Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
A look around the West Indies: The spices of life are secondary metabolites

Adrian Demeritte, William M. Wuest*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, USA

ARTICLE INFO

Keywords:
Natural products
Antibiotics
Drug discovery
Caribbean
Anticancer

ABSTRACT

Natural products possess a wide range of bioactivities with potential for therapeutic usage. While the distribution of these molecules can vary greatly there is some correlation that exists between the biodiversity of an environment and the uniqueness and concentration of natural products found in that region or area. The Caribbean and pan-Caribbean area is home to thousands of species of endemic fauna and flora providing huge potential for natural product discovery and by way, potential leads for drug development. This can especially be said for marine natural products as many of are rapidly diluted through diffusion once released and therefore are highly potent to achieve long reaching effects. This review seeks to highlight a small selection of marine natural products from the Caribbean region which possess antiproliferative, anti-inflammatory and antipathogenic properties while highlighting any synthetic efforts towards bioactive analogs.

1. Introduction

Natural products (NPs) have been reported to exhibit a wide range of medicinally relevant bioactivities and therefore play a dominant role in the discovery and development processes towards lead compounds for human medicine. These pharmaceutically relevant small molecules bridge an important gap in antipathogenic, anticancer, anti-inflammatory and immunomodulatory efforts that nonchemical therapeutic practices would simply not be able to accomplish alone. Also known as secondary metabolites due their mechanism of synthesis or specialized metabolites due to their potential use in primary life sustaining roles, these compounds are synthesized mainly by bacteria, fungi and plants and can be unique to an organism or a specific taxonomic group. There are various reviews on NPs from these organisms in the literature, in fact, there are over 326,000 known NPs to date according to the SuperNatural 2 general database. Even then, overlap in structural similarity and rediscovery of known NPs may hint that existing discovery models have been largely exhausted, prompting other areas for drug discovery to arise. For instance, high-throughput screening (HTS) has gained much popularity over the past few decades. However, while the advent of HTS has brought about the potential for faster identification of biologically relevant molecules and even yielded some new drugs, there is an overall lack of pharmaceutical properties from these synthetic compounds due to a lack of chemical diversity. In many cases NPs owe their success in drug discovery to their structural diversity and therefore are still needed to increase the potential for the identification of biologically relevant molecules.

There is some correlation that exists between the biodiversity of an environment and the uniqueness of natural products found in that region or area. That said, further exploration of biologically rich areas with large numbers of endemic species, better known as “biodiversity hot-spots”, hold a better chance of changing the narrative that the existing model of drug discovery through NPs may be exhausted.

Though most directly obtained through harvesting from their natural sources, this process can at times be tedious, time consuming and expensive. Moreover, supply can be greatly outweighed by demand, or can be inconsistent due to varied biosynthesis caused by conditions differing from the ecological environment of the producing organism. Total synthesis serves to fill in that gap. Throughout the years, a wide variety of NPs with medicinally relevant bioactivities have been synthesized in academic research labs and pharmaceutical companies around the world. In many cases, total synthesis was combined with a greater exploration of chemical space through the production of corresponding analogs of target NPs which, themselves, could increase the number of bioactive compounds for therapeutic usage but also ultimately expand understanding of the mechanism of action for their respective NPs.

This review seeks to provide information on the combination of the aforementioned by focusing on a small selection of synthesized natural products with medicinally relevant biological activity originally isolated from the Caribbean and pan Caribbean region along with respective bioactive analog campaigns of select compounds. This region was...
chosen because many of the countries in this area rely heavily on tourism and travel as a major contributor to their gross domestic product (GDP), with many island nations dominating the top twenty spots worldwide for the aforementioned. Recent unfortunate circumstances, namely destruction of natural resources caused by hurricane Dorian, the strongest Atlantic hurricane on record to directly impact landmass, and travel restrictions due to COVID-19 related precautions, have greatly impacted this major industry and, subsequently, variably affected financial stability in this area. Thus, this review serves to highlight the potential for lead drug discovery in this region towards investment in industries orthogonal to tourism, to dilute its share on respective GDPs.

2. Isolation, to synthesis and beyond

While efforts in natural product isolation help to generate new lead molecules for drug discovery and development, analog production offers an alternative, as well as an extension, to the classical drug discovery pipeline by providing a basis for further chemical and biological studies on bioactive secondary metabolites. There can be many takeaways from analog development. For instance, the creation of a dimensionally similar minimized scaffold may maintain or even improve biological activity while overcoming limitations of synthetic accessibility, viability in approach, or analysis capabilities. Alternatively, one may discover or introduce new and exciting biological properties through varied structural modifications. Herein, we present two such examples from our own laboratory of the diversification and target identification of antimicrobial natural products enabled by total synthesis as an inspiration for future work on lesser explored molecules below.

2.1. Carolacton

One specific example of the prior comes from our lab in the total synthesis of the natural product Carolacton (1). Carolacton is a secondary metabolite isolated from the myxobacterium Sorangium cellulosum, with the ability to affect Streptococcus mutans cells transitioning to a biofilm at nanomolar concentrations. After completing the total synthesis of this molecule in 2014, elucidation of the cause of biofilm-specific activity in Streptococcus mutans was limited through molecular genetic techniques as the bioactivity of carolacton was monitored by LIVE/DEAD staining and CFU/mL counts which have to low throughput analysis of carolacton-treated cells. We sought to promote further analysis of the activity of carolacton by creating a simplified analog of 1 with quantifiable biofilm inhibitory activity. In 2017 we were able to demonstrate that a simplified analog, named C3 (2), inhibited 50% of biofilm formation with an IC50 of 63 μM. It is significant to note that this initial observation of biofilm inhibition was the first instance of a quantifiable IC50 value for carolacton or its analogs. This finding also showed the importance of chain length and, in a follow up paper in 2019, we were able to simplify the carolacton side chain while oversaturating the carolacton macrocycle to produce a drastically simplified analog, (+)-2 (3). This analog not only maintained activity with an IC50 of 44 μM but also allowed for the first observation of a minimum inhibitory concentration (MIC) value for any compound structurally related to carolacton at 250 μM. This analog effectuated the preliminary screening of S. mutans mutants, aiding in the identification of a carbon catabolite control protein (Ccpa) as the putative target of carolacton. This analog further supported by uptake experiments. Moreover, the simplified analog (-)-11 provided improved potency with an MIC of 8 μM in both IRM and IDM when compared to values of 4 (125 μM and 125 μM) and 5 (500 μM and 250 μM). This ability to discern previously unknown mechanisms of action represents yet another important takeaway from analog development. These aspects, when applied to already potent bioactive small molecules, can lead to the discovery of previously unknown information regarding mechanism of action (MOA) or even the discovery of more easily accessible natural product derivatives which maintain necessary bioactivity. Not included in this short section, but of equal importance, are methods and strategies to improve solubility, stability, absorption, and dissolution of bioactive secondary metabolites which are pertinent when it comes to the bioavailability of these NPs in

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Progression towards simplified Carolacton analog (+)-2.

2.2. Baulamycins

Another example from our group comes from our synthesis of baulamycins A (4) and B (5). The baulamycins were isolated from an extract derived from Streptomyces tempisquensis (Playa Grande, Costa Rica) and were shown to inhibit in vitro bacterial iron acquisition. The initial isolation paper of these compounds showed discrepancies in their broad spectrum activity, particularly against Staphylococcus aureus in both iron rich and iron depleted media (IRM and IDM respectively). This inconsistency, along with ambiguity in absolute and relative stereochemistry of 4 and 5, prompted our efforts to leverage diverted total synthesis (DTS) towards a better understanding of the biological mode of action of these compounds. Through the total synthesis of the baulamycins along with eight rationally designed analogs (8–16) (Figure 2), we were able to identify a common chemotype as well as attribute broad spectrum activity in iron-rich media to nonselective membrane lysis which was further supported by uptake experiments. Moreover, the simplified analog (-)-11 provided improved potency with an MIC of 8 μM in both IRM and IDM when compared to values of 4 (125 μM and 125 μM) and 5 (500 μM and 250 μM). This ability to discern previously unknown mechanisms of action represents yet another important takeaway from analog development. These aspects, when applied to already potent bioactive small molecules, can lead to the discovery of previously unknown information regarding mechanism of action (MOA) or even the discovery of more easily accessible natural product derivatives which maintain necessary bioactivity. Not included in this short section, but of equal importance, are methods and strategies to improve solubility, stability, absorption, and dissolution of bioactive secondary metabolites which are pertinent when it comes to the bioavailability of these NPs in...
human medicine. Indeed, when the above-mentioned is combined with natural product isolation from biodiverse regions, a powerful method for lead drug discovery emerges. Thus, this review seeks to not only highlight secondary metabolites from the Caribbean region with interesting bioactivities but also to prompt the future usage of methods like DTS, diversity-oriented synthesis (DOS)/function oriented synthesis (FOS), and complexity-to-diversity strategies (CTD) towards the development of bioactive NP analogs and thereby stimulate discovery.

3. The Caribbean, the cradle of marine natural product research

The Caribbean is an archipelago of habitat rich tropical and semi-tropical islands, comprised of nearly 30 nations and territories stretched across 4 million square kilometers of ocean. Due to this region’s geography and climate it is one of the world’s greatest centers of endemic biodiversity, and hence one of the planet’s 35 biodiversity hotspots. In fact, there are over 11,000 plant species on land and a further 12,046 species have been reported to occur in the Caribbean sea, many of which are endemic to the region. As said before, bioactive secondary metabolites can have a variety of effects towards the survival of their parent organisms by acting as necessitating factors to attract, deter, or kill other organisms. In turn, one can assume that a greater variety of secondary metabolites with novel structures are produced in environments with a larger biodiversity, as to provide producers with a selective advantage against competing organisms, induce antimicrobial effects against pathogenic microbes, or even to act as an adaptation to nonbiological impacts which bring about the aforementioned biodiversity such as light or elevated temperature. While there is an abundance of natural products derived from the various common species of plants in this region, many of which are endearingly referred to as “bush medicine” by locals and natives (eg. love vine, cerasee, and arrowroot), this review will focus on marine derived natural products (MNPs). This is because many MNPs are released into the water, where they are rapidly diluted and hence need to be highly potent to have any effect; though it should be noted that there are other methods for these compounds to take effect as well which may not require high potency (contact aversion, predation etc.). In turn, it is widely accepted that a large number of natural products and novel chemical entities exist in the ocean, particularly in biodiverse areas, with biological activities that may be useful towards lead drug discovery for the treatment of various human diseases.

Many MNPs are derived from various species of gorgonians, tunicates, algae, mollusks, and sponges, and the Caribbean is home to a wide variety of the aforementioned. In fact, in the last 60 years there have been over 1296 collections of specimens from these organisms from around the world in search of new and novel MNPs. Remarkably, a staggering 55% of these collections have been from the phylum porifera. This preference may be because a great diversity of symbiotic organisms often thrive inside or on the body of a sponge. This unique tolerance towards symbiotic organisms combined with their simple body organization, allows for a plethora of evolutionary solutions along with production of various bioactive secondary metabolites. Unfortunately, prevalence of the necessary species for novel natural product biosynthesis does not coincide with expanded efforts to retrieve them. In recent years, collection for specimens for NP isolation towards development of pharmacological products has slowed. In fact, from 2010 to 2014 there were a total of seven collections worldwide yielding pharmacological products from the ocean with zero collections occurring from 2012 to 2014. Though this may hint that marine natural product isolation may be losing interest from federal funding industries and pharmaceutical companies, recent reviews on the matter show otherwise. For instance, there has been a steady increase in the number of new compounds and papers regarding marine natural products over the years. Moreover, discovery efforts from isolation groups in some areas of the region remain strong (e.g. Puerto Rico), however, efforts towards this method of NP discovery across the region can improve. After all, NMR research has its origin in the Caribbean with the discovery of two nucleosides, spingothymidine and spingouridine isolated from the Caribbean sponge Cryptotethya crypta in the 1950’s, which served as lead structures for the development of the synthetic antivirals cytarabine and vidarabine, however, this story has been extensively covered in other reviews and will not be belabored here.

Though several NPs have been isolated in specific areas in this region, many of the species that the following natural products were collected from can be found throughout the Caribbean. It must be noted that because the vast majority of specimen collections were conducted by academic researchers with limited resources as opposed to large pharmaceutical corporations, a majority of the following have only been tested in bioassays for cancer cytotoxicity or with narrow bioassays overall for targeted effectiveness. That said, the potential for natural products isolated in this area to have use in treating cardiovascular diseases, central nervous system disorders, diabetes, immunological disorders, and infections (e.g. bacterial, viral, parasitic etc.) remains largely unexplored. What follows is a small sampling of natural products isolated from this region which have some pharmaceutical relevance and undergone analog development and yielded some success.
4. Natural products which have benefited from analog development

Natural products greatly contribute to the discovery and development of cancer chemotherapy drugs as over 70% of compounds in clinical use have some origin in a bioactive secondary metabolite.\(^2\) In fact, from the 1940’s to the end of 2014, of the 175 small molecules approved, 49% were either directly derived from natural products or natural products themselves.\(^2\) It should come as no surprise then, that several compounds with cytotoxic activity against various cancer cell lines have been isolated from the Caribbean region. Most notably, Trabectinid (14) (Figure 3) was isolated from the Caribbean ascidian *Esteinascidia turbinata* by Wright et al.\(^30\) and Rinehart et al.\(^31\). Acting as a novel DNA alkylator with broad spectrum antineoplastic activity, Trabectinid (ET-743, Ecteinascidin 743, Yondelis®) was the first anticancer marine natural product approved for clinical use in cancer chemotherapy and is utilized in the treatment of advanced soft tissue sarcoma as well as relapsed ovarian cancer when used in combination with pegylated liposomal doxorubicin.\(^32\) Though first synthesized by the Corey group in 1996,\(^33\) (14) is now commercially made through a semi-synthetic process starting from cyanosafacin B, a readily available antibiotic from the bacterium *Pseudomonas fluorescens*, to coincide with demand.\(^34\) In terms of analogs, lurbinectedin (PM1183, ZEPZELCA™) (15) was recently FDA approved for the treatment of metastatic small cell lung cancer\(^35\) while zalypsis (16) is in phase II studies for the treatment of endometrial and cervical cancer.\(^36\)

\(\text{(+)-Curcuphenol (17)}\) was originally isolated from the marine sponge *Didiscus flavus* (Long Island, Bahamas)\(^37\) but was later isolated from several marine sponges *Didiscus oxeata*, *Epipolasis* sp., and *Myrmekioderma styx* throughout the Caribbean.\(^37\)–\(^39\) The compound appears to have a wide range of activity. While also showing some cancer targeting activity in an independent manner of a p53 mechanism, both 17

![Figure 3. Examples of MNPs isolated from the Caribbean and pan-Caribbean region with pharmaceutical relevance along with notable analogs.](image-url)
and 18 have reported activity against MRSA, with 17 also showing activity against Candida albicans and Cryptococcus neoformans.17 Even possessed antimalarial activity against Palsmodium falciparium D6 and W2 clones (MIC = 3.6 μg/mL and 1.8 μg/mL respectively). These enantiomers have been synthesized several times17–20 and due to their wide range of activity have also undergone analog studies. Most notably, Gul et al. produced a pyridine analog 19 (IC_{50} = 0.6 μM) which was shows more potent in vitro against Leishmania donovani than pentamidine, the drug of choice for the treatment of Leishmaniasis, a mosquito borne protozoan disease that occurs in over 88 countries.21 Successful studies like this show the potential for the identification of the varied bioactivities of NPs though analog development. Salinosporamide A (NPI-0052, Marizomib) (20) is a unique beta lactone which was isolated from a culture of Salinospora tropica (Unspecified, Bahamas) and exhibited potent activity against the human colon adenocarcinoma tumor cell line (HCT-116) (IC_{50} = ~2 ng/mL) as a 20S proteasome inhibitor. This activity prompted rapid clinical development eventually leading to this compounds evaluation in Phase I human clinical studies as well as a wide range of non-clinical studies (myeloma, colon, pancreatic, non-Hodgkin’s Lymphoma etc).22 20 is now in phase II clinical trials and through optimization studies by Nguyen et al. ultimately lead to the development of a synthetic derivative (−)-homosalinosporamide A (21) which maintained both chymotrypsin-like and caspase-like activity to that of 20.23

(−)-Discodermolide (22) was isolated from the deep water Caribbean sea sponge Discoderma dissoluta (Lucay, Grand Bahama Island, Bahamas) and was found to inhibit in vitro proliferation of cultures murine P388 leukemia cells (IC_{50} = 0.5 μg/mL).24 This compound was found to attack cancer cells in a similar manner to the successful cancer drug Taxol® by stabilizing microtubules involved in many aspects of cellular biology, and thus, showed promise as a potent anticancer drug. This MOA prompted several total syntheses of this molecule and eventually analog studies by several groups25–28, even including a commercial scale total synthesis by Novartis.29 Though initial clinical trials were not successful, this is still a promising lead structure. An example of successful analog development comes from, Smith et al. who produced several analogs of (22) with one analog 51 (23) sharing similar in vitro IC_{50} values against A549 (1.8 nM) and SKOV3 ovarian carcinoma cells (6.1 nM) to that of Taxol® (1.4 nM and 3.3 nM respectively) improving on the potency of the parent molecule (3.8 nM and 31.3 nM respectively) and providing a potent, synthetically accessible potential alternative to Taxol®.26

In 2009 Ammosamides A and B (24 and 25) were isolated from a culture of Streptomyces strain CNR-698 collected at a depth of 1618 m (Little San Salvador, Bahamas). These compounds were originally found to possess activity against HCT-116 cells by targeting the cellular cytokeratin protein myosin, each with IC_{50} = 320 nM.29,30 Throughout the next few years 25 would be synthesized several times by notable groups31–34, however, in 2012 Reddy et al. synthesized several analogs and tested for their quinone reductase 2 (QR2) activity. Though many of the analogs showed decreased activity the most potent of the bunch, a derivative methylated at the 8-amino group (26), resulted in an increase in QR2 inhibitory activity from an IC_{50} of 61 nM to an IC_{50} of 4.1 nM.35 Though there are other examples of ammosamide analogs36 this specific case efficiently demonstrates that small changes in structure can effectively improve potency of an already potent natural product.

(+)-Neopelotide (27) is a macrolide isolated from the deep-water sponge of the Neopolitidae family, (442 m off Northwest Coast, Jamaica). 27 was found to be a potent inhibitor of the in vitro proliferation of A549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and the P388 murine leukemia cell lines, with IC_{50} values of 1.2, 5.1, and 0.56 nM, respectively by targeting mitochondrial complex III.37,38 There have been several syntheses of 27 since its isolation and numerous analogs have been produced for SAR studies.39–42 Most notably, Fuwa and coworkers developed (−)-8,9-dehydroneopelotide (28), an analog which was more potent against A549 (0.5 nM) cells, and maintained activity against MCF-7 (33 nM) and P388 (0.72 nM) compared to the parent macrolide (IC_{50} values of 1.6, 19 and 0.50 nM respectively).43 29 is a further structurally simplified analog by Fuwa et al. which showed general retention of activity when tested against A549 cells (IC_{50} = 43.9 nM) while noticeably reducing step count for a potent cancer cell line inhibitor while identifying tolerable areas for structural modification in future SAR studies.

Lastly, Carmaphycins A and B (30 and 31) were isolated from the cyanobacterium Symplocia sp. (Unspecified, Curaçao) and exhibited potent proteasome inhibition (IC_{50} = 2.5 and 2.6 nM, respectively) and potent cytotoxicity against lung (H-460: EC_{50} = 9.0 and 6.0 nM, respectively) and colon (HTC-116: EC_{50} = 19 nM and 43 nM, respectively) cancers.44 Though excellent potential anticancer agents, these compounds are included, instead, for the analog development of potent antimalarial compounds based off of the structure of 31. Lamonte et al. sought to produce an antimalarial proteasome inhibitor with low host cytotoxicity and improved antimalarial potency. This was done by leveraging the known cytotoxic effects and potency of 31 on cancer cell

Figure 4. MNPs targeting cancer isolated from the Caribbean and pan-Caribbean region with activity against various cancer cells lines.
lines by inferring antimalarial properties derived from structural similarity to known epoxymycin containing compounds epoxymixin and carfilzomib, known for their potent antiprotozoal and antimalarial activities against *P. falciparum*. The result was derivative of 31, named analog 18 (32) (IC\(_{50} = 3.27\) nM), with a 100-fold wider therapeutic window than 31.\(^{73}\) Examples like these demonstrate the power that analog synthesis can have in the discovery of compounds for medicinal use through modification of bioactive secondary metabolites.

This section contained just a brief overlook of some natural products isolated from the Caribbean and pan-Caribbean region which have had some success in lead drug discovery due to their potent activity, novel mechanisms of action or unique structures. The following sections will highlight other natural products isolated from this region which possess cancer targeting, antipathogenic, or other medicinal capabilities and may show potential for future drug development. These compounds will also illustrate the structural variation of natural products which can be found in this region, which further lends to drug discovery.

5. Natural products targeting cancer

There is great therapeutic potential for many structurally diverse natural products found in this region with modest activity. In fact, several natural products have been isolated with specific activity against colon cancer cell lines (Figure 4). For instance, Lucentaycins A-D (33-36) are structurally unique tripeptides isolated from the marine derived actinomyocyte *Nocardiopsis lucentius* (saline pond, Little San Salvador, Bahamas) with cytotoxicity towards HCT-116 cell line.\(^{74}\) Most of the *in vitro* activity from this extract was found to be derived from 33 (MIC = 0.2 μM), with 34 (MIC = 11 μM) also having modest activity. This potency, along with novelty of its 3-methyl-4-ethylideneproline unit, prompted several synthetic efforts towards the total synthesis of 33\(^{75}\) eventually leading to revision of the geometry of the proline olefin to the E-isomer from the putative structure.\(^{76,77}\) Other than the isolation of another metabolite in this family, Lucentaycin E, there have been little analog studies on this family.\(^{78}\)

Peridinin (37) is a carotenoid recently isolated and characterized from *Pseudopergorgia acerosa* (North Coast, Tobago), though it was originally isolated over 100 years earlier from various dinoflagellates. Although the main compound responsible for photosynthesis in the sea, 37 was also found to have antitumor and anticanerogenicic properties later identified to be through up-regulation of DR5 expression.\(^{79,80}\) Total syntheses of this compound have been carried out but the Katsumara and de Lera groups.\(^{81,82}\)

Another group of natural products which has activity against HT-116 cells are the cyclic peptides Microsporins A and B (38 and 39). These metabolites were isolated from culture extracts of the marine-derived fungus *Microsporum cf. gypseum* obtained from the bryozoan *Bugula* sp. (U.S. Virgin Islands) and possessed potent activity (A: IC\(_{50} = 0.6\) μg/mL) and modest (B: IC\(_{50} = 8.5\) μg/mL) *in vitro* activity against HCT-116 by acting as histone deacetylase (HDAC) inhibitors.\(^{83}\) In addition, 38 exhibited greater *in vitro* inhibition against both a mixture of HDACs from HeLa cell nuclear extract and HDACB (which is implicated as a therapeutic target in various diseases, including cancer, X-linked intellectual disability, and parasitic infections) than the known anticaner HDAC agent vorinostat. To date, there have been few syntheses and little analog development for these molecules apart from a solid phase synthesis of 38 by Silverman et al.\(^{83,84}\)

Kalkitoxin (40) was isolated from the cyanobacterium *Lyngbya majusula* (now *Moorea producens*) (Playa Kalki, Curacao) and was later found to potently and selectively inhibit hypoxia-induced activation of hypoxia-inducible factor-1 (HIF-1) in T47D breast tumor cells (IC\(_{50} = 5.6\) nM) by suppression of mitochondrial oxygen consumption at electron transport chain complex I.\(^{85,86}\) Though 40 has been synthesized several times,\(^{85,87}\) analogs were proposed by Umezawa et al. in 2012.\(^{88}\) Though only isomers of 40, these compounds managed to maintain cytotoxic activity in biological assays (brine shrimp) and analogs of this compound have yet to be tested against human cancer cell lines.

Lastly, Epoxyphomalin A and B (41 and 42) were isolated from the facultative marine fungus *Phoma* sp. obtained from the marine sponge *Ectyplasia perax* (Caribbean Sea, Dominica). 41 and 42 are structurally related to a small family of sesquiterpene cyclohexenones, however an epoxyphenylo moiety linked to a decalin ring system is unique chemical entity only shared by macrophorins.\(^{89,90}\) 41 showed superior cytotoxicity at nanomolar concentrations towards 12 of a panel of 36 human tumor cell lines with a mean IC\(_{50} \)value of 114 ng/mL with notable activity in breast (MAXF 401NL; IC\(_{50} = 10\) ng/mL), bladder (BXF 1218 L; IC\(_{50} = 17\) ng/mL) and ovary (OVXF OVCAR; IC\(_{50} = 17\) ng/mL) cancer cell lines.\(^{90}\) These compounds were found to exert their potent cytotoxic effects through inhibition of the 20S proteasome.\(^{91}\) Though epoxyphenylo and its congeners are well studies, there have been no total syntheses of these molecules to date.

6. Antipathogenic natural products

There are numerous global health challenges involving pathogenic diseases which are caused by various species of viruses, bacteria, fungi, protozoa, and worms. Natural products have played a crucial role in the treatment of such diseases like HIV/AIDS, tuberculosis, pneumonia, and malaria. Though not well studied or as thoroughly tested for their cancer targeting properties, several natural products have been isolated from the Caribbean and pan-Caribbean region which possess antipathogenic properties (Figure 5).

An example of potential antibiotics from this region comes from Caminodies A-D (43-46). These are novel antimicrobial glycolipids isolated from the marine sponge *Caminus sphaeroconus* (Toucan Caves, Dominica) found to have activity against *E. coli* by thwarting pathogenicity through inhibiting their type III secretory system, without killing the bacteria (IC\(_{50} = 20\) μM).\(^{92}\) 43 was also found to have traditional antimicrobial activity against gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC = 12 μg/mL) and vancomycin-resistant *Enterococcus* (VRE) (MIC = 12 μg/mL) while 44 and 46 were later found to be the more potent compounds of the family with stronger activity against MRSA (B: MIC = 6.3 μg/mL; D: MIC = 6.3 μg/mL) and VRE (B: MIC = 6.3 μg/mL; D: MIC = 3.1 μg/mL) respectively.\(^{93}\) 43 has been synthesized by Sun et al.\(^{94}\) and 44 was synthesized by Zhang et al.\(^{95}\), however there are limited studies in the synthesis and testing of analogs based off of this family.

Forazoline A (47) was isolated from an *Actinomadura* sp. culture from the ascidian *Ceteacinsidida turbinata* (Unspecified, Florida Keys) and was found to activity against the fungal pathogen *Candida albicans* via a putative novel mechanism.\(^{96}\) 47 demonstrated *in vitro* activity (MIC = 16 μg/mL) through either directly affecting phospholipids or through interaction with a protein target complimenting the activity of knockout protein complex Lep3p. Though this compound possesses the ability to be an excellent antifungal drug lead, the total synthesis of this molecule has yet to be completed, however this may be due to recent revisions to the putative structure.\(^{77}\)

Another natural product with activity against *C. albicans* along with several other disease fungi is hecitholin (48). This unique lipopeptide was originally isolated from a cultured strain of the cyanobacterium *M. producens* (Hector Bay, Jamaica) and was found to act on actin component of the fungal cytoskeleton through hyperpolymerization of the aforementioned (IC\(_{50} = 20\) nM). This potent activity prompted the agrochemical company Dow to complete the total synthesis of this compound in 2002.\(^{96}\)

Carmabin A (49) was also isolated from the marine cyanobacterium *M. producens* (coral Coast, Panama) in 1998 and exhibited some antimarial activity towards the W2 chloroquine-resistant malaria strain (IC\(_{50} = 4.3\) μM) and cytotoxic activity towards mammalian vero cells (IC\(_{50} = 9.8\) μM).\(^{99,100}\) Years later, this compound was reisolated along with three new linear tetrapeptides Dragomamin and Dragonamides A and B (50-52). The prior two metabolites also exhibited good
antimalarial activities ($IC_{50} = 6.0$ and $7.7 \mu M$, respectively), however 52 lacked activity suggesting that an aromatic amino acid at the carboxy terminus is necessary for antimalarial activity in this compound series.\textsuperscript{100} Additionally, 50 was found to exhibit a better differential toxicity between parasite and mammalian cells ($IC_{50} = 182.3 \mu M$) hypothesized to be caused by the removal of three carbons in the aliphatic chain. Total synthesis of 49 and 50 was carried out by Ye et al. in 2018\textsuperscript{101} and synthesis of 51 was completed by Chen et al. in 2005.\textsuperscript{102}

### 7. Other compounds with notable activity/medicinal use

As said before, NPs isolated from this region have been known to have a variety of uses and bioactivities. Though not quite falling under a broad genre of medicine a few compounds isolated from this region which exhibit notable activity (Figure 6). The Jamaicamides (53–55) were isolated from a collection of *M. producens* (Hector’s Bay, Jamaica) and were found to have sodium channel blocking activity ($LC_{50} = 5 \mu M$).\textsuperscript{103} Though not extremely potent, these compounds still hold some potential in analog development, as sodium channel blockers are an important class of drugs, and are the molecular targets for drugs used in the prevention of acute and chronic pain, cardiac arrhythmias, epilepsy, and bipolar disorder. To date, only a partial synthesis of 55 has been completed.\textsuperscript{104}

Continuing with sodium channels, Antillatoxin A and B (56 and 57) are structurally unique highly methylated lipopeptides that were also isolated from extracts acquired from *M. producens* (Collado Reef, Puerto Rico) and were found to have differential toxicity to mammalian and parasite cells. These compounds were synthesized by Ye et al. in 2018\textsuperscript{101} and by Chen et al. in 2005.\textsuperscript{102}
Rico; and Bush Key, Dry Tortugas). The latter of the two exhibited significant sodium channel activating properties (EC50 = 1.7 μM).\textsuperscript{105} Though not a medicinal use, the potent ichthyotoxic activity of 56 along with its unique structure prompted efforts towards its total synthesis by Yokokawa et al. in 1998 and again by Lee et al. in 2006.\textsuperscript{106-108}

In a separate vein of activity, the Kempopeptides (58–60) were also isolated from Moorea producents (Summerland Keys, Florida) and were found to have an array of serine protease inhibitory activities.\textsuperscript{109,110} Molassamide (61) was later isolated from a sample of Dichothrix utahensis (Key Largo, Florida; and Brewer’s Bay, U.S. Virgin Islands) and was found to be ten times more potent than 58. Despite having excellent activity against elastase and chymotrypsin (IC50 = 0.032–0.52 μM and 0.23–2.6 μM, respectively) there are no published total syntheses of any of the previously mentioned cyclodesipeptides.

The Pseudopterosins (62 and 63) are a class (over 17 members) of marine diterpene glycosides isolated from the gorgonian soft coral Pseudopterogorgia elisabethae (Unspecified, Bahamas) known to possess superior anti-inflammatory and analgesic properties compared to the commercial drug indomethacin.\textsuperscript{111} Not only have the pseudopterosins (A-D) been licensed to OsteoArthritis Sciences Inc. for medicinal use as anti-inflammatory drugs, but 64, a synthetic derivative of 62, completed Phase I and II clinical trials as a wound healing agent, however faced difficulty in a lack of aqueous solubility and effectiveness.\textsuperscript{112} Nevertheless, these compounds have found their way to the marketplace as partially purified extracts from P. elisabethae, which primarily contain 63, are used as an additive to prevent irritation in the Estee Lauder cosmetic skin care product Resilience.\textsuperscript{113} Though 64 was first synthesized by Broka et al. in 1988, recently Ramella et al. published a concise total synthesis of the pseudopterosins through an anionic oxy and transannular Michael addition cascade which seems powerful for analog development of this class of natural products.\textsuperscript{114}

8. Summary and conclusion

Natural products play a critical role in the lead drug discovery and development process. Mohammad R. Seyedsayamdost, a giant in the field of natural product discovery from Princeton University, summed up this notion best in a statement from a recent seminar: “for every discovery of a new natural product comes a new opportunity for therapeutic usage”. Here we have included a small selection of natural products from across the Caribbean region with varied bioactivities to showcase the potential application of small molecules collected from this biosphere.

While highlighting synthetic efforts and analog development for some of these compounds, we have also illuminated on several gaps which currently hinder this process. First, there is a lack of new families of isolated MNPs over the past few years, in addition to an overall lack of collections from marine species in search of secondary metabolites with novel structures. Though there has been in increase in isolation recently, greater exploration into areas of these biodiverse regions is needed.

Toward this end, there is a vital need to increase funding to this area of research, which recently has been dwindling. Additionally, countries in this region should take note from territories like Puerto Rico and strive to further establish and promote research facilities geared towards natural product isolation, and increase the study of this practice in local universities; however, separate issues in funding may exist here as well. Moreover, a close study of the literature reveals that many of the current lead or promising NPs from this region are isolated from the same species (eg. Moorea producents). A greater distribution in species collection may lead to identification of more diverse MNPs, and hence further drug discovery. While recent and future isolation efforts may somewhat be hindered by the Nagoya protocol,\textsuperscript{115} which was established in 2014 and requires every party (generally a country) to establish their own national legislation governing access to genetic resources, parties of this region should strive to create amicable laws amidst the search for alternative resources to alleviate the hold that travel and tourism have on the regional GDP.

Second, many of the natural products from this review are from marine environments. Though there is some research into NPs derived from the various endemic plants from this region there remains a noticeable gap in natural products isolated from this region’s rhizosphere. Biodiversity in macroorganisms coincides with biodiversity in microorganisms and this can be labelled true for both land and sea. Further research into NPs from the rhizosphere of this fertile biosphere are also needed and will most likely advance the discovery of novel bioactive compounds from this region.\textsuperscript{116}

Third, many of the NPs isolated from the Caribbean are only tested for their cytotoxicity against paneled cancer cell lines. This issue hints to a more widespread problem regarding a lack of more extensive bioassays. A broader array of testing would, almost certainly, increase the applications of these natural products across the region.

Lastly, an increase in the development of analogs of these bioactive compounds has the potential to not only overcome limitations of synthetic accessibility or viability in approach through the creation of dimensionally similar minimized scaffolds, with maintained or even improved biological activity, but also reveal or introduce new and exciting biological properties through varied structural modifications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was supported by the National Science Foundation (CHE2003692) and the National Institute of General Medical Sciences (GM119426).

References

1 Banerjee P, Erehman J, Gohlke BO, Wilhelms T, Preisner N, Dunkel M. Super Natural II-a database of natural products. Nucleic Acids Res. 2015;43(D1):D935-1939. https://doi.org/10.1093/nar/gku880.

2 Walsh CT. A chemocentric view of the natural product inventory. Nat Chem Biol. 2015;11(9):620–624. https://doi.org/10.1038/nchembio.1894.

3 Jensen PR, Chavarria KL, Fensal W, Moore BS, Ziemert N. Challenges and triumphs to genomics-based natural product discovery. J Ind Microbiol Biotechnol. 2014;41(2):205–209. https://doi.org/10.1007/s10295-013-1553-8.

4 Saymantski P, Markowicz M, Mikić-Olszak E. Adaptation of high-throughput screening in drug discovery-toxicological screening tests. Int J Mol Sci. 2012;13(1):427–452. https://doi.org/10.3390/ijms12010427.

5 MacAron R, Banks MN, Bojanic D, et al. Impact of high-throughput screening in biomedical research. Nat Rev Drug Discov. 2011;10(3):188–195. https://doi.org/10.1038/nrd3636.

6 Wassemann AM, Camargo LM, Auld DS. Composition and applications of focus libraries to phenotypic assays. Protoc. Pharmacol. 2011;65. https://doi.org/10.3389/fphar.2014.00164.

7 Hong J. Natural product diversity and its role in chemical biology and drug discovery. Curr Opin Chem Biol. 2012;15(3):350–354. https://doi.org/10.1016/j.cob.2011.03.004.

8 Kingston DGI. Modern natural products drug discovery and its relevance to biodiversity conservation. J Nat Prod. 2011;74(3):496–511. https://doi.org/10.1021/np100550c.

9 Yao Z-J, Huang P-Q, Richard H. Efficiency in Natural Product Total Synthesis. Wiley; 2018.

10 Nicolaou KC, Rigol S. Perspectives from nearly five decades of total synthesis of natural products and their analogues for biology and medicine. Nat Prod Rep. Published online. 2020. https://doi.org/10.1039/d0np00003e.

11 Baran PS. Natural Product Total Synthesis: As Exciting as Ever and Here to Stay. J Am Chem Soc. 2018;140(14):4751–4755. https://doi.org/10.1021/jacs.8b02266.

12 Bebbington MWP. Natural product analogues: Towards a blueprint for analogue-focused synthesis. Chem Soc Rev. 2017;46(16):5059–5109. https://doi.org/10.1039/c6cs08424a.

13 Crane EA, Gademan K. Capturing Biological Activity in Natural Product Fragments by Chemical Synthesis. Angew Chem - Int Ed. 2016;55(12):3882–3902. https://doi.org/10.1002/anie.201505863.

14 Knoema. Accessed September 15, 2020. https://knoema.com/atlas/topics/Tourism/Travel-and-Tourism-Total-Contribution-to-GDP/Contribution-of-travel-and-tourism-to-GDP-percent-of-GDP/baseRegion-GD.
15 Hallside MS, Brzozowski RS, Wuest WM. A concise synthesis of (+)-discodermolide. J Am Chem Soc. 2014;136(4):11579-11584.

16 van Soest RWM, Boury-Esnault N, Vacelet J, et al. Global diversity of sponges (Porifera). Ocean Our Res Our Futur. 2018;159:2320. https://doi.org/10.1021/acs.orglett.8b00054.

23 De Souza MVN. (+)-Discodermolide. Part 5: Linkage of Fragments C1-4. Tetrahedron Lett. 2009;50(1):431-434. https://doi.org/10.1016/j.tetlet.2008.09.019.

32 Díaz C, Klein E, Cruz-Motta J, et al. Marine Biodiversity in the Caribbean: Regional Estimates and Distribution Patterns. 2010;5:8. https://doi.org/10.1371/journal.pone.0011916.

21 Petersen L-E, Kellermann MY, Schupp PJ. Secondary Metabolites of Marine Sponges: From Natural Products Chemistry to Chemical Ecology. 2020;157:1627-1633. https://doi.org/10.1007/978-90-481-3834-0_12.

19 Steele AD, Ernouf G, Lee YE, Wuest WM. Diverted total synthesis of the Marine Sponge Didiscus Flavus. J Nat Prod. 2014;77(4):1148-1154. https://doi.org/10.1021/jp403027w.

20 Incalci M, Badri N, Galmarini CM, Allavena P. Trabectedin, a drug acting on both tumor cells and the tumor microenvironment. Br J Cancer. 2014;111(4):646-650. https://doi.org/10.1038/bjc.2014.121.

27 Carroll AR, OPP, Davis BR, Keyzers RA, PR, MR. Marine natural products. Nat Prod Rep. 2019;36(1):122-173. https://doi.org/10.1039/c8np00092a.

11 Drees JM, de Krijger R, de Vries J, et al. Neopeltolide, a macrolide from a lithistid sponge. J Antibiot. 2003;56(2):158-159. https://doi.org/10.1038/ant.2003.08.

38 A. Demeritte and W.M. Wuest

Bioorganic & Medicinal Chemistry 28 (2020) 115792

9

21 Petersen L-E, Kellermann MY, Schupp PJ. Secondary Metabolites of Marine Sponges: From Natural Products Chemistry to Chemical Ecology. 2020;157:1627-1633. https://doi.org/10.1007/978-90-481-3834-0_12.

19 Steele AD, Ernouf G, Lee YE, Wuest WM. Diverted total synthesis of the Marine Sponge Didiscus Flavus. J Nat Prod. 2014;77(4):1148-1154. https://doi.org/10.1021/jp403027w.

20 Incalci M, Badri N, Galmarini CM, Allavena P. Trabectedin, a drug acting on both tumor cells and the tumor microenvironment. Br J Cancer. 2014;111(4):646-650. https://doi.org/10.1038/bjc.2014.121.

27 Carroll AR, OPP, Davis BR, Keyzers RA, PR, MR. Marine natural products. Nat Prod Rep. 2019;36(1):122-173. https://doi.org/10.1039/c8np00092a.

11 Drees JM, de Krijger R, de Vries J, et al. Neopeltolide, a macrolide from a lithistid sponge. J Antibiot. 2003;56(2):158-159. https://doi.org/10.1038/ant.2003.08.

38 A. Demeritte and W.M. Wuest

Bioorganic & Medicinal Chemistry 28 (2020) 115792

9
Adrian R. Demeritte was born in Nassau, Bahamas in 1994. He obtained his B.A. degree in chemistry with a concentration in chemical biology from Saint John’s University in Collegeville, Minnesota in 2016. Currently, he is a third-year graduate student in the Wuest Lab at Emory University in Atlanta, GA.

William M. Wuest was born on Long Island, NY in 1981. He obtained his B.S. degree in chemistry/business from the University of Notre Dame (Paul Helquist) in 2003 and a Ph.D. in chemistry from the University of Pennsylvania (Amos B. Smith, III) in 2008. After an NIH NRSA Postdoctoral Fellowship with Christopher T. Walsh at Harvard Medical School, he joined the faculty in the department of chemistry at Temple University as an assistant professor in 2011 where he stayed until 2017 as the Daniel Swern Early Career Development Professor. He moved his research group to Atlanta, GA, where he is currently a Georgia Research Alliance Distinguished Investigator & Associate Professor at Emory University. Research in the Wuest group focuses on the chemical biology of bacterial processes and, more specifically, the role that natural product-inspired analogs play in these events. For this, he and his group have received numerous awards including the NSF CAREER Award, ACS Medicinal Chemistry David W. Robertson Award, the ACS Infectious Diseases Young Investigator Award, the New Investigator Award from the Charles E. Kaufman Foundation, and the Italia-Eire Foundation Distinguished Teacher of the Year Award at Temple University.