, together with suberitenones A and B, and oxaspirosuberitenone (Figure 1) (Solanki et al., 2018). Oxaspirosuberitenone displayed significant antimicrobial activity against MRSA at the highest concentration tested (160 μ M). While all five compounds displayed moderate cytotoxicity against the HepG2, HT-29, and MCF-7 cell lines, only isosuberitenone B and 19-suberitenone B showed significant activity against the A549, HepG2, HT-29, and MCF-7 tumor cell lines (Solanki et al., 2018).

Erebusinone (Figure 1) and erinacine are found in *Isodictya erinacea*. Erinacine has shown cytotoxicity (LD_{50} 50 μ g/mL) against L5178Y mouse lymphoblastoid cells (Moon et al., 2000), while eribusinone together with a ceramide and eribusinonamine from *Isodictya antarctica* showed modest antimicrobial activity against *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *E. faecium*, and *C. albicans* (Park, 2004). Further, an unidentified sponge yielded a sesquiterpene alcohol, a non-nitrogenous eudesmane with antibiotic activity against the Gram + bacteria *S. aureus* (Urban et al., 1995). Finally, rhapsamine (Figure 1), a linear C28 polyene from the only calcareous sponge studied, *Leucetta leptorhopsis*, displays a LC_{50} of 1.8 μ M in the KB nasopharyngeal cell line, while in the NCI 60 cell-line panel displays a similar level of cytotoxicity with little selectivity (Jayatilake et al., 1997).

CNIDARIA

NPs from Antarctic cnidarians are only known from octocorals so far, including a series of sesquiterpenes and polyoxygenated steroids isolated from *Alyonium paessleri* (Palermo et al., 2000; Rodriguez-Brasco et al., 2001), *Ainigmaptilon antarcticus* (Iken and Baker, 2003), and *Dasystenella acanthina* (Gavagnin et al., 2003) (Table 1). Of the latter, all steroids show significant activities as growth inhibitors of several human

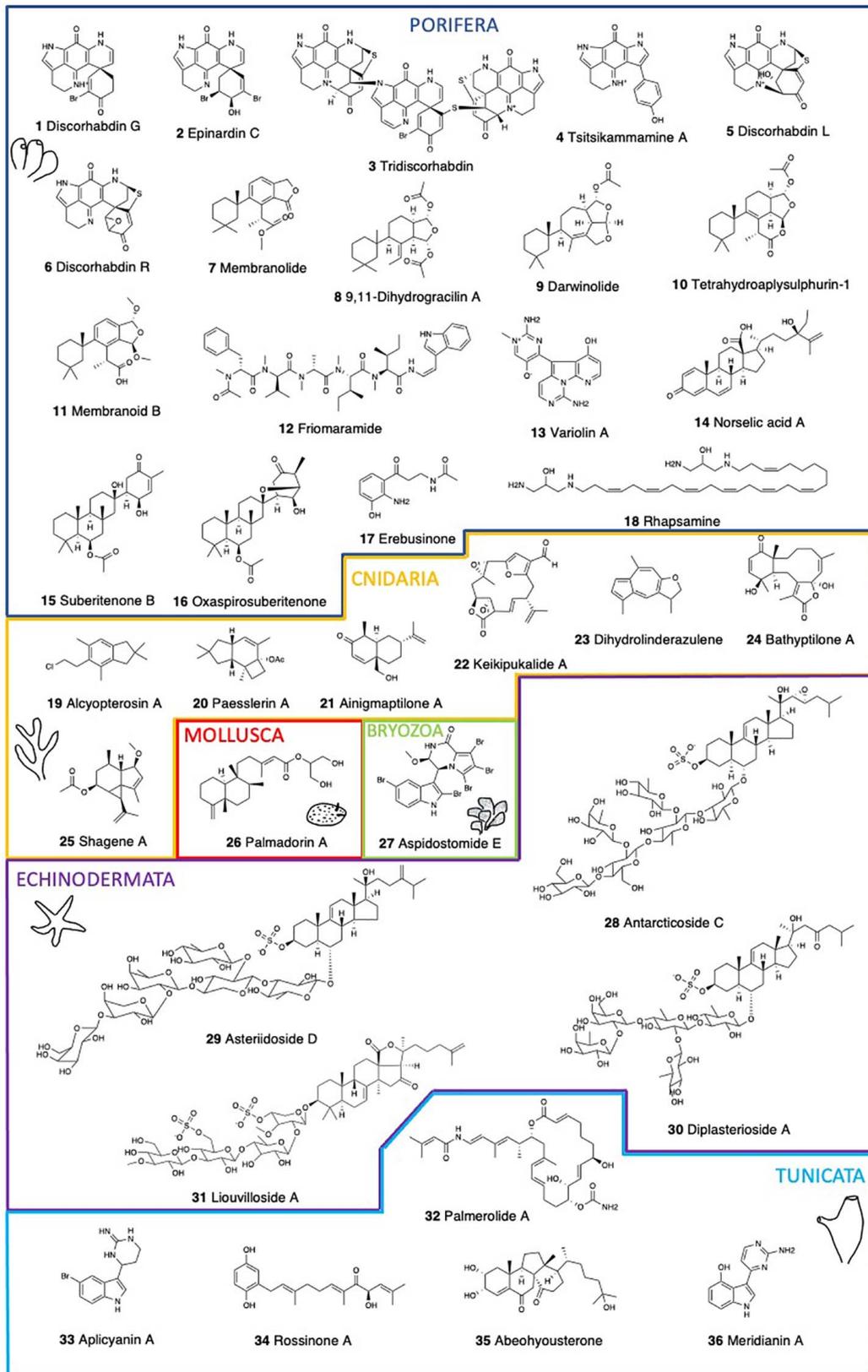


FIGURE 1 | Chemical structure of the main bioactive compounds described in Antarctic marine benthic invertebrates.

tumor cell lines (Mellado et al., 2004). Higher levels of activity were observed against the cell lines LN-caP (prostate carcinoma), and K-562 (chronic myelogenous leukemia), with most compounds displaying GI_{50} values $< 2 \mu\text{g/mL}$ (Mellado et al., 2004). In addition, these steroids showed cytostatic effects and are cytotoxic against one or two cell lines, except $3\alpha,11\alpha$ -diacetoxy-25-hydroxycholest-4-en-6-one, that was active against seven of the assayed cell lines, including DU-145 (prostate carcinoma), IGROV (ovarian adenocarcinoma), SK-MEL-28 (melanoma), PANC1 (pancreas carcinoma), and LOVO (colon adenocarcinoma) (Mellado et al., 2004).

The first illudalane sesquiterpenoids isolated from the marine environment were those from the soft coral *A. paessleri*. Alcyopterosins A-O (**Figure 1**) are also the first nitrate esters reported as MNPs (Palermo et al., 2000). Alcyopterosin E shows mild cytotoxicity toward Hep-2 (human larynx carcinoma) cell line with IC_{50} of $13.5 \mu\text{M}$, while alcyopterosin A, C, and H were cytotoxic toward HT-29 (human colon carcinoma) at $10 \mu\text{g/mL}$ (Palermo et al., 2000). The minor metabolites paesslerins A (**Figure 1**) and B show moderate cytotoxicity against human tumor cell lines (Rodriguez-Brasco et al., 2001). The paesslerane and illudalane carbocyclic skeletons could be biogenetically related by a protoilludane cation as a common precursor. On the other hand, the gorgonian coral *Ainigmaptilon antarcticus* possesses ainigmaptilone A (**Figure 1**), displaying antibiotic activity toward three sympatric Antarctic bacteria at as low as 5mg/mL and being lethal to fouling sympatric diatoms at natural concentration (0.275mg/mL) (De Marino et al., 1997a; Amsler et al., 2000).

Keikipikalides A–E (**Figure 1**), furanocembranoid diterpenes, along with pukalide aldehyde and the norditerpenoid ineleganolide are found in the deep-sea octocoral *Plumarella delicatissima* (Thomas et al., 2018). This family of diterpenes displays activity against the leishmaniasis parasite, *L. donovani*, from 1.9 to $12 \mu\text{M}$, with no corresponding mammalian cytotoxicity below $50 \mu\text{M}$. Most of these compounds contain the neurotoxic pharmacophore of lophotoxin which may be a liability for this specificity (Abramson et al., 1991). On the other hand, blue alcyonaceans present characteristic pigments contributing to the amazing colors of the benthic communities and displaying also several bioactivities (Patiño-Cano et al., 2018). The gorgonian *Acanthogorgia laxa* presents linderazulene and a ketolactone, both displaying good antifouling properties against a wide array of organisms. Although, the ketolactone can be produced from linderazulene by oxidation, there is some controversy regarding its possible origin as an artifact (Li and Scheuer, 1984). A compound closely related to linderazulene, 8,9-dihydrolinderazulene (**Figure 1**), displays cytotoxicity against several tumor cell lines, like PC-3, HCT-116 and MCF-7/ADR with IC_{50} values of 9.46 , 14.49 and 16.06mg/mL , respectively (Chen et al., 2014). Antifouling assays show that azulenoid sesquiterpenoids are also involved in the control of biofouling by marine invertebrates (Patiño-Cano et al., 2018).

Three briarane diterpenes, bathyptilone A–C (**Figure 1**) isolated from the sea pen, *Anthoptilum grandiflorum* have been screened against four cancer cell lines. Bathyptilone A is highly toxic to a pluripotent embryonal carcinoma cell line, NTera-2

(NT2), effectively killing tNT2 cells at an IC_{50} of 29nM (Thomas et al., 2019). Due to their similarity with developing neuronal cells, this cell line is considered valid for assessing neurotoxicity (Stern et al., 2014). Moreover, seven steroids from *Anthomastus bathyproctus* were tested against the human tumor cell lines MDA-MB-231 (breast adenocarcinoma), A-549 (lung carcinoma), and HT-29 (colon adenocarcinoma). Four of them displayed weak activity as inhibitors of cell growth, only one of them being a potent inhibitor with GI_{50} values of $21.2 \mu\text{M}$ for MDA-MB-231, $16.5 \mu\text{M}$ for A-549, and $15.3 \mu\text{M}$ for HT-29 (Mellado et al., 2005). Finally, two new terpenoids, shagene A (**Figure 1**) and B were isolated from an undescribed genus of octocoral. Shagene A has an IC_{50} value of $5 \mu\text{M}$ on the infected macrophage stage of the leishmaniasis parasite, *L. donovani*, showing a 10-fold increase in activity with no cytotoxicity up to $100 \mu\text{g/mL}$. Shagene B showed no activity ($> 20 \mu\text{g/mL}$) indicating the relevance of the methoxy substituent at C-8 (von Salm et al., 2014).

MOLLUSCA

Molluscs, and particularly gastropods, are a very important source of bioactive compounds, with some drugs already in the market (see Avila et al., 2008; Avila and Angulo-Preckler, 2020). Antarctic molluscs are also rich in natural products with potentially relevant bioactivities (Avila and Angulo-Preckler, 2020 and references therein) (**Table 1**). Here, gastropod nudibranchs are among the most interesting, as for example the compounds of the slug *Doris kerguelensis*, displaying a wide arsenal of NPs, including different skeletons (Avila and Angulo-Preckler, 2020), among which the diterpenoids palmadorins (**Figure 1**) inhibit human erythroleukemia (HEL) cells at low micromolar IC_{50} 's and also inhibit Jak2, STAT5, and Erk1/2 activation in HEL cells, causing apoptosis at 5mM (Maschek et al., 2012). The structure-activity profile of the cytotoxicity of palmadorin indicates that the cis-fused labdane diterpene system may be conformable to develop potent chemotherapy tools based on the inhibition of several key enzymes implicated in the JAK/STAT pathway (Maschek et al., 2012). Several other compounds have been described in Antarctic molluscs and, for some of them, their ecological activities are described but their potential pharmacological activities remain yet to be discovered.

BRYOZOA

Bryozoans have emerged over the last decades as a source of biologically active and structurally diverse compounds, with several Antarctic species being bioactive, all of them within the Cheilostomata (Figuerola et al., 2013, 2014; Angulo-Preckler et al., 2015; Figuerola and Avila, 2019) (**Table 1**). The alkaloid tambjamine A is found in *Bugula longissima* (Lebar et al., 2007), although its bioactivity has not yet been investigated, tambjamine A was previously reported bioactive from the tropical bryozoan *Sessibugula translucens* (Carté and Faulkner, 1983). Several compounds are found in *Aspidostoma giganteum*, like aspidostomides A–H (**Figure 1**) and aspidazide A, but only

aspidostomide E presented bioactivity, being moderately active against the 786-O renal carcinoma cell line with an IC_{50} of $7.8 \mu\text{M}$ (Patiño-Cano et al., 2014). *Aspidostoma giganteum* is found along the Magellanic and Antarctic regions, with records in Patagonia, Tierra del Fuego, Malvinas, and the South Shetland Islands. Since this bioactivity is reported in Patagonia (Argentina) specimens, it is unknown whether Antarctic specimens are also bioactive. Despite their huge potential, the scarce information available from this abundant and biodiverse phylum is an important gap, and at the same time a promising large source of pharmacologically interesting NPs.

NEMERTEA

Ribbon worms are known to be voracious predators or scavengers, provided with an eversible proboscis to capture prey and secreting a quite thick and copious mucus covering their bodies. Their mucus secretion is usually toxic to both potential predators and preys, presenting several identified compounds with potential pharmacological use, some of them being in clinical trials (Göransson et al., 2019). The mucus of the Antarctic species *Parborlasia corrugatus* presents cytotoxic peptide compounds and hemolytic activity toward erythrocytes, among its compounds, parbolysins are currently being investigated in detail (Göransson et al., 2019; Jacobsson et al., unpublished data) (Table 1).

ECHINODERMATA

Asteroidea

Starfish contain steroidal glycosides and saponins which are responsible for their general toxicity and antiviral activity against several human pathogenic viruses (McKee et al., 1994; Comin et al., 1999). Sulfated steroidal glycosides ubiquitously found in starfish can be classified into two major structural classes, asterosaponins and polyhydroxysteroid glycosides, displaying a wide range of biological activities, such as cytotoxic, hemolytic, ichthyotoxic, repellent, antineoplastic, antimicrobial, antifungal, antiviral, and anti-inflammatory activities (Minale et al., 1993) (Table 1). *Henricia* sp. presents thirty-four steroid constituents where seven asterosaponins are cytotoxic (Iorizzi et al., 1996). Antarcticoside C (Figure 1) displays the strongest cytotoxic activity with an IC_{50} value $<3.3 \mu\text{g/ml}$ (Iorizzi et al., 1996). This is one of the best examples among the echinoderms of the structural variety of polyhydroxysteroid constituents co-occurring in the same organism. Similarly, a large variety of steroid glycosides are found in an unidentified sea star of the Asteroidea family. Some of these compounds are moderately cytotoxic against human non-small-cell lung carcinoma cells (NSCLC-L16), with the sulphated steroid asterasterol C showing a moderate activity with $IC_{50} > 30 \mu\text{g/ml}$ (De Marino et al., 1997b). Also, asteriidoside C, D (Figure 1), and E, were the most active steroidal sulfates with IC_{50} values of $19.7 \mu\text{g/ml}$, $11.4 \mu\text{g/ml}$, and $18.1 \mu\text{g/ml}$, respectively (De Marino et al., 1998). Some more asterosaponins, the diplasteriosides A (Figure 1) and B from *Diplasterias brucei* show potent cytotoxic activity against different human cancer

cell lines (Ivanchina et al., 2011). For HCT-116 cells, only diplasterioside A was toxic. Both compounds show moderate toxicity toward T47D cells and are most toxic against RPMI-7951 cells with IC_{50} 67 and $60 \mu\text{M}$, respectively. Compounds with the ergostane skeleton are more hemolytically active than those with the cholestane one, and the presence of an additional methyl group at C_{24} in the side chain of diplasterioside B causes reduction of its cytotoxic properties compared to diplasterioside A (Ivanchina et al., 2011). These compounds have already been synthesized by using Fmoc carbonate as an orthogonal protecting group which can be removed and the product subsequently glycosylated to reduce the number of steps (Sangwan et al., 2020). Finally, 19 steroids, 13 steroidal oligoglycosides, and six polyhydroxylated steroids are found in *Acodontaster conspicuosus*, where half of them were active against at least one Antarctic marine bacterium (De Marino et al., 1997a), suggesting that they may play an important role in deterring microbial fouling and could be further investigated for potential antibiotic and antifouling properties.

Holothuroidea

Triterpene glycosides and saponins are secondary metabolites typically found in sea cucumbers. Two trisulfated triterpene glycosides, liouvillosides A (Figure 1) and B, are found in the sea cucumber *Staurocucumis liouvillei* (Maier et al., 2001). Both glycosides were found to be virucidal against herpes simplex virus type 1 (HSV-1) at concentrations below $10 \mu\text{g/ml}$, while little or no cytotoxicity was detected within 8 h of cell exposure (Maier et al., 2001). Other liouvillosides also found in *S. liouvillei* and *S. turqueti* have not been yet tested for bioactivity (Antonov et al., 2008, 2011; Silchenko et al., 2013). Similarly, achlionicesides from the elaspod *Achlionice violaeuspida* are not studied yet for their bioactivity (Antonov et al., 2009).

Ophiuroidea

Also saponins and steroids are responsible here for the antiviral activity against several human pathogenic viruses (McKee et al., 1994; Comin et al., 1999). Three steroids from the brittle star *Ophiosparte gigas* are characterized by the hydroxylation at C-3a and C-21 and the cis- Ah3 ring fusion. One of them is extremely cytotoxic even at the lowest concentration of $0.12 \mu\text{g/ml}$, whereas the other two are active against HIV-1 with EC_{50} values of ca. $50\text{--}100 \mu\text{g/ml}$ (D'Auria et al., 1993).

TUNICATA

Antarctic ascidians display high levels of endemism, reaching 25–51% of endemic species (Primo and Vázquez, 2009). While most ascidian metabolites are amino acid derived (Wang and Namikoshi, 2007), ascidians of the genus *Aplidium* are noted for possessing terpene derivatives (Zubía et al., 2005). Examples of NPs from Antarctic ascidians include palmerolide A, ecdysteroids, meridianins, aplicyanins, and rossinones (Figure 1; Table 1) (Diyabalanage et al., 2006; Miyata et al., 2007; Seldes et al., 2007; Reyes et al., 2008; Appleton et al., 2009; Núñez-Pons et al., 2010, 2012, 2015; Núñez-Pons and Avila, 2015).

However, it is often unclear whether tunicates are the true producers of the molecules or whether associated microbes may play a role in their synthesis and chemical ecology (Núñez-Pons et al., 2012). *Aplidium* species are the source of numerous nitrogen-containing metabolites belonging to unprecedented structural families of NPs (Zubía et al., 2005). Six bromoindole derivatives, aplicyanins A–F (Figure 1) from *A. cyaneum* are cytotoxic against human tumor cell lines A-549, HT-29, and MDA-MB-231, and show antimitotic properties (for aplicyanins B, D, E, and F), thus suggesting a key role for the acetyl group at N-16 in their biological activity (Reyes et al., 2008). These compounds are reduced forms of the structurally related meridianins isolated from *A. meridianum* and can therefore be considered their biogenetic precursors. Meridianins are a family of indole alkaloids consisting of an indole framework linked to an aminopyrimidine ring. Meridianins A–E (Figure 1) from *A. meridianum* present cytotoxicity toward LMM3 (murine mammary adenocarcinoma cell line) at IC₅₀ values of 11.4 μM for meridianin B, 9.3 μM for meridianin C, 33.9 μM for meridianin D, and 11.1 μM for meridianin E (Franco et al., 1998). Aiming to find possible molecular targets for a set of MNPs, it was reported that some meridianins can interact with proteins involved in neurodegenerative diseases (Llorach-Parés et al., 2017, 2018). In fact, meridianins are found particularly interesting as potential therapeutic agents against Alzheimer disease (AD) (Llorach-Parés et al., 2017) and computational chemistry and *in vitro* assays have recently shown promising results (Llorach-Parés et al., 2020). Currently there is no treatment that cures or even slows AD progression, and therefore, there is a need for new and improved therapeutic molecules for these diseases, as their impact is expected to increase due to the shift in world demography. Although we are far from having solutions, potential benefits of a treatment for AD are huge and would clearly result in improving patients health and reducing societal costs.

Furthermore, rosinones A (Figure 1) and B are biologically active meroterpene derivatives from *Aplidium* species (Appleton et al., 2009; Núñez-Pons et al., 2012). Rossinones possess anti-inflammatory, antiviral, and antiproliferative activities (Appleton et al., 2009). In an *in vitro* anti-inflammatory assay with activated human peripheral blood neutrophils, rosinones inhibited superoxide production when either N-formyl-methionyl-leucyl-phenylalanine (fMLP) (IC₅₀ 1.9 and 2.5 μM, respectively) or phorbol myristate acetate (PMA) (IC₅₀ 0.8 and 0.7 μM, respectively) were used to activate the respiratory burst (Tan and Berridge, 2000). Also a selective antiviral activity toward DNA virus HSV-1, versus the RNA virus PV-1 is described for both compounds, with antiviral activity at 2 μg/disk. Both compounds also present antimicrobial activity against the Gram + bacterium *B. subtilis* and the fungi *Trichophyton mentagrophytes* at 60 μg/disk (Appleton et al., 2009).

An enamide-bearing polyketide, the palmerolide A (Figure 1) from the common tunicate *Synoicum adareanum* targets melanoma (UACC-62, LC₅₀ = 18 nM), colon cancer cell line (HCC-2998, LC₅₀ = 6.5 μM) and renal cancer cell lines (RXF 393, LC₅₀ = 6.5 μM) (Diyabalanage et al., 2006; Riesenfeld et al., 2008; Murray et al., 2020). Palmerolide A is stable for extended time

periods and does not readily yield a single hydrolysis product. Later studies isolated palmerolides A (0.002 μM), D (0.025 μM), and G (0.007 μM). All palmerolides containing the C-2'/C-3' olefin are very potent V-ATPase inhibitors, whereas palmerolide F (0.063 μM) which lacks the above mentioned olefin is significantly less potent (Noguez et al., 2011). Palmerolide E, lacking the entire carboxamide functionality, appears to retain inhibitory activity (IC₅₀ 5 μM) toward melanoma while losing effectiveness against V-ATPase (IC₅₀ > 10 μM). This suggests that different parts of the side chain are responsible for the activities exhibited against UACC-62 and V-ATPase (Noguez et al., 2011). Most of these palmerolides are potent V-ATPase inhibitors and have sub-micromolar activity against melanoma but palmerolides are less neurotoxic than other V-ATPase inhibitors. Palmerolide C is a congeneric macrolide of palmerolide A exhibiting similar bioactivity toward the UACC-62 human melanoma cell line (IC₅₀ = 110 nM) (Sayyad et al., 2020). *S. adareanum* also presents the known ecdysteroid dialusterol B, as well as five more ecdysteroids, hyousterones A–D (Miyata et al., 2007). These ecdysteroids were evaluated for solid tumor selective cytotoxicity using colon (colon 38, HCT-116), lung (H-125M), leukemia (L1210, CCRF-CEM), and normal (CFU-GM) cell lines. Abeohyosterone (Figure 1) possesses moderate cytotoxicity toward several cancer cell lines while hyousterones A and C, bearing the 14R-hydroxy group, were weakly cytotoxic (Miyata et al., 2007).

Finally, 21 fatty acids and some sterols are found in the pelagic *Salpa thompsoni*, with the total fatty acids fraction being strongly hemolytic, and the polyunsaturated acids DHA: 6ω3 and EPA: 5ω3 as the most potent compounds (Mimura et al., 1986). Slight changes in the position and the geometry of the double bond seem to affect the potency of hemolytic activity of these compounds.

MANAGING BIODISCOVERY IN ANTARCTICA

Studying and using bioactive MNPs while conserving biodiversity is crucial, and further synthesizing the useful bioactive compounds in the laboratory is a must. The tenth Conference of the Parties (CoP10) to the Convention on Biological Diversity (CBD) held in Nagoya (2010) led to the adoption of a global Strategic Plan for biodiversity 2011–2020, the Nagoya Protocol on Access to Genetic Resources, and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS Protocol), as well as a strategy to mobilize resources for global biodiversity. European policies defend that all these protocols shall indeed include marine biotechnology. In fact, the new resources obtained from marine research and the so-called blue biotechnologies are currently considered an emerging sector, with a promising growth of 10% per year and a global market of €2.4 billion estimated in 2008⁴. Biodiversity, and all the services it provides, has a significant economic value that is seldom

⁴https://ec.europa.eu/maritimeaffairs/sites/maritimeaffairs/files/docs/publications/blue-growth_en.pdf

captured in markets, as recognized by the European Union, 2020 biodiversity target. In the short term, economic impacts have to be considered in terms of research activities and involved SMEs. In a medium to long term period, commercialization of bioactive products discovered would generate economic impacts in anticancer, against neurodegenerative diseases, antimicrobial, antiviral, antifungal, antiparasitic, enzymes (protease inhibitors, etc.), antioxidant (skin protection), and potentially many other applications. Antarctic MNPs may be an important source of new drugs for the future, and therefore should be explored according to the mentioned regulations. Furthermore, Antarctic studies are regulated by the Antarctic Treaty system (ATS) and the Madrid Protocol, establishing what we can and what we cannot do for research there. Sustainable Development Goals (SDGs), moreover, have to be considered here too. In fact, all regulations try to protect biodiversity (and thus, chemodiversity) while carrying out biodiscovery research.

CONCLUDING REMARKS

In this minireview we showcase the diverse bioactivities described in Antarctic MNPs, their original chemical structures, and the huge potential they possess. A total of 37 species have been reported, including 15 Porifera, eight Cnidaria, one Mollusca, one Bryozoa, one Nemertea, six Echinodermata, and five Tunicata. The amazing biodiversity of the Antarctic benthos holds, as well as their inherent chemodiversity, must be protected by all means to avoid their disappearance according to the established regulations. In fact, the current popularity of MNPs in cosmetic, food, pharmaceutical industries, etc. is rising concerns about sustainability all over the planet. If we aim to use this chemodiversity for human benefits we must keep the biological diversity, solving the supply problem, using

synthesis, targeting biosynthetic gene clusters (BGCs), and using all the omics, informatic tools and databases currently available to move forward without damaging the ecosystems. When MNPs are obtained by cultures these concerns diminish considerably. The current research gaps and the potential future developments have been indicated here, and even if the interest on bioprospecting MNPs is exponentially growing, still new techniques and approaches have to improve to overcome the common bottlenecks in MNPs pipelines, speeding the process and decreasing research costs to fully exploit the benefits of biodiscovery in Antarctic MNPs in a near future in a sustainable way.

AUTHOR CONTRIBUTIONS

CA: idea and conceptualization. CA and CA-P: literature review, writing, and editing. Both authors contributed to the article and approved the submitted version.

FUNDING

This work was developed within the frames of the BLUEBIO and CHALLENGE research projects (CTM2016-78901 and PID2019-107979/ANT, Spanish government) and with support from a 2017SGR1120 grant of the Catalan government. CA-P was supported by the Ramon Areces Foundation.

ACKNOWLEDGMENTS

Thanks are due to all the members of the BLUEBIO and CHALLENGE research projects for their support. This is an AntICON (SCAR) contribution.

REFERENCES

- Abida, H., Ruchaud, S., Rios, L., Humeau, A., Probert, I., De Vargas, C., et al. (2013). Bioprospecting marine plankton. *Mar. Drugs* 11, 4594–4611. doi: 10.3390/md11114594
- Abramson, S. N., Trischman, J. A., Tapiolas, D. M., Harold, E. E., Fenical, W., and Taylor, P. (1991). Structure/activity and molecular modeling studies of the Lophotoxin family of irreversible nicotinic receptor antagonists. *J. Med. Chem.* 34, 1798–1804. doi: 10.1021/jm00110a007
- Amsler, C. D., Moeller, C. B., McClintock, J. B., Iken, K. B., and Baker, B. J. (2000). Chemical defenses against diatom fouling in Antarctic marine sponges. *Biofouling* 16, 29–45. doi: 10.1080/08927010009378428
- Angulo-Preckler, C., Cid, C., Oliva, F., and Avila, C. (2015). Antifouling activity in some benthic Antarctic invertebrates by *in situ* experiments at deception Island, Antarctica. *Mar. Environ. Res.* 105, 30–38. doi: 10.1016/j.marenvres.2015.02.001
- Angulo-Preckler, C., San Miguel, O., García-Aljaro, C., and Avila, C. (2017). Antibacterial defenses and palatability of some shallow-water Antarctic sponges. *Hydrobiologia* 806, 123–138. doi: 10.1007/s10750-017-3346-5
- Ankisetty, S., Amsler, C. D., McClintock, J. B., and Baker, B. J. (2004). Further membranolid diterpenes from the antarctic sponge *Dendrilla membranosa*. *J. Nat. Prod.* 67, 1172–1174. doi: 10.1021/np0340551
- Antonov, A. S., Avilov, S. A., Kalinovsky, A. I., Anastuyuk, S. D., Dmitrenok, P. S., Evtushenko, E. V., et al. (2008). Triterpene glycosides from antarctic sea cucumbers. 1. Structure of liouvillosides A1, A2, A3, B1, and B2 from the sea cucumber *Staurocucumis liouvillei*: new procedure for separation of highly polar glycoside fractions and taxonomic revision. *J. Nat. Prod.* 71, 1677–1685. doi: 10.1021/np800173c
- Antonov, A. S., Avilov, S. A., Kalinovsky, A. I., Anastuyuk, S. D., Dmitrenok, P. S., Kalinin, V. I., et al. (2009). Triterpene glycosides from Antarctic sea cucumbers. 2. Structure of Achlioniceosides A1, A2, and A3 from the sea cucumber *Achlionice violaceuspidata* (= *Rhipidothuria racowitzai*). *J. Nat. Prod.* 72, 33–38. doi: 10.1021/np800469v
- Antonov, A. S., Avilov, S. A., Kalinovsky, A. I., Dmitrenok, P. S., Kalinin, V. I., Taboada, S., et al. (2011). Triterpene glycosides from Antarctic sea cucumbers III. Structures of liouvillosides A4 and A5, two minor disulphated tetraosides containing 3-O-methylquinovose as terminal monosaccharide units from the sea cucumber *Staurocucumis liouvillei* (Vaney). *Nat. Prod. Res.* 25, 1324–1333. doi: 10.1080/14786419.2010.531017
- Appleton, D. R., Chuen, C. S., Berridge, M. V., Webb, V. L., and Copp, B. R. (2009). Rossinones A and B, biologically active meroterpenoids from the Antarctic ascidian, *Aplidium* species. *J. Org. Chem.* 74, 9195–9198. doi: 10.1021/jo901846j
- Arrieta, J. M., Arnaud-Haond, S., and Duarte, C. M. (2010). What lies underneath: conserving the oceans' genetic resources. *Proc. Natl. Acad. Sci. U.S.A.* 107, 18318–18324. doi: 10.1073/pnas.0911897107
- Avila, C. (2016a). Biological and chemical diversity in Antarctica: from new species to new natural products. *Biodiversity* 17, 1–7.

- Avila, C. (2016b). Ecological and pharmacological activities of Antarctic marine natural products. *Planta Med.* 82, 767–774. doi: 10.1055/s-0042-105652
- Avila, C., and Angulo-Preckler, C. (2020). Bioactive compounds from marine Heterobranchs. *Mar. Drugs* 18:657. doi: 10.3390/md18120657
- Avila, C., Taboada, S., and Núñez-Pons, L. (2008). Antarctic marine chemical ecology: what's next? *Mar. Ecol.* 29, 1–71. doi: 10.1111/j.1439-0485.2007.00215.x
- Beattie, A. J., Hay, M., Magnusson, B., de Nys, R., Smeathers, J., and Vincent, J. F. (2011). Ecology and bioprospecting. *Austral Ecol.* 36, 341–356. doi: 10.1111/j.1442-9993.2010.02170.x
- Bérdy, J. (2012). Thoughts and facts about antibiotics: where we are now and where we are heading. *J. Antibiot.* 65, 385–395. doi: 10.1038/ja.2012.27
- Bory, A., Shilling, A., Allen, J. L., Azhari, A., Roth, A., Shaw, L., et al. (2020). Bioactivity of spongian diterpenoid scaffolds from the Antarctic sponge *Dendrilla antarctica*. *Mar. Drugs* 18, 327. doi: 10.3390/md18060327
- Botič, T., Defant, A., Zanini, P., Žužek, M. C., Frangež, R., Janussen, D., et al. (2017). Discorhabdin alkaloids from Antarctic *Latrunclia* spp. sponges as a new class of cholinesterase inhibitors. *Eur. J. Med. Chem.* 136, 294–304. doi: 10.1016/j.ejmech.2017.05.019
- Buenz, E. J., Verpoorte, R., and Bauer, B. A. (2018). The ethnopharmacologic contribution to bioprospecting natural products. *Annu. Rev. Pharmacol. Toxicol.* 58, 509–530. doi: 10.1146/annurev-pharmtox-010617-052703
- Carroll, A. R., Copp, B. R., Davis, R. A., Keyzers, R. A., and Prinsep, M. R. (2020). Marine natural products. *Nat. Prod. Rep.* 37, 175–223.
- Carté, B., and Faulkner, D. J. (1983). Defensive metabolites from three nembrothid nudibranchs. *J. Org. Chem.* 48, 2314–2318. doi: 10.1021/jo00162a003
- Chen, M., Han, L., Wang, Y., Zhang, X. L., and Wang, C. Y. (2014). A new sesquiterpene from the Hainan gorgonian *Menella kanisa* Grasso. *Nat. Prod. Res.* 28, 1147–1151. doi: 10.1080/14786419.2014.918122
- Ciaglia, E., Malfitano, A. M., Laezza, C., Fontana, A., Nuzzo, G., Cutignano, A., et al. (2017). Immuno-modulatory and anti-inflammatory effects of Dihydrogracilin A, a terpene derived from the marine sponge *Dendrilla membranosa*. *Int. J. Mol. Sci.* 18:1643. doi: 10.3390/ijms18081643
- Comin, M. J., Maier, M. S., Roccatagliata, A. J., Pujol, C. A., and Damonte, E. B. (1999). Evaluation of the antiviral activity of natural sulfated polyhydroxysteroids and their synthetic derivatives and analogs. *Steroids* 64, 335–340. doi: 10.1016/s0039-128x(99)00016-1
- Cushnie, T. P., Cushnie, B., Echeverria, J., Fowsantear, W., Thammawat, S., Dodgson, J. L., et al. (2020). Bioprospecting for antibacterial drugs: a multidisciplinary perspective on natural product source material, bioassay selection and avoidable pitfalls. *Pharm. Res.* 37:125. doi: 10.1007/s11095-020-02849-1
- D'Ambrosio, M., Guerriero, A., Chiasera, G., Pietra, F., and Tatò, M. (1996). Epinaridins A-D, new pyrroloiminoquinone alkaloids of undetermined deep-water green demosponges from pre-Antarctic Indian ocean. *Tetrahedron* 52, 8899–8906. doi: 10.1016/0040-4020(96)00438-3
- D'Auria, M. V., Paloma, L. G., Minale, L., Riccio, R., Zampella, A., and Morbidoni, M. (1993). Isolation and structure characterization of two novel bioactive sulphated polyhydroxysteroids from the Antarctic ophiuroid *Ophioderma longicaudum*. *Nat. Prod. Lett.* 3, 197–201. doi: 10.1080/10575639308043863
- De Marino, S., Iorizzi, M., Palagiano, E., Zollo, F., and Roussakis, C. (1998). Starfish saponins. 55.1 Isolation, structure elucidation, and biological activity of the steroid oligoglycosides from an Antarctic starfish of the family Asteroidea. *J. Nat. Prod.* 61, 1319–1327. doi: 10.1021/np970500e
- De Marino, S., Iorizzi, M., Zollo, F., Minale, L., Amsler, C. D., Baker, B. J., et al. (1997a). Isolation, structure elucidation, and biological activity of the steroid oligoglycosides and polyhydroxysteroids from the Antarctic starfish *Acodontaster conspicuus*. *J. Nat. Prod.* 60, 959–966. doi: 10.1021/np9700578
- De Marino, S., Palagiano, E., Zollo, F., Minale, L., and Iorizzi, M. (1997b). A novel sulphated steroid with a 7-membered 5-oxalactone B-ring from an Antarctic starfish of the family Asteroidea. *Tetrahedron* 53, 8625–8628. doi: 10.1016/s0040-4020(97)00531-0
- Diyabalanage, T., Amsler, C. D., McClintock, J. B., and Baker, B. J. (2006). Palmerolide A, a cytotoxic macrolide from the Antarctic tunicate *Synoicum adareanum*. *J. Am. Chem. Soc.* 128, 5630–5631. doi: 10.1021/ja0588508
- Eisner, T. (1990). Prospecting for nature's chemical riches. *Chemoecology* 1, 38–40. doi: 10.1007/bf01240585
- Fan, X., Bai, L., Zhu, L., Yang, L., and Zhang, X. (2014). Marine algae-derived bioactive peptides for human nutrition and health. *J. Agric. Food Chem.* 62, 9211–9222. doi: 10.1021/jf502420h
- Figuerola, B., and Avila, C. (2019). The phylum bryozoa as a promising source of anticancer drugs. *Mar. Drugs* 17:477. doi: 10.3390/md17080477
- Figuerola, B., Núñez-Pons, L., Moles, J., and Avila, C. (2013). Feeding repellence in Antarctic bryozoans. *Naturwiss* 100, 1069–1081. doi: 10.1007/s00114-013-1112-8
- Figuerola, B., Sala-Comorera, L., Angulo-Preckler, C., Vázquez, J., Montes, M. J., García-Aljaro, C., et al. (2014). Antimicrobial activity of Antarctic bryozoans: an ecological perspective with potential for clinical applications. *Mar. Environ. Res.* 101, 52–59. doi: 10.1016/j.marenvres.2014.09.001
- Ford, J., and Capon, R. J. (2000). Discorhabdin R: a new antibacterial pyrroloiminoquinone from two latruncliid marine sponges, *Latrunclia* sp. and *Negombata* sp. *J. Nat. Prod.* 63, 1527–1528. doi: 10.1021/np000220q
- Franco, L. H., Joffé, E. B., Puricelli, L., Tatian, M., Seldes, A. M., and Palermo, J. A. (1998). Indole alkaloids from the tunicate *Aplidium meridianum*. *J. Nat. Prod.* 61, 1130–1132.
- Gavagnin, M., Mollo, E., Castelluccio, F., Crispino, A., and Cimino, G. (2003). Sesquiterpene metabolites of the Antarctic gorgonian *Dasystemella acanthina*. *J. Nat. Prod.* 66, 1517–1519. doi: 10.1021/np030201r
- Gerwick, W. H., and Fenner, A. M. (2013). Drug discovery from marine microbes. *Microb. Ecol.* 65, 800–806. doi: 10.1007/s00248-012-0169-9
- Gerwick, W. H., and Moore, B. S. (2012). Lessons from the past and charting the future of marine natural products drug discovery and chemical biology. *Chem. Biol.* 19, 85–98. doi: 10.1016/j.chembiol.2011.12.014
- Giordano, D., Costantini, M., Coppola, D., Lauritano, C., Núñez Pons, L., Ruocco, N., et al. (2018). Biotechnological applications of bioactive peptides from marine sources. *Adv. Microb. Physiol.* 73, 171–220. doi: 10.1016/bs.ampbs.2018.05.002
- Göransson, U., Jacobsson, E., Strand, M., and Andersson, H. S. (2019). The toxins of nemertean worms. *Toxins* 11:120. doi: 10.3390/toxins11020120
- Griffiths, H. J. (2010). Antarctic marine biodiversity—what do we know about the distribution of life in the Southern Ocean? *PLoS One* 5:e11683. doi: 10.1371/journal.pone.0011683
- Gupta, P. L., Rajput, M., Oza, T., Trivedi, U., and Sanghvi, G. (2019). Eminence of microbial products in cosmetic industry. *Nat. Prod. Biopros.* 9, 267–278. doi: 10.1007/s13659-019-0215-0
- Höller, U., Wright, A. D., Matthee, G. F., König, G. M., Draeger, S., Hans-Jürgen, A., et al. (2000). Fungi from marine sponges: diversity, biological activity and secondary metabolites. *Mycol. Res.* 104, 1354–1365. doi: 10.1017/s0953756200003117
- Hu, G. P., Yuan, J., Sun, L., She, Z. G., Wu, J. H., Lan, X. J., et al. (2011). Statistical research on marine natural products based on data obtained between 1985 and 2008. *Mar. Drugs* 9, 514–525. doi: 10.3390/md9040514
- Iken, K. B., and Baker, B. J. (2003). Ainigmaptilones, sesquiterpenes from the Antarctic gorgonian coral *Ainigmaptilon antarcticus*. *J. Nat. Prod.* 66, 888–890. doi: 10.1021/np030051k
- Imhoff, J. F., Labes, A., and Wiese, J. (2011). Bio-mining the microbial treasures of the ocean: new natural products. *Biotechnol. Adv.* 29, 468–482. doi: 10.1016/j.biotechadv.2011.03.001
- Iorizzi, M., De Marino, S., Minale, L., Zollo, F., Le Bert, V., and Roussakis, C. (1996). Investigation of the polar steroids from an Antarctic starfish of the family Echinasteridae: isolation of twenty seven polyhydroxysteroids and steroidal oligoglycosides, structures and biological activities. *Tetrahedron* 52, 10997–11012. doi: 10.1016/0040-4020(96)00618-7
- Ivanchina, N. V., Malyarenko, T. V., Kicha, A. A., Kalinovsky, A. I., Dmitrenko, P. S., and Ermakova, S. P. (2011). Structures and cytotoxic activities of two new asterosaponins from the Antarctic starfish *Diplasterias brucei*. *Russ. J. Bioorg. Chem.* 37, 499–506. doi: 10.1134/s1068162011030083
- Jabour-Green, J., and Nicol, D. (2003). Bioprospecting in areas outside national jurisdiction: Antarctica and the Southern Ocean. *Melb. J. Int. L.* 4, 76–111.
- Jaspars, M., De Pascale, D., Andersen, J. H., Reyes, F., Crawford, A. D., and Inanora, A. (2016). The marine biodiscovery pipeline and ocean medicines of tomorrow. *J. Mar. Biol. Assoc. U.K.* 96, 151–158. doi: 10.1017/s0025315415002106

- Jayatilake, G. S., Baker, B., and McClintock, J. (1995). Isolation and identification of a stilbene derivative from the Antarctic sponge *Kirkpatrickia variolosa*. *J. Nat. Prod.* 58, 1958–1960. doi: 10.1021/np50126a028
- Jayatilake, G. S., Baker, B. J., and McClintock, J. B. (1997). Rhapsamine, a cytotoxin from the Antarctic sponge *Leucetta leptorhaphis*. *Tetrahedron Lett.* 38, 7507–7510. doi: 10.1016/s0040-4039(97)01802-9
- Kayser, O., Kiderlen, A. F., and Croft, S. L. (2003). Natural products as antiparasitic drugs. *Parasitology Res.* 90, 55–62.
- Kim, S.-K., and Wijesekera, I. (2010). Development and biological activities of marine-derived bioactive peptides: a review. *J. Funct. Food* 2, 1–9. doi: 10.1016/j.jff.2010.01.003
- Knestrick, M. A., Wilson, N. G., Roth, A., Adams, J., and Baker, B. (2019). Friomaramide, a highly modified linear hexapeptide from an Antarctic sponge, inhibits *Plasmodium falciparum* liver-stage development. *J. Nat. Prod.* 82, 2354–2358. doi: 10.1021/acs.jnatprod.9b00362
- Leal, M. C., Puga, J., Seródio, J., Gomes, N. C. M., and Calado, R. (2012). Trends in the discovery of new marine natural products from invertebrates over the last two decades—where and what are we bioprospecting? *PLoS One* 7:e30580. doi: 10.1371/journal.pone.0030580
- Lebar, M. D., Heimbegner, J. L., and Baker, B. J. (2007). Cold-water marine natural products. *Nat. Prod. Rep.* 24, 774–797. doi: 10.1039/b516240h
- Li, F., Janussen, D., Peifer, C., Pérez-Victoria, I., and Tasdemir, D. (2018). Targeted isolation of tsitsikammamines from the Antarctic deep-sea sponge *Latrunculia bififormis* by molecular networking and anticancer activity. *Mar. Drugs* 16, 268. doi: 10.3390/md16080268
- Li, F., Janussen, D., and Tasdemir, D. (2020a). New discorhabdin B dimers with anticancer activity from the Antarctic deep-sea sponge *Latrunculia bififormis*. *Mar. Drugs* 18:107. doi: 10.3390/md18020107
- Li, F., Pandey, P., Janussen, D., Chittiboyina, A. G., Ferreira, D., and Tasdemir, D. (2020b). Tridiscorhabdin and didiscorhabdin, the first discorhabdin oligomers linked with a direct C-N bridge from the sponge *Latrunculia bififormis* collected from the deep sea in Antarctica. *J. Nat. Prod.* 83, 706–713. doi: 10.1021/acs.jnatprod.0c00023
- Li, F., Peifer, C., Janussen, D., and Tasdemir, D. (2019). New discorhabdin alkaloids from the Antarctic deep-sea sponge *Latrunculia bififormis*. *Mar. Drugs* 17:439. doi: 10.3390/md17080439
- Li, M. K., and Scheuer, P. J. (1984). A guaianolide pigment from a deep sea gorgonian. *Tetrahedron Lett.* 25, 2109–2110. doi: 10.1016/s0040-4039(01)81173-4
- Llorach-Parés, L., Nonell-Canals, A., Avila, C., and Sanchez-Martinez, M. (2018). Kororamides, Convolutamines, and Indole derivatives as possible tau and dual-specificity Kinase inhibitors for Alzheimer's disease: a computational study. *Mar. Drugs* 16:386. doi: 10.3390/md16100386
- Llorach-Parés, L., Nonell-Canals, A., Sánchez-Martínez, M., and Avila, C. (2017). Computer-aided drug design applied to marine drug discovery: meridianins as Alzheimer's disease therapeutic agents. *Mar. Drugs* 15, 366–395. doi: 10.3390/md15120366
- Llorach-Parés, L., Rodríguez-Urgelles, E., Nonell-Canals, A., Alberch, J., Avila, C., Sanchez-Martinez, M., et al. (2020). Meridianins and lignarenone B as potential GSK3 β inhibitors and inducers of structural neuronal plasticity. *Biomolecules* 10:639. doi: 10.3390/biom10040639
- Ma, W. S., Mutka, T., Vesley, B., Amsler, M. O., McClintock, J., Amsler, C., et al. (2009). Norselic acids A-E, highly oxidized anti-infective steroids that deter mesograzers, from the Antarctic sponge *Crella* sp. *J. Nat. Prod.* 72, 1842–1846. doi: 10.1021/np900382x
- Maier, M. S., Roccatagliata, A. J., Kuriss, A., Chludil, H., Seldes, A. M., Pujol, C. A., et al. (2001). Two new cytotoxic and virucidal trisulfated triterpene glycosides from the Antarctic sea cucumber *Staurocucumis liouvillei*. *J. Nat. Prod.* 64, 732–736. doi: 10.1021/np000584i
- Martins, A., Vieira, H., Gaspar, H., and Santos, S. (2014). Marketed marine natural products in the pharmaceutical and cosmeceutical industries: tips for success. *Mar. Drugs* 12, 1066–1101. doi: 10.3390/md12021066
- Maschek, J. A., Mevers, E., Diyabalanage, T., Chen, L., Ren, Y., McClintock, J. B., et al. (2012). Palmadorin chemodiversity from the Antarctic nudibranch *Austrodoris kerguelensis* and inhibition of Jak2/STAT5-dependent HEL leukemia cells. *Tetrahedron* 68, 9095–9104. doi: 10.1016/j.tet.2012.08.045
- Mayer, A. M., Glaser, K. B., Cuevas, C., Jacobs, R. S., Kem, W., Little, R. D., et al. (2010). The odyssey of marine pharmaceuticals: a current pipeline perspective. *Trends Pharmacol. Sci.* 31, 255–265. doi: 10.1016/j.tips.2010.02.005
- Mayer, A. M., Rodriguez, A. D., Tagliatela-Scafati, O., and Fusetani, N. (2013). Marine pharmacology in 2009–2011: marine compounds with antibacterial, Antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous systems, and other miscellaneous mechanisms of action. *Mar. Drugs* 11, 2510–2573. doi: 10.3390/md11072510
- Mazarrasa, I., Olsen, Y. S., Mayol, E., Marbà, N., and Duarte, C. M. (2014). Global unbalance in seaweed production, research effort and biotechnology markets. *Biotechnol. Adv.* 32, 1028–1036. doi: 10.1016/j.biotechadv.2014.05.002
- McClintock, J. B., Amsler, C. D., Baker, B. J., and Van Soest, R. W. M. (2005). Ecology of Antarctic marine sponges: an overview. *Integr. Comp. Biol.* 45, 359–368. doi: 10.1093/icb/45.2.359
- McKee, T. C., Cardellina, J. H., Riccio, R., D'Auria, M. V., Iorizzi, M., Minale, L., et al. (1994). HIV-inhibitory natural products. 11. Comparative studies of sulfated sterols from marine invertebrates. *J. Med. Chem.* 37, 793–797. doi: 10.1021/jm00032a012
- Mellado, G. G., Zubía, E., Ortega, M. J., and López-González, P. J. (2005). Steroids from the Antarctic octocoral *Anthomastus bathyproctus*. *J. Nat. Prod.* 68, 1111–1115. doi: 10.1021/np050080q
- Mellado, G. G., Zubía, E., Ortega, M. J., and López-González, P. J. (2004). New polyoxygenated steroids from the Antarctic octocoral *Dasytenella acanthina*. *Steroids* 69, 291–299. doi: 10.1016/j.steroids.2004.02.005
- Mimura, T., Okabe, M., Satake, M., Nakanishi, T., Inada, A., Fujimoto, Y., et al. (1986). Fatty acids and sterols of the tunicate, *Salpa thompsoni*, from the Antarctic Ocean: chemical composition and hemolytic activity. *Chem. Pharmaceut. Bull.* 34, 4562–4568. doi: 10.1248/cpb.34.4562
- Minale, L., Riccio, R., and Zollo, F. (1993). Steroidal oligoglycosides and polyhydroxysteroids from Echinoderms. *Prog. Chem. Org. Nat. Prod.* 62, 308.
- Miyata, Y., Diyabalanage, T., Amsler, C. D., McClintock, J. B., Valeriote, F. A., and Baker, B. J. (2007). Ecdysteroids from the Antarctic tunicate *Synoicum adareanum*. *J. Nat. Prod.* 70, 1859–1864. doi: 10.1021/np0702739
- Moles, J., Torrent, A. M., Alcaraz, M. J., Ruhí, R., and Avila, C. (2014). Anti-inflammatory activity in selected Antarctic benthic organisms. *Front. Mar. Sci.* 1:24. doi: 10.3389/fmars.2014.00024
- Molinski, T. F., and Faulkner, D. J. (1987). Metabolites of the Antarctic sponge *Dendrilla membranosa*. *J. Org. Chem.* 1987, 296–298. doi: 10.1021/jo00378a031
- Molinski, T. F., and Faulkner, D. J. (1988). An antibacterial pigment from the sponge *Dendrilla membranosa*. *Tetrahedron Lett.* 29, 2137–2138. doi: 10.1016/s0040-4039(00)86692-7
- Moon, B., Baker, B. J., and McClintock, J. B. (1998). Purine and nucleoside metabolites from the Antarctic sponge *Isodictya erinacea*. *J. Nat. Prod.* 61, 116–118. doi: 10.1021/np970358h
- Moon, B., Park, Y. C., McClintock, J. B., and Baker, B. (2000). Structure and bioactivity of erbusinone, a pigment from the Antarctic sponge *Isodictya erinacea*. *Tetrahedron* 56, 9057–9062. doi: 10.1016/s0040-4020(00)00760-2
- Murray, A. E., Avalon, N. E., Bishop, L., Davenport, K. W., Delage, E., Dichosa, A. E. K., et al. (2020). Uncovering the core microbiome and distributions of palmerolide in *Synoicum adareanum* across the Anvers Island archipelago, Antarctica. *Mar. Drugs* 18:298. doi: 10.1101/2020.02.20.958975
- Newman, D. J., and Cragg, G. M. (2012). Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.* 75, 311–335. doi: 10.1021/np200906s
- Newman, D. J., and Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. *J. Nat. Prod.* 79, 629–661. doi: 10.1021/acs.jnatprod.5b01055
- Nishimura, S., Arita, Y., Honda, M., Iwamoto, K., Matsuyama, A., Shirai, A., et al. (2010). Marine antifungal theonellamides target 3 β -hydroxysterol to activate Rho1 signaling. *Nat. Chem. Biol.* 6, 519–526. doi: 10.1038/nchembio.387
- Noguez, J. H., Diyabalanage, T. K., Miyata, Y., Xie, X. S., Valeriote, F. A., Amsler, C. D., et al. (2011). Palmerolide macrolides from the Antarctic tunicate *Synoicum adareanum*. *Bioorgan. Med. Chem.* 19, 6608–6614. doi: 10.1016/j.bmc.2011.06.004
- Núñez-Pons, L., and Avila, C. (2015). Natural products mediating ecological interactions in Antarctic ecosystems: A mini-review of the known molecules. *Nat. Prod. Rep.* 32, 1114–1130. doi: 10.1039/c4np00150h

- Núñez-Pons, L., Carbone, M., Vázquez, J., Rodríguez, J., Nieto, R. M., Varela, M. M., et al. (2012). Natural products from Antarctic colonial ascidians of the genera *Aplidium* and *Synoicum*: variability and defensive role. *Mar. Drugs* 10, 1741–1764. doi: 10.3390/md10081741
- Núñez-Pons, L., Forestieri, R., Nieto, R. M., Varela, M., Nappo, M., Rodríguez, J., et al. (2010). Chemical defenses of tunicates of the genus *Aplidium* from the Weddell Sea (Antarctica). *Pol. Biol.* 33, 1319–1329. doi: 10.1007/s00300-010-0819-7
- Núñez-Pons, L., Nieto, R. M., Avila, C., Jiménez, C., and Rodríguez, J. (2015). Mass spectrometry detection of minor new meridianins from the Antarctic colonial ascidians *Aplidium falklandicum* and *Aplidium meridianum*. *J. Mass Spectrom.* 50, 103–111. doi: 10.1002/jms.3502
- Palermo, J. A., Rodriguez-Brasco, M. F., Spagnuolo, C., and Seldes, A. M. (2000). Illudalane sesquiterpenoids from the soft coral *Alcyonium paessleri*: the first natural nitrate esters. *J. Org. Chem.* 65, 4482–4486. doi: 10.1021/jo991740x
- Pandey, A., and Yarzabal, L. A. (2019). Bioprospecting cold-adapted plant growth promoting microorganisms from mountain environments. *Appl. Microbiol. Biotechnol.* 103, 643–657. doi: 10.1007/s00253-018-9515-2
- Park, Y. C. (2004). *Chemical Investigation of Three Antarctic Marine Sponges*. Graduate thesis. Tampa, FL: University of South Florida.
- Pascoal, F., Magalhães, C., and Costa, R. (2020). The link between the ecology of the prokaryotic rare biosphere and its biotechnological potential. *Front. Microbiol.* 11:231. doi: 10.3389/fmicb.2020.00231
- Patiño-Cano, L. P., Quintana Manfredi, R., Pérez, M., García, M., Blustein, G., Cordeiro, R., et al. (2018). Isolation and antifouling activity of azulene derivatives from the Antarctic gorgonian *Acanthogorgia laxa*. *Chem. Biodivers.* 15:e1700425. doi: 10.1002/cbdv.201700425
- Patiño-Cano, L. P., Muniain, C., Knott, M. E., Puricelli, L., and Palermo, J. A. (2014). Bromopyrrole alkaloids isolated from the Patagonian bryozoan *Aspidostoma giganteum*. *J. Nat. Prod.* 77, 1170–1178. doi: 10.1021/np500012y
- Patridge, E., Gareiss, P., Kinch, M. S., and Hoyer, D. (2016). An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov.* 21, 204–207. doi: 10.1016/j.drudis.2015.01.009
- Perry, N. B., Ettouati, L., Litaudon, M., Blunt, J., Munro, M., Parkin, S., et al. (1994). Alkaloids from the antarctic sponge *Kirkpatrickia varialosa*. Part 1: Variolin B, a new antitumour and antiviral compound. *Tetrahedron* 50, 3987–3992. doi: 10.1016/s0040-4020(01)89673-3
- Primo, C., and Vázquez, E. (2009). Antarctic ascidians: An isolated and homogeneous fauna. *Polar Res.* 28, 403–414. doi: 10.1111/j.1751-8369.2009.00110.x
- Reen, F. J., Gutiérrez-Barranquero, J. A., Dobson, A. D., Adams, C., and O’Gara, F. (2015). Emerging concepts promising new horizons for marine biodiscovery and synthetic biology. *Mar. Drugs* 13, 2924–2954. doi: 10.3390/md13052924
- Reyes, F., Fernández, R., Rodríguez, A., Francesch, A., Taboada, S., Avila, C., et al. (2008). Aplicyanins A-F, new cytotoxic bromoindole derivatives from the marine tunicate *Aplidium cyaneum*. *Tetrahedron* 64, 5119–5123. doi: 10.1016/j.tet.2008.03.060
- Riesenfeld, C. S., Murray, A. E., and Baker, B. J. (2008). Characterization of the microbial community and polyketide biosynthetic potential in the palmerolide-producing tunicate *Synoicum adareanum*. *J. Nat. Prod.* 71, 1812–1818. doi: 10.1021/np800287n
- Rocha-Martin, J., Harrington, C., Dobson, A. D., and O’Gara, F. (2014). Emerging strategies and integrated systems microbiology technologies for biodiscovery of marine bioactive compounds. *Mar. Drugs* 12, 3516–3559. doi: 10.3390/md12063516
- Rodriguez-Brasco, M. F., Seldes, A. M., and Palermo, J. A. (2001). Paesslerins A and B: novel tricyclic sesquiterpenoids from the soft coral *Alcyonium paessleri*. *Organic Lett.* 3, 1415–1417. doi: 10.1021/ol006684x
- Ronowicz, M., Peña Cantero, A. L., Mercado Casares, B., Kuklinski, P., and Soto Ángel, J. J. (2019). Assessing patterns of diversity, bathymetry and distribution at the poles using Hydrozoa (Cnidaria) as a model group. *Hydrobiologia* 833, 25–51. doi: 10.1007/s10750-018-3876-5
- Sacristán-Soriano, O., Angulo-Preckler, C., Vázquez, J., and Avila, C. (2017). Potential chemical defenses of Antarctic benthic organisms against marine bacteria. *Polar Res.* 36:1390385. doi: 10.1080/17518369.2017.1390385
- Sangwan, R., Mishra, V. N., and Mandal, P. K. (2020). Synthesis of a common pentasaccharide moiety of diplasteriosides A and B belong to starfish Asterosaponins isolated from the *Diplasterias brucei*. *Tetrahedron Lett.* 61:152421. doi: 10.1016/j.tetlet.2020.152421
- Sayyad, A. A., Kaim, K., and Kaliappan, K. P. (2020). Synthetic studies on palmerolide C: synthesis of an advanced intermediate towards the revised structure of palmerolide C. *Organic Biomol. Chem.* 18, 5937–5950. doi: 10.1039/d0ob01140a
- Seldes, A. M., Brasco, M. F., Franco, L. H., and Palermo, J. A. (2007). Identification of two meridianins from the crude extract of the tunicate *Aplidium meridianum* by tandem mass spectrometry. *Nat. Prod. Res.* 21, 555–563. doi: 10.1080/14786410601133517
- Shilling, A., Witowski, C. G., Maschek, J., Azhari, A., Vesely, B., Kyle, D., et al. (2020). Spongian diterpenoids derived from the Antarctic sponge *Dendrilla antarctica* are potent inhibitors of the *Leishmania* parasite. *J. Nat. Prod.* 83, 1553–1562. doi: 10.1021/acs.jnatprod.0c00025
- Shin, J., Seo, Y., Rho, J., Baek, E., Kwon, B., Jeong, T. S., et al. (1995). Suberitenones A and B: Sesterterpenoids of an unprecedented skeletal class from the Antarctic sponge *Suberites* sp. *J. Org. Chem.* 60, 7582–7588. doi: 10.1021/jo00128a034
- Silchenko, A. S., Kalinovsky, A. I., Avilov, S. A., Andryjashchenko, P. V., Dmitrenok, P. S., Kalinin, V. I., et al. (2013). Triterpene glycosides from Antarctic sea cucumbers IV. Turquetoside A, a 3-O-methylquinovose containing disulfated tetraoside from the sea cucumber *Staurocucumis turqueti* (Vaney, 1906) (= *Cucumaria spatha*). *Biochem. Syst. Ecol.* 51, 45–49. doi: 10.1016/j.bse.2013.08.012
- Solanki, H. R., Angulo-Preckler, C., Calabro, K., Kaur, N., Lasserre, P., Cautain, B., et al. (2018). Suberitane sesterterpenoids from the Antarctic sponge *Phorbis areolatus* (Thiele, 1905). *Tetrahedron Lett.* 59, 3353–3356. doi: 10.1016/j.tetlet.2018.07.055
- Soldatou, S., and Baker, B. J. (2017). Cold-water marine natural products, 2006 to 2016. *Nat. Prod. Rep.* 34, 585–626. doi: 10.1039/c6np00127k
- Stern, M., Gierse, A., Tan, S., and Bicker, G. (2014). Human Ntera2 cells as a predictive in vitro test system for developmental neurotoxicity. *Archives Toxicol.* 88, 127–136. doi: 10.1007/s00204-013-1098-1
- Suarez-Jimenez, G. M., Burgos-Hernandez, A., and Ezquerro-Brauer, J. M. (2012). Bioactive peptides and decapeptides with anticancer potential: Sources from marine animals. *Mar. Drugs* 10, 963–986. doi: 10.3390/md10050963
- Tan, A. S., and Berridge, M. V. (2000). Superoxide produced by activated neutrophils efficiently reduces the tetrazolium salt, WST-1 to produce a soluble formazan: a simple colorimetric assay for measuring respiratory burst activation and for screening anti-inflammatory agents. *J. Immunol. Methods* 238, 59–68. doi: 10.1016/s0022-1759(00)00156-3
- Thomas, D. N., Fogg, G. E., Convey, P., Fritsen, C. H., Gili, J. M., Gradinger, R., et al. (2008). *The biology of Polar Regions*. Oxford: Oxford University Press. doi: 10.1093/acprof:oso/9780199298112.001.0001
- Thomas, S. A., Sanchez, A., Kee, Y., Wilson, N. G., and Baker, B. J. (2019). Bathypylones: Terpenoids from an Antarctic sea pen, *Anthoptilum grandiflorum* (Verrill, 1879). *Mar. Drugs* 17:513. doi: 10.3390/md17090513
- Thomas, S. A., Von Salm, J. L., Clark, S., Ferlita, S., Nemani, P., Azhari, A., et al. (2018). Keikipikalides, furanocembrane diterpenes from the Antarctic deep sea octocoral *Plumarella delicatissima*. *J. Nat. Prod.* 81, 117–123. doi: 10.1021/acs.jnatprod.7b00732
- Trimurtulu, G., Faulkner, D., Perry, N. B., Ettouati, L., Litaudon, M., Blunt, J., et al. (1994). Alkaloids from the antarctic sponge *Kirkpatrickia varialosa*. Part 2: Variolin A and N(3′)-methyl tetrahydrovariolin B. *Tetrahedron* 50, 3993–4000. doi: 10.1016/s0040-4020(01)89674-5
- Tripathi, A., Schofield, M. M., Chlipala, G. E., Schultz, P. J., Yim, I., Newmister, S. A., et al. (2014). Baulamycins A and B, broad-spectrum antibiotics identified as inhibitors of siderophore biosynthesis in *Staphylococcus aureus* and *Bacillus anthracis*. *J. Am. Chem. Soc.* 136, 1579–1586. doi: 10.1021/ja4115924
- Turk, T., Ambrozic Avguštin, J., Batista, U., Strugar, G., Kosmina, R., Civović, S., et al. (2013). Biological activities of ethanolic extracts from deep-sea Antarctic marine sponges. *Mar. Drugs* 11, 1126–1139. doi: 10.3390/md11041126
- Upadhyay, P., Shrivastava, R., and Agrawal, P. K. (2016). Bioprospecting and biotechnological applications of fungal laccase. *3 Biotech.* 6:15. doi: 10.1007/s13205-015-0316-3
- Urban, S., Wilton, H., Lu, C. C., and Capon, R. J. (1995). A New sesquiterpene alcohol from an Antarctic sponge. *Nat. Prod. Lett.* 6, 187–192. doi: 10.1080/10575639508043157

- von Salm, J. L., Wilson, N. G., Vesely, B. A., Kyle, D. E., Cuce, J., and Baker, B. J. (2014). Shagenes A and B, new tricyclic sesquiterpenes produced by an undescribed Antarctic octocoral. *Organic Lett.* 16, 2630–2633. doi: 10.1021/o1500792x
- von Salm, J. L., Witowski, C. G., Fleeman, R., McClintock, J. B., Amsler, C., Shaw, L., et al. (2016). Darwinolide, a new diterpene scaffold that inhibits methicillin-resistant *Staphylococcus aureus* biofilm from the Antarctic sponge *Dendrilla membranosa*. *Org. Lett.* 18, 2596–2599. doi: 10.1021/acs.orglett.6b00979
- Wang, W., and Namikoshi, M. (2007). Bioactive nitrogenous metabolites from ascidians. *Heterocycles* 74, 53–88. doi: 10.3987/rev-07-sr(w)2
- Waters, A. L., Hill, R. T., Place, A. R., and Hamann, M. T. (2010). The expanding role of marine microbes in pharmaceutical development. *Curr. Opin. Biotechnol.* 21, 780–786. doi: 10.1016/j.copbio.2010.09.013
- Yang, A., Baker, B. J., Grimwade, J., Leonard, A., and McClintock, J. B. (1995). Discorhabdin alkaloids from the Antarctic sponge *Latrunculia apicalis*. *J. Nat. Prod.* 58, 1596–1599. doi: 10.1021/np50124a020
- Zubía, E., Ortega, M. J., and Salvá, J. (2005). Natural products chemistry in marine ascidians of the genus *Aplidium*. *Mini Rev. Organ. Chem.* 2, 389–399. doi: 10.2174/157019305774322707

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Avila and Angulo-Preckler. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.